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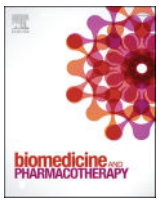

Review

Effects of chronic stress on cancer development and the therapeutic prospects of adrenergic signaling regulation

Hao Zhang [a,b,1], Yuwei Yang [c,1], Yan Cao [c,*], Jingzhi Guan [b,**]

[a] Department of Oncology, The Eighth Medical Center, Chinese PLA (People's Liberation Army) General Hospital, Beijing 100091, China
[b] Department of Oncology, The Fifth Medical Center, Chinese PLA (People's Liberation Army) General Hospital, Beijing 100071, China
[c] College of Pulmonary & Critical Care Medicine, Chinese PLA General Hospital, Beijing Key Laboratory of OTIR, Beijing, 100091, China

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ABSTRACT

Long-term chronic stress is an important factor in the poor prognosis of cancer patients. Chronic stress reduces the tissue infiltration of immune cells in the tumor microenvironment (TME) by continuously activating the adrenergic signaling, inhibits antitumor immune response and tumor cell apoptosis while also inducing epithelial-mesenchymal transition (EMT) and tumor angiogenesis, promoting tumor invasion and metastasis. This review first summarizes how adrenergic signaling activates intracellular signaling by binding different adrenergic receptor (AR) heterodimers. Then, we focused on reviewing adrenergic signaling to regulate multiple functions of immune cells, including cell differentiation, migration, and cytokine secretion. In addition, the article discusses the mechanisms by which adrenergic signaling exerts pro-tumorigenic effects by acting directly on the tumor itself. It also highlights the use of adrenergic receptor modulators in cancer therapy, with particular emphasis on their potential role in immunotherapy. Finally, the article reviews the beneficial effects of stress intervention measures on cancer treatment. We think that enhancing the body's antitumor response by adjusting adrenergic signaling can enhance the efficacy of cancer treatment.

1. Introduction

Due to acute stress (such as surgery, exercise), chronic stress (such as depression, social stress, and long-term cancer treatment) [1], and α/β-AR regulators [2], the levels of catecholamines in cancer patients and the catecholamine signaling pathway fluctuate. Chronic stress continuously activates the sympathetic adrenal medulla (SAM) axis and the hypothalamic-pituitary-adrenal (HPA) axis, increasing the release of catecholamines and glucocorticoids [3]. Catecholamines (CA) include norepinephrine (NE), epinephrine (EPI), and dopamine [4]; these neuroendocrine factors reshape the TME and adjust the systemic immune response by binding to the corresponding receptors on immune cells or stromal cells. Among them, the signaling pathway caused by NE and EPI activating AR is called "adrenergic signaling."

Chronic stress exerts its pro-tumorigenic effects in two main ways: directly on the tumor itself and indirectly by modulating the body's immune system. On the one hand, most immune cells infiltrating tumor tissues express AR and are regulated by adrenergic signals [5–8]. EPI and NE can bind to α and β-AR on the surface of immune cells, regulate the expression of cytokines or inhibitory ligands, suppress the body's antitumor immune response, and help the tumor escape immune surveillance [9–14]. For example, β-AR signaling significantly inhibits the proliferation of antigen-specific $CD8^+$ T cells and interferon-γ (IFN-γ) production [15], inhibits NK cell activity [10,16], recruits tumor-associated macrophages (TAM) [17] and myeloid-derived suppressor cells (MDSC) [18], and reduces the efflux of lymphocytes in lymph nodes [19]. On the other hand, tumor cells induce intratumoral nerve infiltration through the secretion of various neurotrophic factors [20]. Sympathetic release of EPI/NE can promote tumor cell proliferation, evasion of apoptosis, invasion, and distant metastasis [21] by binding to receptors on tumor cells, and it can also induce tumor vasculogenesis and lymphangiogenesis [22–25].

Based on the functional role of adrenergic signaling in tumors, researchers have begun exploring whether blocking adrenergic signal transduction is beneficial for antitumor therapy. Currently, most studies focus on β-AR blockers. For example, β-AR blockers can reduce the

* Correspondence to: College of Pulmonary & Critical Care Medicine, Chinese PLA General Hospital, Beijing 100091, China.
** Corresponding author.
E-mail addresses: aizerfore@gmail.com (H. Zhang), yangyw309@163.com (Y. Yang), pollyanna1023@aliyun.com (Y. Cao), jzjz1970@hotmail.com (J. Guan).
[1] Hao Zhang and Yuwei Yang are co-first authors who equally contributed to this manuscript.

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impact of chronic stress-induced tumor occurrence and progression. The use of β-AR blockers can enhance the antitumor efficacy of immune checkpoint inhibitors [26–29], increase T-cell infiltration [30,31], reduce tumor angiogenesis [32], and decrease the infiltration of myeloid-derived suppressor cells (MDSC) [33]. Recent studies have shown that using α2-AR agonists has a synergistic effect on immunotherapy, reducing the accumulation of immature MDSC and promoting their in vitro maturation [34], increasing macrophage abundance in the TME and recruiting and activating $CD4^+$ and $CD8^+$ T lymphocytes[35], and upregulating innate and adaptive immune responses in macrophages and T cells [35]. In addition to medication, mind-body behavioral management, including cognitive-behavioral therapy, positive mindfulness-based stress reduction, and physical exercise, modulates adrenergic signaling [36–38].

Here, we first review the adrenergic signaling pathways in cancer and the key role of this signal in regulating tumor-associated immune cells and promoting tumor occurrence and cancer development. Then, we summarize the application of adrenergic receptor modulators in cancer treatment, particularly emphasizing their potential role in immunotherapy. Using these modulators is expected to increase cancer patients' sensitivity to immunotherapy, providing new possibilities for treatment. Finally, we review the beneficial effects of stress intervention measures on cancer growth, emphasizing the importance of reducing tumor burden while relieving patient stress. By comprehensively utilizing these strategies, we can address cancer treatment challenges more effectively and provide patients with more effective treatment options.

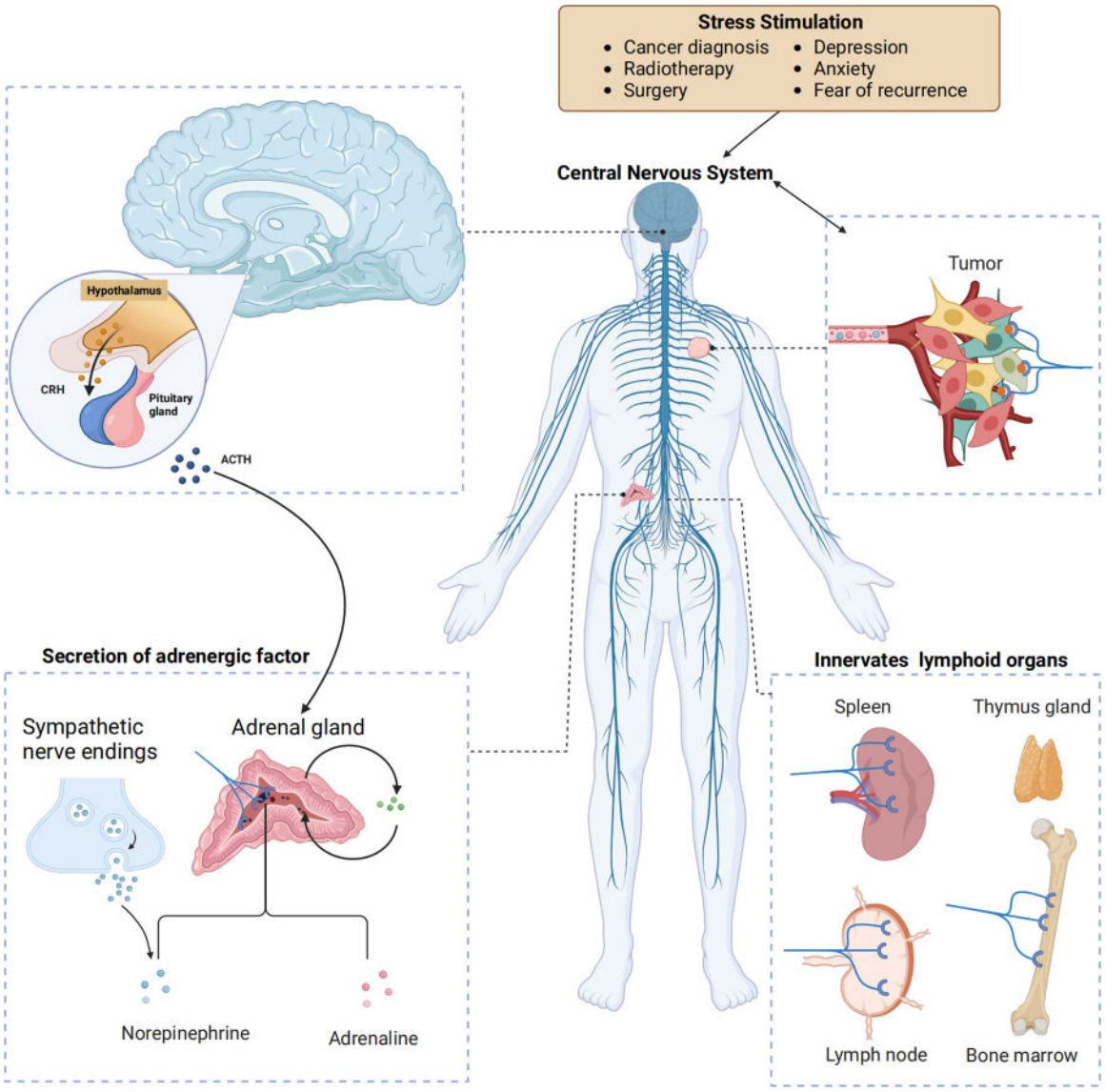

Fig. 1. Cancer patients typically endure significant physiological and psychological stress [59–62], including factors such as diagnosis [63], radiotherapy and chemotherapy [63,64], surgery [65], cancer pain [66], depression [67], fear of recurrence [68], and more. Stress can transiently activate the SAM axis, stimulating chromaffin cells in the adrenal medulla and sympathetic postganglionic fibers to release catecholamines (including dopamine, NE, and EPI) [69]. Additionally, stress can activate the hypothalamic-pituitary-adrenal (HPA) axis, with hypothalamic neurons synthesizing and secreting corticotropin-releasing hormone (CRH) acting on the anterior pituitary, promoting the synthesis and release of adrenocorticotropic hormone (ACTH), ultimately leading to adrenal cortex synthesis of glucocorticoids. Glucocorticoids, by promoting the expression and activity of tyrosine hydroxylase and facilitating NE methylation, directly or indirectly stimulate the synthesis and secretion of NE and EPI [70–72]. Furthermore, tumors recruit neural progenitor cells to the tumor microenvironment (TME) to form perineural networks [73,74]. Invasive sympathetic postganglionic fibers in tumors can release NE, signaling through α- and β-adrenergic receptors on the surface of tumor cells, immune cells, and stromal cells [73].

2. Stress response and signal transduction

Stress response refers to the body's physiological, behavioral, and psychological stress responses in the face of various physical and psychological stressors, which are aimed at helping the organism adapt to and combat external challenges [39,40]. Cancer patients undergo various stresses during diagnosis and treatment (see Fig. 1), triggering stress responses that activate the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic nervous system (SNS), releasing EPI, NE, and glucocorticoids. Stress responses can be categorized as acute or chronic, depending on the duration and intensity of the stress. Acute stress is an intense, sudden, stressful stimulus suffered over a short period (minutes to hours). In contrast, chronic stress is a prolonged period (lasting for a few hours, weeks, or months) in a stressful situation [41].

Acute and chronic stress have different effects on the body's immune system. Generally speaking, acute stress can quickly mobilize the immune system and speed up the initiation of immune responses. Research shows acute stress can enhance innate and adaptive immune responses, vaccine-induced immune responses, and antitumor immune responses [42–44]. The immune enhancement induced by acute stress benefits the body, as it is an adaptive effect to restore internal balance [45]. In animal studies, there are conflicting results regarding the impact of acute stress on the growth of primary tumors. Some studies have found that acute stress promotes the growth of primary tumors [46–50], while others indicate that acute stress inhibits primary tumor development [51,52]. The inconsistent results may be influenced by factors such as the source of stress, tumor models, and animal species. Despite the inconsistent effects on primary tumors, most studies suggest that stress contributes to the promotion of tumor metastasis. When the body is subjected to chronic stress beyond its adaptive capacity, adaptive effects shift to maladaptive effects, and short-term stress turns into harmful chronic stress [53,54]. Chronic stress causes immune dysfunction or suppression [55], affecting innate and adaptive immunity, reducing the effectiveness of vaccination and wound healing, and leading to decreased antitumor immunity and resistance to infection [43,44,56,57]. Because each person's physical condition and coping mechanisms are unique [58], and there are significant individual differences, it is a complex and critical issue to use stress reasonably to enhance protective immunity and reduce the adverse effects of chronic stress.

Pressure triggers a neuroendocrine response, releasing neuroendocrine factors that act on α and β-AR to complete various regulations. NE and EPI act through different subtypes of AR [75]. NE has a stronger binding ability to α-AR, while EPI has a stronger affinity for β-AR. AR is a G protein-coupled receptor superfamily member, with seven hydrophobic transmembrane domains, including a C-terminal intracellular domain, an N-terminal extracellular domain, and three intracellular and extracellular loops [75]. AR can be roughly divided into three classes: α1, α2, and β-AR, based on the differences in the intracellular C-terminal region. α1-AR and α2-AR are further subdivided into α1A, α1B, α1D and α2A, α2B, and α2 C, while β-AR is divided into β1, β2, and β3 [28]. α and

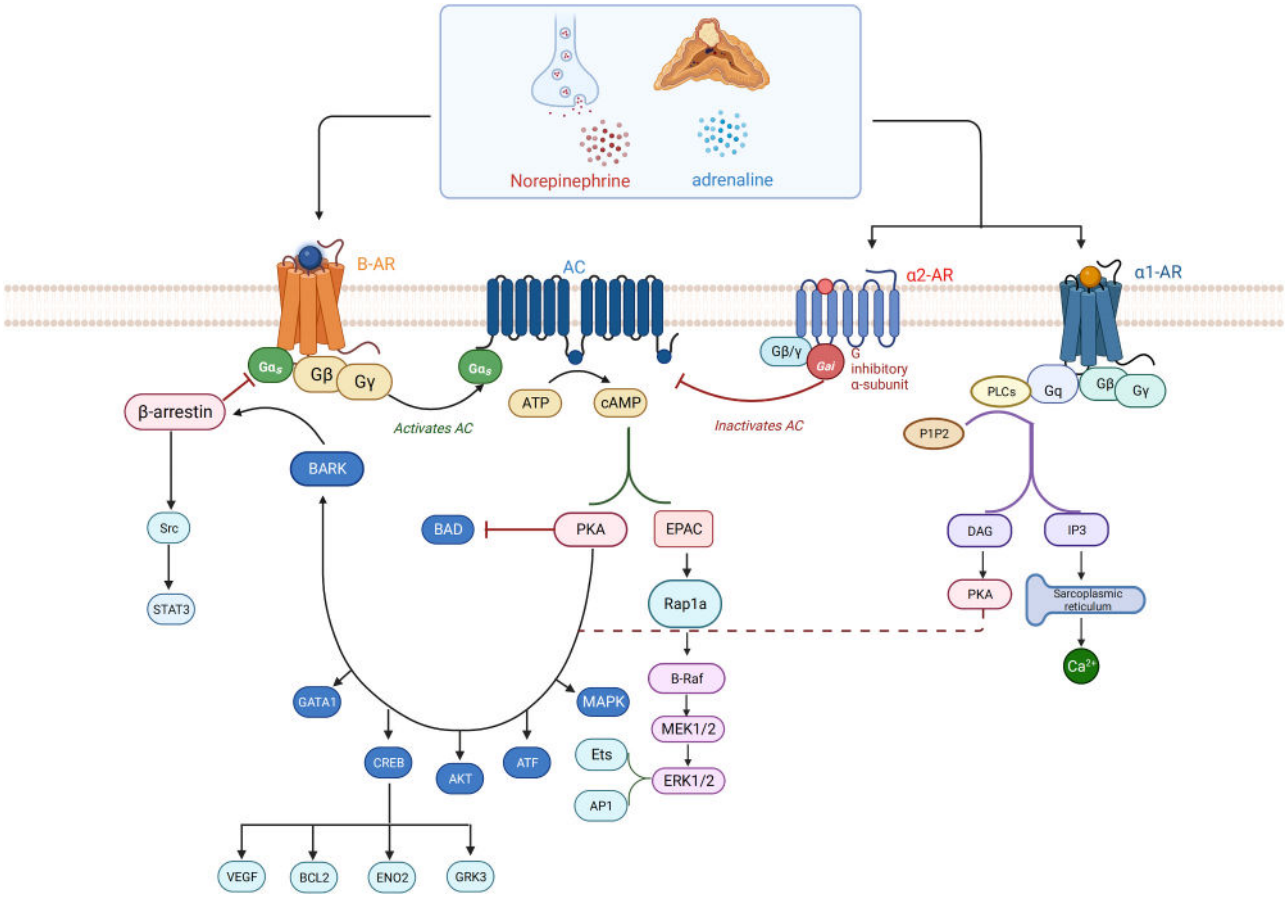

Fig. 2. Overview of the adrenergic signaling pathway. The chromaffin cells of the adrenal medulla and sympathetic nerve terminals produce epinephrine (EPI) and norepinephrine (NE). (1) EPI and NE bind to β-AR on the cell surface, activating adenylate cyclase (AC), which converts ATP to cAMP. Then, cAMP activates PKA to phosphorylate various intracellular target proteins, including MAPK, AKT, CREB, and transcription factors ATF, GATA1, BAD, and BARK. BARK recruits β-arrestin to the cell membrane surface to inhibit β-AR signaling. (2) cAMP directly activates the exchange protein activated by cAMP (EPAC), which further activates the Rap1a-mediated B-Raf/MEK/ERK signaling pathway, and ERK regulates AP-1 and Ets transcriptional activity. (3) EPI and NE binding to α2-AR inhibit AC, reducing cAMP production. (4) EPI and NE binding to α1-AR hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) to produce inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 induces Ca^{2+} release into the cytoplasm, and DAG activates PKA.

β-AR transmit information through different G protein-coupled receptors. After AR is activated, the conformation of the G protein-coupled receptor changes, and the α subunit bound to GTP (Gαs, Gαi, and Gαq) separates from the β and γ subunits, becoming involved in downstream signal transduction processes [76]. The distribution of different AR subtypes in human tissues also varies. α1-AR and α2-AR are widely distributed in human tissues [77]. β1-AR is mainly expressed in the heart, mediating the heart's response to catecholamines. β2-AR is mainly distributed in vascular and bronchial smooth muscle, while β3-AR is mainly expressed in adipose tissue, stomach, and gallbladder [78].

As shown in Fig. 2, when EPI and NE stimulate α and β-AR [79], different Gα subunits separate from Gβ/γ subunits, triggering different downstream signals [80]. First, after β-AR binds to Gas protein, it activates adenylyl cyclase (AC), stimulating AC to generate cAMP [81]. cAMP mainly regulates cell function through two major downstream effect systems. The first system is the PKA-independent pathway, where cAMP activates protein kinase A (PKA) [82] to phosphorylate various intracellular target proteins [83], including MAPK, protein kinase B (AKT), and cAMP response element-binding protein (CREB) signaling pathways, as well as transcription factors ATF, GATA1, and β-adrenergic receptor kinase (BARK [84]). At the same time, BARK induces β-arrestin to bind to phosphorylated active receptors, thereby inhibiting β-AR signal transduction and temporarily desensitizing β-AR signal transduction. It also activates the Src/Ras/mitogen-activated protein kinase (MAPK [85]) pathway. In the non-classical pathways induced by β-AR signal transduction, GRK2 or GRK5/6 phosphorylate β-AR in an agonist concentration-dependent manner [14] and then recruit β-arrestin 1/2. Among them, β-arrestin 1 activates cAMP-PKA signal transduction, and β-arrestin 2 activates MAPK-ERK1/2 signal transduction [86,87]. In addition, PKA can also phosphorylate BAD (Bcl-2 family pro-apoptotic member), leading to its inactivation and promoting cell survival [88].

For the PKA-independent pathway, the guanine nucleotide exchange factor (EPAC) contains a cAMP binding site regulated by cAMP [89]. EPAC can activate Ras-like guanosine triphosphatase (Rap1A) [90], which further activates the B-Raf-MEK-extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway [91]. The elevation of ERK1/2 can phosphorylate AP-1 and Ets [84]. However, α2-AR plays the opposite role, reducing adenylyl cyclase (AC) and inhibiting cAMP production through coupling the Gαi pathway [92]. In addition, α1-AR induces the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) to produce inositol trisphosphate (IP3) and diacylglycerol (DAG) through the

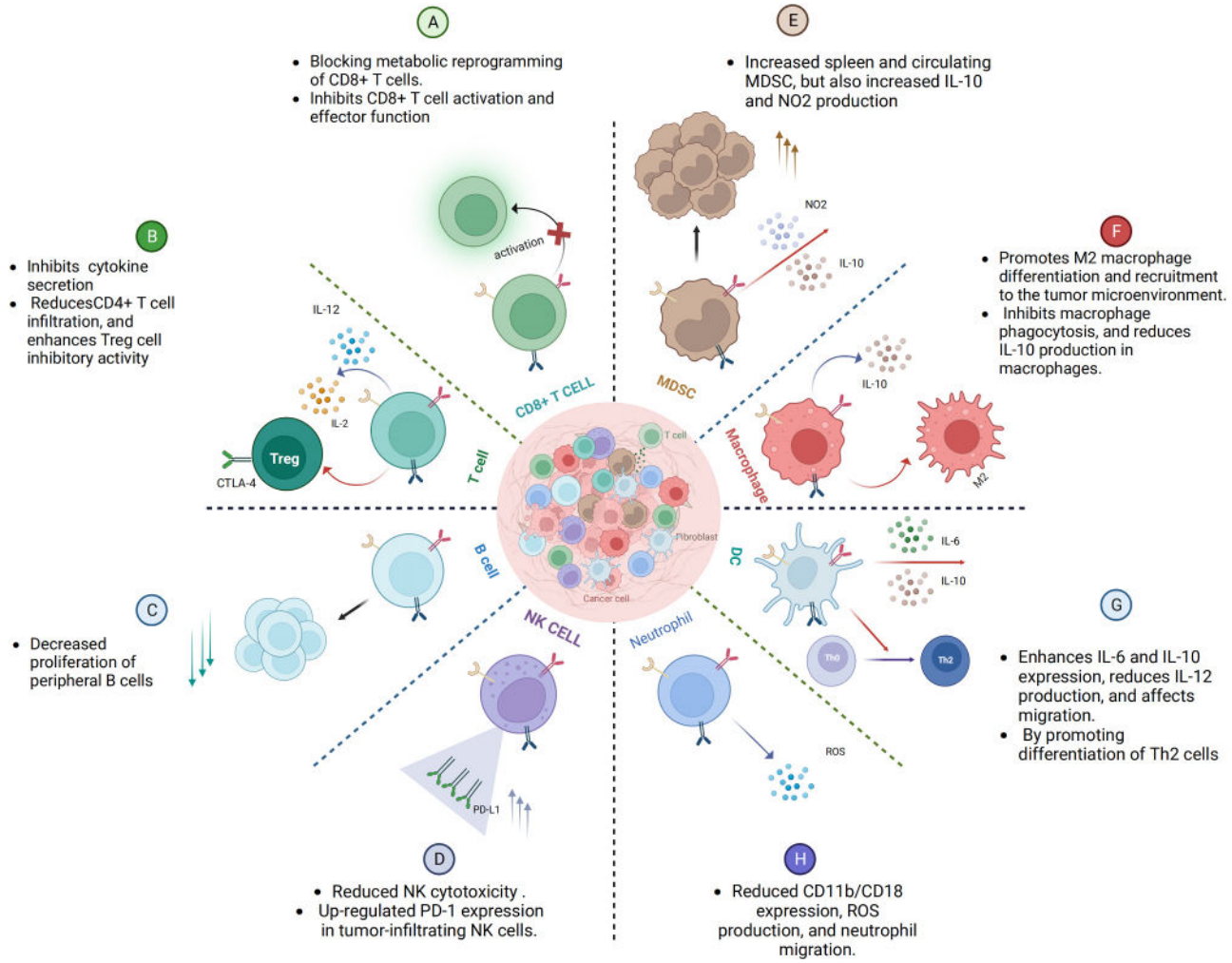

Fig. 3. Stress-activated adrenergic signaling regulates immune cell function. (A) Blocking metabolic reprogramming of $CD8^+$ T cells inhibits the activation and effector function of $CD8^+$ T cells. (B) Inhibition of T-cell factor secretion reduces $CD4^+$ T cell infiltration in the TME and enhances the suppressive activity of Treg cells. (C) Decrease peripheral B cell proliferation. (D) Decrease NK cytotoxicity and upregulate PD-1 expression in tumor-infiltrating NK cells. (E) Increased splenic and circulating MDSC with concomitant increases in IL-10 and NO2 production. (F) Induction of M2 macrophage differentiation and recruitment to TMEs converted to tumor-associated macrophages; inhibition of macrophage phagocytosis and reduced IL-10 production in macrophages. (G) Increased dendritic cell (DC) IL-6 and IL-10 expression decreased IL-12 production; α-AR signaling promoted DC migration, while β-AR signaling inhibited DC migration. Induction of Th2 phenotype production via DC. (H) Reduced neutrophil CD11b/CD18 expression, ROS production, and migration.

Gαq family of α subunits [93]. Among these, IP3 induces the release of Ca^{2+} stored in the endoplasmic reticulum into the cytoplasm, and DAG can activate the intracellular target PKA [94].

3. Adrenaline signaling reshapes the tumor immune microenvironment

The body regulates the immune system by synthesizing and secreting neuroendocrine factors through the neuroendocrine system [95]. Stress induces the production of neuroendocrine factors that modulate the function of immune cells by binding to the appropriate receptors on the immune cells. Innate immune cells express α1, β2, and α2-AR, while adaptive immune cells mainly express β2-AR [10,96,97]. Additionally, both primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid organs are also regulated by adrenergic signaling [98], which can control lymphocyte trafficking to regulate adaptive immune responses [99]. We summarize the main aspects of adrenergic regulation of immune cell function in cancer (Fig. 3).

3.1. T lymphocytes

T lymphocytes are a crucial part of the antitumor immune response in the TME [100]. Improving the infiltration of T lymphocytes in the TME is extremely important for enhancing the effectiveness of radiotherapy, chemotherapy, and immune activators [101–103]. The sympathetic nervous system has a controlling effect on all primary and secondary immune organs. When the sympathetic nervous system is stimulated, the postganglionic fibers release NE, which activates the P38 kinase activity through the β-AR/Gs/PKA pathway, upregulating the expression of the Fas ligand, leading to changes in T cell reactivity and cell apoptosis [104]. It also leads to a decrease in the number of $CD4^+$ T cells in the primary lymphoid organ (thymus) [105] and regulates the outward migration of T lymphocytes in the secondary lymphoid organ (lymph node) via β2-AR [19].

$CD4^+$T cells, under the influence of adrenergic signals, can produce cytokines that promote tumor effects or transform into inhibitory immune cells. β2-AR signals increase the proportion of regulatory T (Treg) cells in $CD4^+$ T lymphocytes by inducing the expression of Foxp3 in $CD4^+$T cells [106] and enhance the inhibitory activity of Treg cells by increasing the expression of cytotoxic T lymphocyte-associated protein 4 (CTLA4) [107]. Adrenergic signals can also activate β-AR signals on $CD4^+$ T cells, causing Th1 cells to transform into Th2 cells and increase the production of IL-6 and IL-10 by Th2 cells. In addition, adrenergic signals can inhibit the release of IL-2, IL-12, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (INF-γ) by $CD4^+$ T cells [97,108].

The expression of β2-AR in $CD8^+$ T cells is related to their differentiation stage, with the expression of β2-AR in memory $CD8^+$ T cells (Tcm and Tem) significantly higher than in naive T cells. Therefore, memory $CD8^+$ T cells are more susceptible to adrenergic signaling. NE reduces the expansion of memory $CD8^+$ T cells and inhibits the production of IL-2 and IFN-γ when memory $CD8^+$ T cells are restimulated [109]. IL-2 and β2-AR jointly regulate the activation and function of $CD8^+$ T cells, as IL-2 can increase the expression of β2-AR on effector $CD8^+$ T cells [110]. Studies have also found that β2-AR signaling can inhibit metabolic reprogramming during $CD8^+$ T cell activation, suppressing glucose uptake and glycolysis, thereby inhibiting the activation and effector function of $CD8^+$ T cells [111]. Conversely, blocking β-AR signaling can increase glycolysis and oxidative phosphorylation in tumor-infiltrating lymphocytes (TIL) [112]. Chronic stress reduces the number of TIL [113], impairs their metabolism, suppresses their activity, and increases the expression of programmed cell death protein 1 (PD-1) and cytotoxicity [111,114]. Furthermore, α-AR is also involved in regulating T lymphocyte proliferation and cytokine production. Activation of α2-AR can inhibit lymphocyte proliferation and reduce the production of cytokines such as IFN-γ and IL-4 [115]. In summary, NE and EPI in the TME shape the tumor immune-suppressive microenvironment by binding to AR on the surface of T lymphocytes. This includes inhibiting cell function, promoting metabolic dysfunction and exhaustion of T cells, and inducing the formation of suppressive immune cells [116].

3.2. B lymphocytes

Like T lymphocytes, stress can induce B lymphocytes to mobilize into the blood and reduce efflux, affecting the redistribution of B lymphocytes [41,117,118]. B lymphocytes may play a crucial role in tumor immunity, and there are various B lymphocyte populations in the TME, including immature B cells, memory B cells, activated memory B cells, and plasma cells [119]. Stimulating β2-AR on B lymphocytes can increase CD86 expression [120] and the secretion of IgG1 and IgE [121], but does not affect class switch recombination[122]. Meanwhile, the interaction between CD86 on the surface of B lymphocytes and CD28 on the surface of Th2 cells promotes the secretion of IL-4 by Th2 cells [121,123]. In the presence of IL-4, activated B cells can increase IgE secretion through the β2-AR-cAMP-PKA signaling pathway[122]. Further research has found that β2-AR-induced IgE increase depends on p38 MAPK activation rather than PKA [122]. Additionally, soluble CD23 (sCD23) levels increase in a β2-AR-induced p38 MAPK-dependent manner and upregulate IgE through interaction with CD21/CD19 [122]. Studies have found that perioperative breast cancer patients taking β-blockers and COX2 inhibitors can increase tumor-infiltrating B cells [124]. Tumor-infiltrating B lymphocytes are an important component of tertiary lymphoid structures in tumor tissue, closely related to antitumor immune activation and immune therapy response [125]. However, no studies in tumor-related fields have clarified how adrenergic signaling in TME regulates B lymphocytes, and most of the existing studies have focused on non-tumor fields. It is necessary to explore how adrenergic signaling in the TME of stress tumor models affects the function of B lymphocytes and the relationship between B lymphocytes and other immune cells.

3.3. Monocytes and macrophages

Stable-state monocytes circulate in the blood, bone marrow, and spleen; however, monocytes migrate to tissues during inflammatory stimulation and differentiate into macrophages and DC [126,127]. The impact of β-AR on monocyte function is mainly immune suppression and anti-inflammatory, such as downregulating TNF-α expression [128], inhibiting phagocytosis of Candida albicans129, and reducing the production of IL-18 and IL-12 when monocytes are stimulated by LPS [129]. β-AR stimulation in monocytes regulates the release of inflammatory factors, for example, increasing the production of IL-18 [130] and upregulating the expression and release of CD23 induced by IL-4 [131,132]. In addition to β-AR, monocytes also express α-AR on their surface, and stimulation by LPS and β2-AR agonists upregulates the expression of α1B and α1D-AR mRNA [130,133]. As monocytes differentiate into macrophages in vitro, the AR subtype changes [134], and the response to β-AR stimulation is lost [135].

Research has shown that treating mice with isoproterenol before the spread of tumor cells to the metastatic site increases the expression of CCL2 in lung stromal cells and the expression of CCR2 in monocytes and macrophages. This leads to increased output of lung monocytes and infiltration of macrophages before metastasis, promoting the settlement of tumor cells [136]. β-AR signaling increases the infiltration of macrophages (CD11b+, F4/80+) at the primary tumor site, promotes M2-like macrophage differentiation, and induces the expression of pro-metastasis genes [17]. Interestingly, macrophages stimulated by β-adrenaline exhibit an M2 phenotype but do not entirely fit the M1/M2 lineage [137]. Yan C and others found that NE stimulation promotes the release of neuropeptide Y (NPY) from Myc-CaP cells and enhances intratumoral infiltration of $CD68^+$ TAM in a depression mouse model and patients with depressive symptoms [138]. In addition, NE inhibits the phagocytic efficiency of macrophages by activating β-AR [139].

β2-AR signaling reduces the production of IL-6, IL-1β, and TNF-α by monocyte-derived macrophages [140], whereas α-AR signaling increases the secretion of pro-inflammatory cytokines [141,142]. In summary, adrenaline signaling affects macrophage polarization and cytokine production, promoting the recruitment of TAM in the TME to exert pro-cancer effects.

3.4. Dendritic cells

It has been found that stress induces an increase in more immature phenotypes (MHCII- and CD86-) of DC cells, resulting in their inability to activate $CD8^+$ T cells and negatively affecting $CD8^+$ T cell-dependent antitumor immune responses [143]. The activation of α, β-AR has opposite effects on DC migration ability, with α-AR signaling promoting DC migration, while β-AR signaling inhibits DC migration [144,145]. Several studies have shown that NE regulates DC secretion factors through β-AR signaling, inhibiting IL-12 production, increasing IL-10 and IL-33 production to suppress TH1 response, and promoting Th2 differentiation [144,146,147]. EPI can also promote the generation of dominant Th2/Th17 phenotypes induced by bone marrow-derived DC [148]. The role of Th17 cells in tumor immunity is still unclear. Stimulation of β2-AR can reduce the cross-presentation ability of mature DCs while retaining the exogenous peptide presentation ability; cross-presentation inhibition is related to impaired phagosome antigen degradation [149]. Subsequent studies have shown that β2-AR activation can inhibit the cross-presentation of DC antigen proteins to $CD8^+$ T cells but retains its exogenous major histocompatibility complex (MHC) class I peptide presentation ability [150]. α2-AR agonists can inhibit the hydrolysis of phagosome proteins in mouse DCs, reduce the expression of surface molecules IA(b) and CD86, and inhibit the proliferation of cognate helper T cells [151].

The degree of antitumor response of dendritic cells (DC) is related to their mature state when they migrate. Research has found that immature DC, when stimulated by β2-AR, enhances antitumor response and significantly reduces tumor growth. However, no significant effect was observed on tumor-loaded antigen-matured DC [152]. In addition, chronic stress can enhance the expression of vascular endothelial growth factor (VEGF), matrix metalloproteinase 2 (MMP2), and MMP9 in tumor cells [22], which significantly affects the maturation of precursor dendritic cells, promoting tumor evasion of the host immune system [153]. This also explains why stress-induced tumor-bearing mice produce more DC, but effective DC cells are fewer than normal mice [143]. Dendritic cells (DC) play an important role in capturing, processing, and presenting antigens; tumor cells evade immune recognition by inhibiting DC function and interfering with antigen processing and presentation [154]. Therefore, it is necessary to understand further the impact of stress on DC function in cancer and whether it hinders immunotherapy.

3.5. Natural killer cells

Many studies suggest that the main mechanism through which SNS activation promotes cancer progression is by reducing NK cell activity via β-AR signaling. Chronic stress has decreased the toxicity of tumor-infiltrating lymphocytes and NK cells in ovarian cancer patients [155]. NE and EPI stimulation of β-AR inhibits NK cell cytotoxicity [156,157], decreasing resistance to tumor metastasis [15,158,159]. However, EPI may also enhance NK cell cytotoxicity at lower levels [160], and using α-AR agonists can enhance NK cell function [161]. In breast cancer patients under chronic stress, NK cell response to IFN-γ is weakened, and their cytotoxic capacity is impaired [162]. Furthermore, Kimberly A. and others found that the impaired cytotoxic capacity of NK cells is related to changes in the surface expression of the killer immunoglobulin-like receptor CD158b [163]. In addition to reducing NK cell cytotoxicity, β-AR signaling also decreases the adhesion of NK cells to endothelial cells [164].

Adrenaline can regulate the mobilization and redistribution of NK cells [6,165]. Surgery stress reduces the concentration of circulating NK cells and the expression of FAS ligand and CD11a on their surface [166]. Several studies have shown that acute stress regulates the redistribution of NK cells by activating β-AR receptors. For example, β-AR blockers reverse the decrease in lung and blood NK cells [167]. Giving β-AR blockers during exercise can inhibit the migration of NK cells [168]. In addition, β-AR also participates in regulating NK antiviral activity. Reducing stress can enhance the activity of NK cells in breast cancer patients [169]. Mice treated with β2-AR agonists are more susceptible to MCMV infection [170], but lacking β2-AR expression impairs the expansion and memory of NK cells during MCMV infection [171]. The above shows that stress can lead to impaired cytotoxicity of NK cells and decreased antitumor function. As a major component of innate immunity, NK cells can recognize and kill tumor cells and virus-infected cells in the early stages [172,173]. Two typical subgroups are $CD56brightCD16^-$ and $CD56dimCD16^+$. However, there is no research yet to confirm whether adrenaline signaling can affect the specific phenotype of NK cells by changing the expression of CD56 and CD16, thereby affecting the number of NK cells and antitumor immunity in peripheral blood and TME.

3.6. Myeloid-derived suppressor cells

The signals of the sympathetic nervous system can induce the differentiation of hematopoietic stem cells into bone marrow cell lineages, leading to an increase in mononuclear cells, myeloid-derived suppressor cells (MDSC), and neutrophils [42–144]. while impairing the generation of lymphocytes and red blood cells [174]. β-AR signals can promote further differentiation of MDSC into polymorphonuclear (PMN)-MDSC and monocytic (M)-MDSC [18,175]. However, the absence of α-AR signals can lead to the accumulation of MDSC [34], demonstrating the different effects of α and β-AR signals on MDSC. Activation of the brain reward system in tumor patients can reduce the release of sympathetic nervous system signals, thereby reducing the production of MDSC in the bone marrow and significantly increasing the expression of granzyme B on CD8+ T cells, ultimately weakening tumor growth [176]. Genetic elimination of β2-AR or the use of β receptor blockers can restore mice's tumor immunity, further confirming this receptor's critical role in immune regulation [175].

The stimulation of β-AR signals can cause MDSC to mobilize from the bone marrow into the circulation and migrate to tumor tissues under various chemokines, exerting immunosuppressive effects [34,177,178]. Surgery is a common cancer treatment and a source of acute stress, which can induce an increase in MDSC in the TME [179] and promote tumor metastasis by promoting early infiltration to metastatic sites [180,181]. β2-AR signal transduction not only increases the frequency of MDSC in tumor tissues but also enhances the immunosuppressive function of MDSC by downregulating apoptosis-related genes and upregulating the expression of immune inhibitory molecules (such as arginase 1 and PDL1) [182]. Studies have also found that chronic stress-induced MDSC not only inhibits T cell proliferation [106] but also promotes the transformation and survival of Tregs (regulatory T cells) by secreting immunoregulatory cytokines (such as TGF-β and IL-10) and attracting Tregs to the TME [183], further exerting immunosuppressive effects and promoting tumor progression [184]. Research reports that β2-AR signaling regulates MDSC by altering its metabolism to enhance its immunosuppressive function [11,12]. Specifically, tumor growth leads to increased expression of β2-AR on MDSC, and β2-AR signaling affects the metabolic processes of MDSC, including promoting fatty acid oxidation, autophagy, and the production of prostaglandin E2. These metabolic changes further enhance the immunosuppressive function of MDSC. In summary, β2-AR signal transduction affects tumor progression by increasing the number of MDSC, improving the survival of MDSC, upregulating the expression of immune inhibitory molecules, and altering the metabolism of MDSC, ultimately leading to immunosuppression in the TME and tumor progression.

3.7. Neutrophils

Chronic stress promotes the generation of monocytes and neutrophils in the bone marrow [174]. Multiple studies have indicated neutrophils express various adrenergic receptors (AR), with β2-AR being the main type [8,185]. In addition to inflammatory factors directly stimulating the expression of AR receptors in neutrophils, different diseases, intense exercise, and surgery can also affect the expression of AR receptors [186–189]. High concentrations of adrenaline stimulation mildly affect the expression of adhesion molecules CD15, CD44, and CD54 [190]. Prolonged exposure to adrenaline can promote the production of myeloperoxidase (MPO) and the release of IL-6 in neutrophils but inhibit the production of IFN-γ and IL-10, causing damage to neutrophil activation and phagocytic activity [185]. Stress-stimulated mice had suppressed neutrophil phagocytic activity and increased melanoma metastasis [191]. In another study using a stress-induced mouse tumor model, adrenaline rapidly released the S100A8/A9 complex by activating neutrophil β2-AR and activated MPO produced oxidized or hydrolyzed phospholipids. These lipids reactivated dormant tumor cells by upregulating FGFR signaling in tumor cells [192]. β2-AR signaling can inhibit the respiratory burst of neutrophils [193] and their adhesion to endothelial cells [194]. Adrenaline can rapidly mobilize the number of neutrophils by stimulating α-AR [195], and a gout animal model overexpressing α2B-AR has confirmed this by increasing the migration ability of neutrophils to enhance the infiltration of neutrophils in the inflammatory environment [196]. Due to the regulation of neutrophil migration by AR, in the case of continuous adrenaline stress, neutrophils will flow into the wound, delaying wound healing [197], which may lead to poor postoperative outcomes and even inflammation in cancer patients. In conclusion, adrenaline may play a significant role in processes such as inflammation and tumor metastasis by affecting the function of neutrophils. Researchers can explore how adrenergic signaling affects the function and activation status of neutrophils to reveal the mechanism of adrenergic effects on neutrophils.

3.8. Other immune cells

Most studies on eosinophils, basophils, and mast cells have focused on allergic reactions, but AR signaling also regulates their activity. It has been reported that EPI injection decreases circulating eosinophils, while β-AR antagonists have the opposite effect [198]. β-AR agonists can affect the survival of eosinophils and reduce the number of eosinophils adhering to the vascular endothelium at the site of inflammation, preventing their entry into the airways [199,200]. Basophils express different types of AR, and the activation of α2-AR can inhibit histamine secretion by basophils during allergies [201]. EPI reduces antigen activation of basophils from the peripheral blood of atopic donors, and propranolol can reverse the inhibitory effect of EPI [202]. β2-AR activation can also inhibit histamine release from human lung mast cells and peripheral blood mast cells [203,204]. Gamma Delta (γδ) T cells account for about 5 % of the total T cells in the blood, participating in defending against infectious diseases and inhibiting the occurrence and progression of tumors[205]. Studies have reported that γδT lymphocytes are mobilized by psychological stress, exercise, and β-AR agonists, and the degree of mobilization is greater than that of $CD8^+$ T lymphocytes but less than NK cells [206]. Another study confirmed that EPI can rapidly mobilize CD4(-) CD8(-) γ/δT cells [207]. However, research on these immune cells is still relatively limited, and further exploration is needed to understand their role in tumor immunity.

In summary, chronic stress suppresses the activity of immune cells and activates immunosuppressive cells, reshaping the tumor immune microenvironment and inhibiting the body's immune response, ultimately promoting tumor progression. Normal antitumor immune response forms the basis of cancer treatment, including surgery, radiotherapy, chemotherapy, and immunotherapy. Therefore, it is necessary to manage stress appropriately to mitigate its detrimental effects on cancer.

4. Adrenergic signaling regulates the biological behavior of tumors

The adrenaline signal, in addition to causing immune dysfunction to promote cancer progression, also acts directly on the tumor itself to regulate various biological behaviors of the tumor. Here, we focus on discussing the role of adrenaline signaling in regulating the biological behavior of tumors, including promoting tumor initiation, cell proliferation, anti-cell death, inducing EMT, and activating invasion and metastasis.

4.1. DNA damage and oncogene activation

Research reports that prolonged chronic stress can lead to DNA damage, promoting the occurrence of tumors [208,209]. Researchers investigated the mechanism of stress-induced DNA damage (Fig. 4). They found that catecholamines activate β-arrestin-1/PI3K/AKT-mediated phosphorylation of E3 ubiquitin ligase murine double minute 2 (MDM2) through β2-AR signaling [210] and promote Mdm2-mediated tumor ubiquitination and p53 degradation of suppressor proteins [210], leading to chromosomal instability as well as tumorigenesis [211]. The genetic loss of propranolol and ARRB1 can inhibit the accumulation of DNA damage during stress [212]. Further research reveals that isoproterenol generates ROS through the PKA signal, causing DNA damage [213]. Inhibiting PKA can reduce the accumulation of isoproterenol-induced DNA damage [210]. Additionally, adrenaline signaling can stimulate the activation of various oncogenes. In ovarian cancer samples, NE levels are correlated with pSrc levels, and it has been demonstrated that β-AR/PKA enhances tumor cell proliferation, invasion, and migration by regulating Src phosphorylation at residue Y419 [214]. Similarly, the expression of Her-2 in breast cancer is associated with β-AR, where EPI activates transcription activator 3 (STAT3) through β2-AR, subsequently activating the ERBB2 promoter to stimulate Her-2 expression [215]. However, it is still unclear whether long-term activation of β-AR inhibiting DNA damage repair increases the rate and probability of cancer in the body.

4.2. Tumor cell proliferation and apoptosis

Stress hormones play a critical role in regulating the proliferation and apoptosis of tumor cells and have been validated in various cancers (Fig. 5). Specifically, α1 and β-AR signaling activate the MEK-MAPK-ERK-1 signaling pathway, inducing the transcriptional activation of growth genes (such as JUN, Fos, Myc), promoting cell proliferation. It has been shown that β2-AR/Src inhibits nest loss apoptosis in ovarian cancer cells by activating the Y397 adhesion patch kinase (FAK) site when ovarian tumor cells are stimulated with epinephrine or NE [216]. Simultaneously, stress upregulates the expression of anti-apoptotic proteins BCL-2 and MCP-1 within tumor cells and [217], through the β2-AR-PKA pathway, promotes the phosphorylation and inactivation of the pro-apoptotic protein BAD [218], thereby reducing cancer cell sensitivity to apoptosis. Blocking AR signaling significantly reduces the expression of anti-apoptotic proteins [217]. Research on a prostate cancer mouse model also confirms that stress hormones reduce cell apoptosis through the β2-AR/PKA/BAD anti-apoptotic signaling pathway, thereby promoting the occurrence of prostate cancer.

Several in vitro experiments have shown that after cancer cells are stimulated by AR signaling, the number of G1 and G2 phases is reduced, and the proliferation is promoted dose-dependent [219–223]. However, there exist some contrary findings. β2 agonists via the β2-AR/cAMP/PKA pathway can block the Raf-1/Mek-1/Erk1/2 pathway [224], thus reducing cell proliferation in vitro and tumor growth in vivo [225].

This contradiction may be related to the molecular mechanisms of

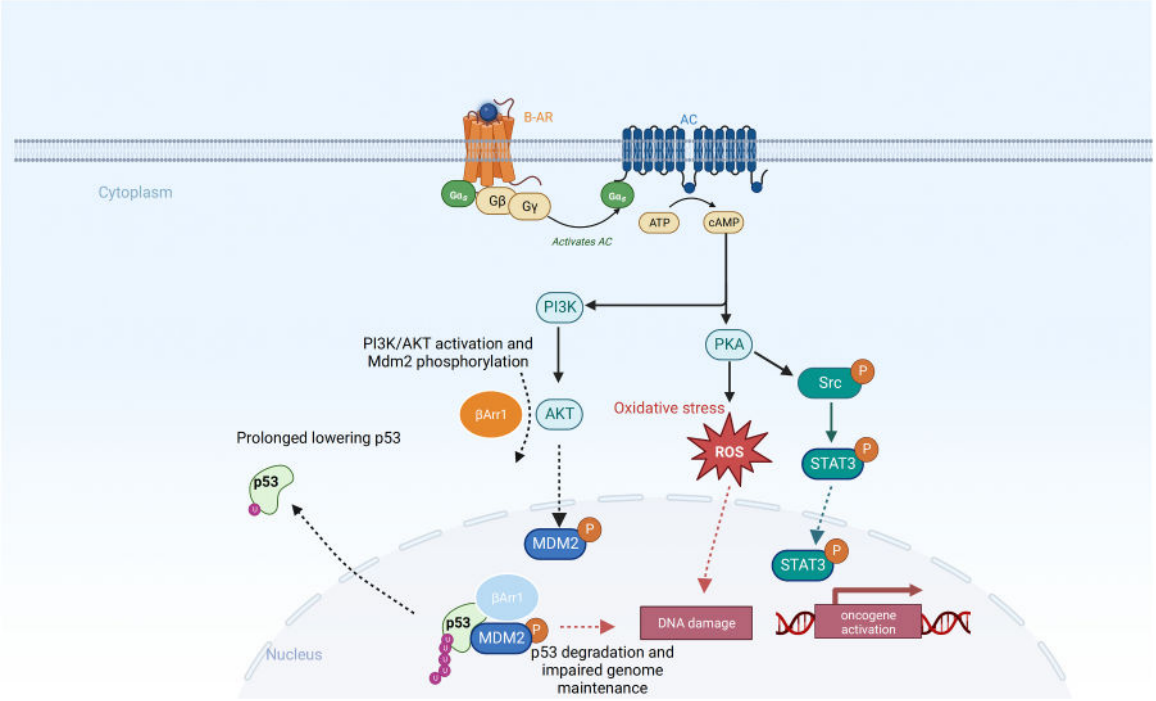

Fig. 4. β-AR signaling regulates DNA damage and oncogene activation in cancer cells. (1) β-AR signaling activates PI3K-AKT through cAMP, activating MDM2 and tumor suppressor protein ubiquitination and p53 degradation mediated by β-arr1, resulting in chromosomal instability and tumorigenesis. (2) cAMP activates PKA-Src-STAT3, activating oncogenes and inducing DNA damage through ROS activation.

downstream pathways under AR signals in different tumors, and further research is needed for clarification. In addition, β3-AR is involved in regulating melanoma cell proliferation and apoptosis and inducing the expression of stem cell markers. Stimulation of β3-AR induces a metabolic shift in melanoma cells from oxidative metabolism to glycolysis, maintaining the Warburg effect characteristic of tumor cells [226,227]. Therefore, stress hormones have complex regulatory effects on the survival and proliferation of tumor cells, and future research will contribute to a more comprehensive understanding of these regulatory mechanisms.

4.3. Extracellular matrix invasion

EMT is the process of epithelial cells transforming into mesenchymal cells, acquiring the ability to invade and migrate [228]. It has been shown that NE can induce EMT through activation of β2-AR (Fig. 6) [229], which allows tumor cells to cross the basement membrane, invade surrounding tissues, and even enter blood vessels or lymphatic vessels for long-distance metastasis [230]. NE, through the activation of the β2-AR-hypoxia-inducible factor-1α (HIF-1α)-Snail signaling pathway, can decrease the expression of E-cadherin and increase the expression of vimentin, inducing EMT changes in gastric adenocarcinoma cells and enhancing the migration and invasion capabilities of tumor cells [229]. On the other hand, research has found that silencing β2-AR can lead to changes in cell morphology and gene expression, increasing the expression of vimentin and N-cadherin, promoting cell invasion, and transforming into benign prostate epithelial cells, which are typical features of EMT [231]. This may be related to changes in the activity of Rap1, which can promote cell-cell adhesion and cell-matrix adhesion, maintaining the epithelial cell phenotype of pancreatic cells [232]. Therefore, inhibiting β2-AR can reduce intracellular cAMP levels, leading to Rap1 inactivation and the loss of cell adhesion and EMT adhesion. We believe that the reasons for the differential effects of β2-AR signaling may be related to the TME and the expression levels of β2-AR.

4.4. Angiogenesis

As tumors grow unchecked, cells continuously form blood vessels to obtain oxygen and nutrients [233]. Newly formed nerve fibers regulate angiogenesis [234,235], while activation of the sympathetic nervous system is considered a key switch for tumor angiogenesis, primarily achieved by altering the metabolism of endothelial cells. The loss of β2-AR in endothelial cells increases the expression of mitochondrial cytochrome c oxidase assembly factor COA6, elevating the oxidative phosphorylation level of endothelial cells, thereby inhibiting angiogenesis [74]. In addition, various pro-angiogenic factors produced by tumor cells play a crucial role in angiogenesis, with VEGF being particularly important [234]. Activation of β-AR not only upregulates the expression of VEGF but also stimulates tumor cells to increase the synthesis and release of various pro-angiogenic factors, including IL-8, IL-6, and matrix metalloproteinases (MMP)-2 and MMP-9 [236–238]. Furthermore, β-AR signaling can reduce the expression of anti-angiogenic factors. Phosphorylation of PKA inhibits TSP1 production through epigenetic regulation [239] and also phosphorylates GRK3, which inhibits the expression of TSP1 and fibrinolytic plasminogen activator inhibitor 2 (PAI2) [240]. Additionally, it has been confirmed that β3-AR is involved in recruiting circulating stromal cell precursors, maintaining the secretion of pro-inflammatory cytokines, and promoting angiogenesis. Further studies indicate that blocking β3-AR can reduce tumor angiogenesis by inducing apoptosis of endothelial cells [241].

The growth of solid tumors often leads to hypoxia in the microenvironment, stimulating the release of more NE by the sympathetic nervous system, thereby significantly enhancing the angiogenic effect of NE. Hypoxia can also result in the elevation of HIF-α/HIF-β [242,243], activating angiogenesis-related genes, inducing the expression of VEGF, and promoting tumor angiogenesis [244]. In addition, catecholamines, besides inducing tumor cells to secrete pro-angiogenic factors, can also stimulate stromal cells (such as TAM) in the TME to release MMP-9, enhancing the angiogenic capability [245,246]. Catecholamines stimulating α-AR can also induce the proliferation and migration of

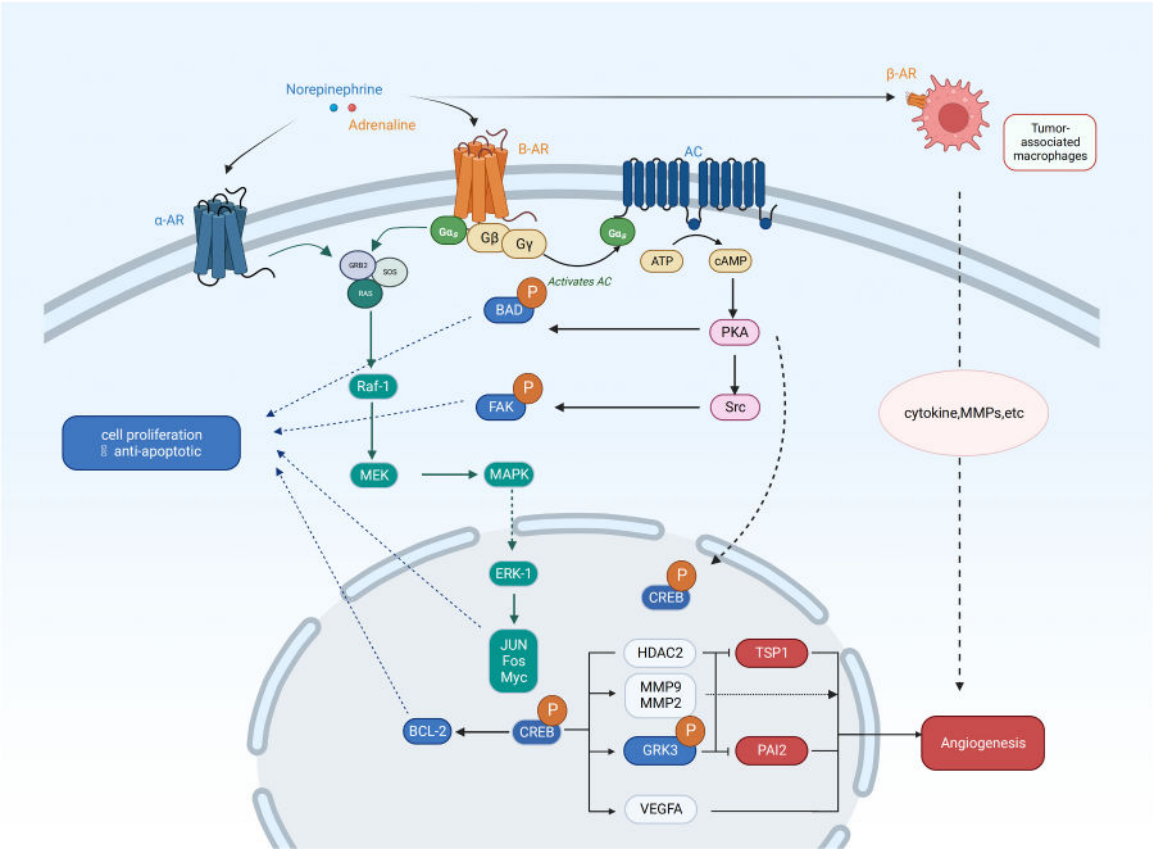

Fig. 5. Adrenergic signaling regulates tumor cell proliferation, apoptosis, and tumor angiogenesis. (1) β-AR signaling activates PKA through cAMP, and PKA enhances the anti-apoptotic ability of tumor cells through the phosphorylation of BAD, Src-FAK, and CREB-Bcl-2 signaling pathways. (2) α1 and β-AR signaling activate the MEK-MAPK-ERK-1 signaling pathway, inducing the transcriptional activation of growth genes (JUN, Fos, Myc) to stimulate cell proliferation. (3) After PKA phosphorylates CREB, the expression levels of MMP2, MMP9, and VEGFA increase, inducing histone deacetylase 2 (HDAC2) to inhibit the production of thrombospondin-1 (TSP1) through epigenetic regulation. PKA phosphorylation of GRK3 inhibits the expression of TSP1 and the fibrinolytic activator inhibitor 2 (PAI2).

endothelial cells and promote the formation of capillaries. The hypoxic environment may further enhance these effects [247,248]. The synergistic action of these factors strengthens tumor angiogenesis and invasive development. Future research will need to delve deeper into the interrelationships among neurotransmitters, growth factors, and hypoxia to better reveal the intricate mechanisms of the regulation network for tumor angiogenesis, providing a more profound understanding of precise intervention in tumor therapy.

4.5. Invasion and metastasis

Tumor invasion and metastasis are among the primary causes of cancer-related deaths [249]. In this complex process, the tumor at the primary site breaks through the basement membrane and invades the circulatory system through local invasion. Tumor cells are transported to distal sites throughout the body to form small, hidden metastases. This series of steps has been described as an "invasive-metastatic cascade "[250,251] and is regulated by the adrenergic system (Fig. 7). In addition to the previously mentioned promotion of distant tumor metastasis by angiogenesis, stress hormones can induce tumor cells to release MMP-2, MMP-7, and MMP-9, promoting cancer cell migration by degrading the extracellular matrix [22,25]. Multiple studies have indicated [252–256] that β-AR signaling can facilitate the pre-migration effects of tumors, while propranolol can block this effect. Stimulation by NE induces endothelial cells to release growth-regulated oncogene α (GROα) and β1-integrin, increasing the adhesive strength of breast cancer cells [257].

In prostate cancer, the activation of β-AR signaling contributes to the formation of bone metastases. Osteoblasts stimulated by isoprenaline increase CXCL12 secretion through the β2-AR-HIF-1α signaling pathway and bind to CXCR4 on the surface of prostate cancer cells, thereby promoting invasion, metastasis and EMT of prostate cancer cells [240]. Furthermore,β-AR signaling promotes lung metastasis of circulating breast cancer cells by upregulating the expression of CCL2 in lung stromal cells and CCR2 in monocytes/macrophages, reshaping the pre-metastatic ecological niche [136]. Adrenergic signaling can also induce the differentiation of macrophages into M2 macrophages, inducing the expression of pro-metastatic molecules and enabling distant metastasis of in situ tumors [17].

Moreover, adrenaline activation of lactate dehydrogenase A (LDHA) produces lactate, adjusting the pH to favor ubiquitination and stabilization of MYC mediated by ubiquitin-specific protease 28 (USP28). Simultaneously, it activates the transcription of SLUG, stimulating breast cancer stem cells and promoting distant breast cancer metastasis [258]. NE induces phosphorylation of L-type voltage-dependent calcium channels (VDCC) via the β-AR-PKA pathway, and VDCC stimulates the cytosolic action of insulin-like growth factor 2 (IGF2), which induces sustained activation of the insulin-like growth factor receptor (IGF-1R), thereby promoting cancer metastasis [259]. Research on the impact of α2A-AR on cervical cancer suggests that its presence can improve patient prognosis by inhibiting the PI3K/Akt/mTOR pathway and suppressing cell proliferation, migration, and invasion [260]. In future studies, a deeper understanding of adrenergic signaling's regulatory mechanisms in the invasion and metastasis processes will contribute to developing more precise and effective cancer therapies.

In summary, chronic stress-induced sustained activation of

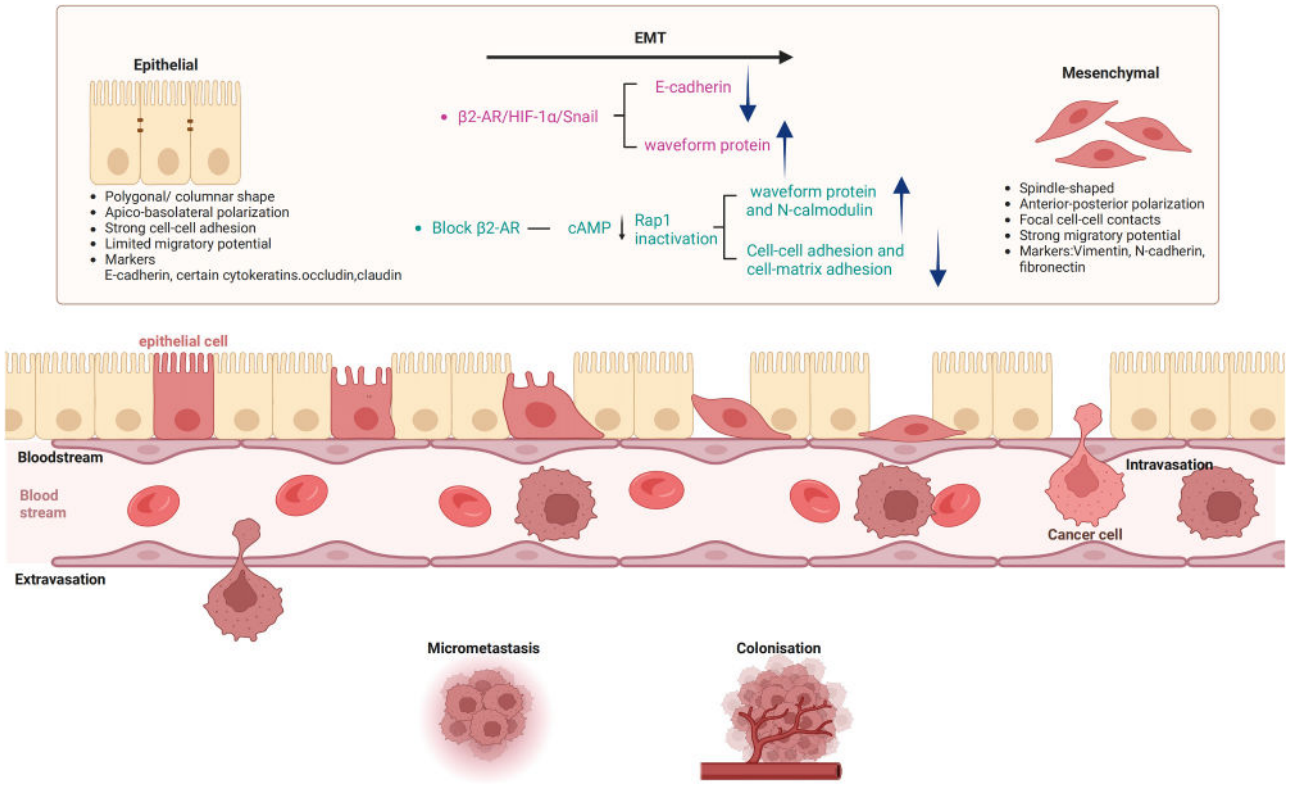

Fig. 6. Adrenergic signaling regulates EMT. (1) Norepinephrine activates the β2-AR-HIF-1α-Snail signaling pathway, reducing the expression of E-cadherin and increasing the expression of vimentin, inducing EMT changes in cancer cells. (2) Silencing of β2-AR decreased intracellular cAMP levels, leading to inactivation of Rap1, inhibition of cell-cell adhesion and cell-matrix adhesion, and increased expression of waveform protein and N-calmodulin.

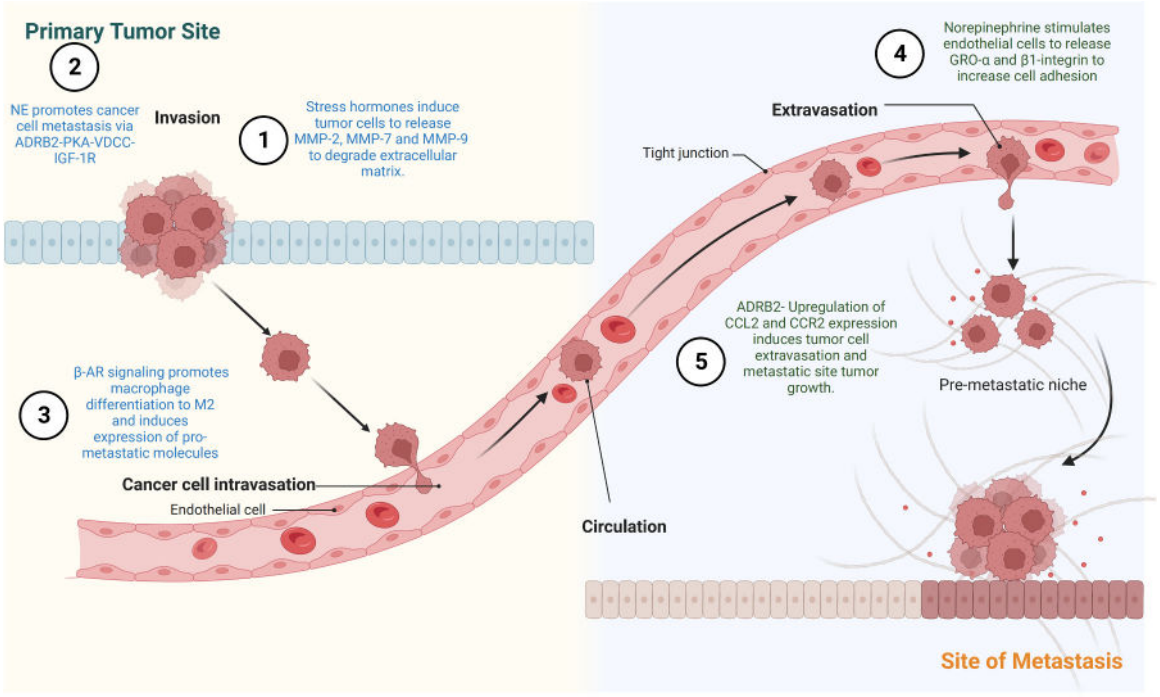

Fig. 7. Adrenergic signaling regulates the invasion and metastasis of tumors: (1) Stress hormones induce the release of MMP-2, MMP-7, and MMP-9 from tumor cells, degrading the extracellular matrix's tight connections; (2) Norepinephrine promotes cancer cell migration through ADRB2-PKA-VDCC-IGF-1R pathway; (3) β-AR signaling induces macrophage differentiation into M2 type and stimulates the expression of pre-metastatic molecules; (4) Norepinephrine stimulates endothelial cells to release GRO-α and β1-integrin, enhancing cell adhesion; (5) ADRB2 upregulates CCL2 and CCR2 expression to induce tumor cell extravasation and metastatic site tumor growth.

adrenergic signaling has multifaceted effects on the biological behavior of tumors. Adrenergic signaling activation involves multiple pathways, including the regulation of DNA damage repair, EMT induction, cell proliferation modulation, and resistance to apoptosis, as well as influencing tumor angiogenesis and promoting invasion and metastasis. In this complex network, tumor cells, stimulated by adrenergic signals, adapt and promote tumor development by activating different signaling pathways.

5. Reversing the application of chronic stress in cancer treatment

A large body of research consistently demonstrates that chronic stress promotes the occurrence and progression of cancer. Therefore, implementing appropriate interventions to reverse chronic stress can enhance the effectiveness of antitumor treatments for cancer patients. Psychosocial interventions in cancer patients include body therapies (such as massage and tai chi), mindfulness, and cognitive-behavioral therapy. These psychosocial interventions impact patients' physiological and psychological states through multiple pathways. Additionally, pharmacological interventions primarily involve AR receptor modulators, especially β-AR blockers and α-AR agonists, which may alleviate stress responses by modulating adrenergic signaling pathways.

5.1. Psychosocial and behavioral management: psychological support and exercise intervention

Various psychological and behavioral interventions are widely employed in cancer patients to alleviate stress, anxiety, and depression and to enhance the effectiveness of antitumor treatment and quality of life [36]. Cognitive-behavioral therapy (CBT), mindfulness-based stress reduction (MBSR), physical exercise, massage, acupuncture, and other methods have all shown significant efficacy in cancer patients [36–38]. These psychological intervention measures positively impact the immune system, including regulating cellular immunity and reducing inflammation levels.

CBT is a psychological therapy that helps patients identify and change negative thinking and behavior patterns to improve emotional and mental health. Randomized controlled trials with breast cancer patients have shown that CBT-based psychological interventions can reduce pain and negative emotions, boost cell immunity, and improve health conditions [261,262]. MBSR can also alleviate cancer-related stress and control pain and mental pressure in metastatic cancer patients [263,264]. Additionally, it can reduce pro-inflammatory gene expression and inflammation signal transmission [265], promote the recovery of lymphocyte subsets [266], and enhance the effectiveness of early palliative care. Furthermore, researchers have found that enriching the living environment of mice can enhance NK cell antitumor immunity through SNS-dependent NKG2D and CCR5 enhancement [267]. Another study reported that an enriched living environment could activate the β-ARs/CCL2 signaling pathway, inhibit TAM and G-MDSCs infiltration, increase the number of $CD8^+$ T cells, protect mice from tumor growth, and overcome resistance based on PD-L1 checkpoint blockade [268]. In addition, a fatigue-reducing diet can improve sleep quality and fatigue symptoms in breast cancer patients [269], while therapies such as massage [270], tai chi [271], and acupuncture [271] can alleviate pain and fatigue, ultimately improving patient prognosis and quality of life.

Moderate physical activity plays an important role in cancer patients, helping to reduce anxiety and depression by modulating neuroendocrine activity and enhancing immune surveillance [272]. Regular exercise has positive effects on the immune system of cancer patients, including increasing the toxicity activity of NK cells [273–276] and reshaping the T cell repertoire [277–281], thereby reducing systemic inflammation [282] and enhancing immune surveillance. After acute exercise, immune cells are stimulated and infiltrate the tumor within hours. Exercise increases NK cell infiltration into tumors by regulating chemokines, activating receptors, and increasing cytotoxic activity [283–285]. Furthermore, exercise training can reduce the infiltration of immune subgroups (such as MDSC [286] and M2-type TAM [287]) in tumors, increase the infiltration and effector function of $CD8^+$ T cells in tumors [288–290], and positively impact dendritic cells by increasing their infiltration into tumors [291]. Acute exercise can expand the specific cytotoxic T cells (CTL) in blood samples, providing the possibility of isolating, expanding, and transferring CTL from healthy donors to cancer patients, which may help reduce the risk of recurrence and become an effective strategy for adoptive T cell therapy for cancer [292]. Compared to other traditional cancer treatment methods, regular exercise can enhance the body's immunity without harmful side effects. By adjusting the activity and composition of immune cells, regular exercise may become a beneficial adjunctive method in the comprehensive treatment of cancer patients [272].

In summary, mind-body interventions as an integrative therapeutic strategy show potential benefits in regulating patients' psychological status, improving quality of life, and enhancing immune function. However, more in-depth future research is needed to clarify when to intervene, who benefits most, and how to do so most effectively.

5.2. AR receptor modulators

AR receptor modulators play a crucial role in cancer treatment, especially in reversing the promoting effect of chronic stress on cancer progression. Current research is mainly focused on β and α receptor modulators.

5.3. β-AR receptor blockers

Extensive studies have shown that non-selective β receptor blocker propranolol has anti-cancer effects on various cancers such as breast cancer, colon cancer, prostate cancer, ovarian cancer, and melanoma. In 2014, the US Food and Drug Administration approved propranolol as a first-line treatment for proliferative infantile hemangioma [293]. Propranolol reduces tumor growth rate by blocking adrenergic signals. As previously discussed, the multiple effects of adrenergic signal regulation on immune cell function suggest that blocking adrenergic signals may restore stress-induced immune suppression.

Propranolol has become the standard treatment for infantile hemangiomas (IH). Its mechanism of action includes inhibiting IH blood vessel dilation, blocking VEGF-mediated blood vessel formation, and increasing cell apoptosis. In vitro studies have also shown that propranolol reverses the relaxation of hemangioma-derived pericytes induced by adrenaline, reduces the proliferation of HemPericytes and HemEC, and reduces the blood vessel volume derived from HemPericyte/HemEC in vivo [294]. In addition, propranolol also inhibits tube formation of human brain endothelial cells and secretion of MMP-9 [295] and inhibits the expression of VEGF and bFGF in hemangioma-derived stem cells [296], indicating its anti-angiogenic effect.

β-AR signaling blockade can remodel the TME. Qiao G et al. were the earliest to reduce adrenergic stress signaling by first using temperature to mimic emergency stimuli in a mouse tumor model and then by using a β-blocker, and the findings of this study reported that mice treated with propranolol blockade showed an increase in the cell frequency of the $CD8^{+T}$ effector phenotype due to an increase in the $CD8^+$T effector $CD8^+$T cell to $CD4^+$Treg (IFNγ+CD8+) ratio increased and PD-1 expression decreased [114]. β2-AR signaling inhibits CD8+ T cell activation through metabolic remodeling [111], and blocking β2-AR signaling increases glycolysis and oxidative phosphorylation in $CD8^+$ TIL [112]. The functional state of T cells correlates with metabolic remodeling, with naïve and memory T cells preferentially passing through oxidative phosphorylation, whereas effector T cells are dependent on glycolysis [297]. Furthermore, it was found that β-receptor

blockers significantly reduced the depletion of T cells expressing immune checkpoint receptors in the TME [112], and increased the recruitment of CD28 expression related to PD-1 on the surface of TIL [114], which is necessary for the reversal of $CD8^+$T cell depletion by PD-1 targeted therapy [298]. In addition to affecting T cells in the TME, blocking β-AR signaling also regulates the generation and immune function of bone marrow MDSCs. Positive emotions reduced the generation of bone marrow MDSCs in a mouse tumor model, reducing the inhibitory effect of MDSCs on T cells [299]. Similar results were also observed in tumor mice treated with β-receptor blockers, which reduced the abundance of MDSC cells in the TME, decreased the ability of MDSCs to suppress T cell proliferation, and increased the expression of Fas receptors and apoptosis levels on the surface of MDSCs [300]. This may be the reason for the increased sensitivity to anti-PD-1 therapy with β2-AR blockade. In addition, studies have shown that β3-AR antagonists can reduce the immunosuppressive cell subpopulations in the TME and increase the immunoreactive cell subpopulations, thereby regulating the immune tolerance of melanoma. β3-AR antagonists increase the number of NK cells and $CD8^+$T cells and adjust the ratio of M1/M2 macrophages and the level of N1 neutrophils. At the same time, β3-AR blockade also eliminates Treg and MDSC subpopulations in the TME [301]. Surprisingly, research has shown that unstressed MMTV-PyMT mice, when administered the non-selective β-adrenergic receptor antagonist nadolol over the long term, experience increased tumor burden, lung metastasis, and spleen MDSC frequency [302]. On the other hand, stress inhibits tumor growth by reducing MDSC frequency in the lungs and spleen and extracellular vesicle TGF-β content [302]. Notably, TGF-β aids cancer cells in evading the immune system and developing resistance to immunotherapy [303]. To counteract the negative regulatory effects of TGF-β, Yi et al. constructed and validated the antitumor activity of the TGF-β/PD-L1 dual-specific antibodies BiTP (for humans) [304] and YM101 (for mice) [305]. Subsequent studies demonstrated an enhancement in the therapeutic efficacy of YM101 [306] using MSA-2 [307] and bivalent manganese, effectively overcoming immunotherapy resistance.

Surgical removal of the primary tumor is the main treatment for cancer patients. However, the stress response caused by surgery can lead to the release of stress hormones, which may be the reason for the increased susceptibility to tumor metastasis after surgery [308,309]. Research has found that surgery reduces the toxicity of natural killer cells and the expression of cell surface Fas ligand and CD11a. Combined blockade therapy of COX-2 and β-AR counteracts these interferences. Multiple studies have confirmed that perioperative COX-2 and β-AR blockade can prevent tumor metastasis and recurrence [124,166,310]. The combination of two drugs (propranolol and etodolac) attenuates the immunosuppression associated with perioperative stress stimuli, e.g., decreases in pro-metastatic/pro-inflammatory transcription factors, decreases in tumor-infiltrating monocytes, increases in tumor-infiltrating B-cells, and enhances the expression of CD11a on circulating natural killer cells, and by doing so, reduces postoperative spontaneous metastasis and improves survival in a variety of tumor models [124,166,310].

The lack of oxygen in the TME can promote the formation of a more aggressive and invasive phenotype [311]. Hypoxia-inducible factor (HIF) mediates the signaling pathways induced by hypoxia, regulating tumor cell growth [312], vascular formation [313], and metabolic reprogramming [314]. Studies have shown that propranolol can downregulate the expression of hypoxia-induced HIF-1α and HIF-2α, reducing the expression of HIF target genes in vascular endothelial cells, including VEGF, erythropoietin (EPO), and SRY homology box2 (Sox2), thereby inhibiting cell proliferation and inducing apoptosis [315]. In addition, β2-AR signaling negatively regulates autophagy, stabilizes HIF-1α, and promotes the proliferation and survival of hepatocellular carcinoma cells, while ICI118,551 (a β2-AR antagonist) can reverse this process [316]. Propranolol also induces the regression of vascular tumor cells by regulating the HIF1α-VEGF-A signaling pathway to downregulate the activity of PI3-Akt and p38 MAPK [315,317]. Recently, Barathova M and others studied the role of propranolol in the hypoxic TME [318,319], finding that it not only reduces the expression levels of carbonic anhydrase IX (CA IX) and HIF1α but also affects the activity of CA IX by lowering the activity of PKA and CA IX, thereby inhibiting the proliferation and migration of tumor cells in a 3D sphere model. Therefore, blocking β-AR may reduce the ability of tumor cells to adapt to hypoxic stress. These findings provide a theoretical basis for further research into treatment strategies for hypoxic conditions in the TME.

5.4. α-AR receptor modulators

α1-AR antagonists are widely used to treat patients with benign prostatic hyperplasia (BPH), and it was later discovered that they have an anti-proliferative effect on prostate cancer (PCa). It has been reported that the incidence of PCa in BPH patients treated with α1-AR antagonists is significantly lower and related to the cumulative duration of α1-AR antagonist use [320,321]. Some studies have found that tamsulosin (α1-AR antagonist) inhibits the growth of prostate cancer by promoting apoptosis of stromal cells and epithelial cells, leading to G1 cell cycle arrest in PCa cells [296,322]. It can also induce apoptosis in cancer cell lines such as HeLa, LNCaP, and HGC27 [323,324]. Tamsulosin can also induce apoptosis of mesothelioma cells by activating caspase-3 and −8 through α1-AR-Gq/11-PKC, increasing TNF-α expression and Fas-Ligand secretion [325]. In addition, in a xenograft mouse colorectal cancer model, HUHS1015 (a tamsulosin analog) induces cell apoptosis through mitochondrial damage and activation of caspase-3 and −9, inhibiting colon cancer growth [326]. Interestingly, some studies suggest that tamsulosin's anti-cancer effects seem unrelated to its α1-AR antagonist properties [325,327,328].

Previous studies have shown that α2-AR agonists promote cancer progression. Activating the α2-AR signaling pathway promotes breast cancer tumor growth and metastasis, in contrast to the antagonism of α2-AR signaling, reversing this promotion [329]. Stress conditions seem necessary in determining the effectiveness of α2-AR antagonist therapy. Under non-stress conditions, blocking α2-AR can increase the size and distant spread of primary breast cancer [330]. This may be related to the increase in catecholamines caused by α2-AR blockade and the increase in β-AR signaling. Propranolol inhibits the effects of blocking. Therefore, can it be considered that α2-AR agonists can inhibit cancer progression by inhibiting the sympathetic nervous system to reduce β-AR signaling? Previous studies have shown that disrupting α-AR signaling leads to the accumulation of MDSC in tumors, inhibiting tumor immunity and promoting tumor growth [34]. Recent studies suggest that α2-AR activation triggers tumor immune rejection, and α2-AR agonists (clonidine) increase the tumor infiltration of $CD4^+$ and $CD8^+$ T cells and in secondary lymphoid organs (lymph nodes and spleen). TME tumor-associated macrophage infiltration increases, MHC II expression increases, and phagocytic ability increases. When liposomes depleted macrophages in tumor-bearing mice, the antitumor effect of clonidine decreased, and TIL did not increase. The results indicate that macrophages mediate the recruitment and activation of $CD4^+$ and $CD8^+$ T lymphocytes in the TME [35]. However, studies have shown that α2-AR agonists have two extremes in their effects on cancer. Some studies suggest that α2-AR agonists can increase the proliferation of tumor cells [331], while others suggest the opposite [332,333]. The differential effects of α2-AR agonists on cancer may be related to drug dosage, which requires further research to elucidate the specific mechanisms underlying the differences.

Based on the potential shown by AR modulators in cancer treatment, researchers have begun to explore using AR modulators in combination therapy to enhance cancer treatment. We conducted a retrospective summary in Table 1. Overall, adrenergic receptor modulators demonstrate diverse mechanisms of action in cancer treatment, including influencing tumor immune response, inhibiting angiogenesis, regulating

Table 1
Studies related to combination therapy with adrenergic receptor modulators.

Cancer type	Combination drug	Mechanism of action	Research
osteosarcoma	Propranolol and cisplatin	Blocking cell cycle progression and altering actin cytoskeleton dynamics	[26]
soft tissue sarcoma	Propranolol and anti-CTLA4	Increasing the number of tumor-infiltrating T cells to reduce tumor angiogenesis, decreasing intra-tumor MDSC	[27]
Colorectal and triple-negative breast cancer	Propranolol and chloroquine	Reduces cell viability and enhances apoptosis	[334]
colorectal cancer	Propranolol and irinotecan	Reduced depletion of tumor-infiltrating T cells	[335]
colon cancer	Propranolol and etodolac	Increased Marginal Hepatitis (MH)-NK Cytotoxicity Against CT26 Tumor Lineage	[310]
Colorectal cancer, stomach cancer	Propranolol and herpes lysodexviruses	Enhancement of apoptosis and inhibition of angiogenesis in colorectal cancer cells. Enhancement of transmission of lysosomal herpesvirus in gastric cancer.	[336, 337]
colon cancer	Propranolol and ionizing radiation therapy	Increased metabolic activity during $CD8^+$ T cell activation, decreased frequency of immunosuppressive M2 macrophages in tumors	[338]
colorectal cancer	Propranolol and 5-fluorouracil	Inhibition of HIF1α, carbonic anhydrase IX Disruption of hypoxic adaptation mechanisms, activation of apoptosis	[319]
cervix	Propranolol and trabectedin	Enhancement of apoptosis in cervical cancer cells	[339]
multiple myeloma	Propranolol and melphalan or/and bortezomib	Reduces mitochondrial respiration and glycolytic activity in tumor cells and induces apoptosis and autophagy	[340]
pancreatic	Colistin and PD-L1/CTLA4	Induction of apoptosis in pancreatic cancer cells	[219]
colon cancer	Colistin and PD-L1/CTLA4	Upregulation of macrophage and T cell innate and adaptive immune response pathways	[35]

cell apoptosis, and affecting the biological behavior of tumor cells. This provides new ideas and strategies for future cancer treatment. However, further in-depth research is needed to verify its therapeutic effects and potential mechanisms.

6. Conclusion

Current research has provided insight into the mechanisms by which chronic stress contributes to cancer development. Chronic stress induces sustained activation of the HPA axis and SNS, leading to overproduction of NE and EPI and activation of α- and β-adrenergic receptor signaling. This altered adrenergic signaling remodels the TME, leading to a decrease in the number and function of immune cells, an increase in immunosuppressive cells (e.g., MDSC and TAM), and an enhanced immunosuppressive effect. In contrast, α2-adrenergic receptor signaling stimulates antitumor immunity, reduces MDSC infiltration, and promotes macrophage recruitment and activation of antitumor T-cells, resulting in an enhanced antitumor immune response.

Based on the understanding of the adverse effects of chronic stress on tumors, researchers have begun to focus on reducing the pro-cancer effects of chronic stress by modulating adrenergic signaling and exploring the therapeutic effects of combining it with cancer therapies, such as chemotherapy, immunotherapy, and targeted therapies. Several studies have shown that adrenergic receptor modulators show great potential in the combination therapy of cancer. By using β2-adrenergic receptor antagonists or α2-adrenergic receptor agonists, the therapeutic effect of immune checkpoint inhibitors (ICIs) can be improved by increasing the number of $CD8^+$ T cells in the TME and transforming "cold" tumors that are unresponsive or weakly responsive to immune response into "hot" tumors that respond well to immunotherapy.

The researchers also explored the effectiveness of mind-body behavior management in combination with other anticancer therapies. Mind-body behavior management includes CBT, MBSR, and physical exercise, which have shown significant effects in relieving psychological stress and improving the quality of survival in cancer patients. In particular, the positive effects of mind-body behavior management on the immune system have been affirmed, including modulation of cellular immunity and reduction of inflammation levels. These interventions not only improve patients' emotional and mental health through psychotherapeutic approaches but also play a positive role at the level of the immune system and are expected to be an important part of a comprehensive treatment strategy.

However, there are still some shortcomings in the study of chronic stress-promoting mechanisms of cancer. Inconsistency in assessing stress levels in animal models [341] and marked differences in the dosage of AR modulators may lead to discrepancies in study results. Most studies have focused only on the effect of signaling pathways on the overall tumor without insight into the individual differences of immune cells in TME, so there is a need to gain insight into the characterization of immune cells in TME by techniques such as single-cell sequencing. In addition, the drug repurposing of AR modulators is mainly focused on animal models, and the design of preclinical studies is flawed, with studies focusing on clinical relevance and more limited exploration of detailed therapeutic mechanisms. Although the safety of AR modulators has been demonstrated in preclinical models and clinical applications, the safety of AR modulators as combination therapeutic agents needs to be reassessed. Therefore, research on chronic stress-cancer interactions still needs to be explored and validated in greater depth.

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CRediT authorship contribution statement

Yan Cao: Writing – original draft, Conceptualization. **Jingzhi Guan:** Writing – review & editing, Supervision, Conceptualization. **Hao Zhang:** Writing – original draft, Conceptualization. **Yuwei Yang:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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References

[1] A. Mehnert, E. Brähler, H. Faller, M. Härter, M. Keller, H. Schulz, K. Wegscheider, J. Weis, A. Boehncke, B. Hund, K. Reuter, M. Richard, S. Sehner, S. Sommerfeldt, C. Szalai, H.-U. Wittchen, U. Koch, Four-week prevalence of mental disorders in patients with cancer across major tumor entities, J. Clin. Oncol. 32 (2014) 3540–3546, https://doi.org/10.1200/JCO.2014.56.0086.

[2] O. Krizanova, P. Babula, K. Pacak, Stress, catecholaminergic system and cancer, Stress 19 (2016) 419–428, https://doi.org/10.1080/10253890.2016.1203415.

[3] J.P. Herman, J.M. McKlveen, S. Ghosal, B. Kopp, A. Wulsin, R. Makinson, J. Scheimann, B. Myers, Regulation of the hypothalamic-pituitary-adrenocortical stress response, Compr. Physiol. 6 (2016) 603–621, https://doi.org/10.1002/cphy.c150015.

[4] D.S. Goldstein, Catecholamines 101, Clin. Auton. Res 20 (2010) 331–352, https://doi.org/10.1007/s10286-010-0065-7.

[5] L.J. Van Tits, M.C. Michel, H. Grosse-Wilde, M. Happel, F.W. Eigler, A. Soliman, O.E. Brodde, Catecholamines increase lymphocyte beta 2-adrenergic receptors via a beta 2-adrenergic, spleen-dependent process, Am. J. Physiol. 258 (1990) E191–E202, https://doi.org/10.1152/ajpendo.1990.258.1.E191.

[6] M. Schedlowski, W. Hosch, R. Oberbeck, R.J. Benschop, R. Jacobs, H.R. Raab, R. E. Schmidt, Catecholamines modulate human NK cell circulation and function via spleen-independent beta 2-adrenergic mechanisms, J. Immunol. 156 (1996) 93–99.

[7] C.J. Padro, V.M. Sanders, Neuroendocrine regulation of inflammation, Semin Immunol. 26 (2014) 357–368, https://doi.org/10.1016/j.smim.2014.01.003.

[8] A. Scanzano, L. Schembri, E. Rasini, A. Luini, J. Dallatorre, M. Legnaro, R. Bombelli, T. Congiu, M. Cosentino, F. Marino, Adrenergic modulation of migration, CD11b and CD18 expression, ROS and interleukin-8 production by human polymorphonuclear leukocytes, Inflamm. Res 64 (2015) 127–135, https://doi.org/10.1007/s00011-014-0791-8.

[9] Y. Chen, Y. Qian, W. Huang, Y. Zhang, M. Wu, Y. Cheng, N. Yang, Y. Liu, Chronic stress promotes tumor immune evasion via the suppression of MHC-I expression and the upregulation of PD-L1, Am. J. Cancer Res 12 (2022) 5286–5299.

[10] D.M. Nance, V.M. Sanders, Autonomic innervation and regulation of the immune system (1987-2007), Brain Behav. Immun. 21 (2007) 736–745, https://doi.org/10.1016/j.bbi.2007.03.008.

[11] D. Sharma, J.D. Farrar, Adrenergic regulation of immune cell function and inflammation, Semin. Immunopathol. 42 (2020) 709–717, https://doi.org/10.1007/s00281-020-00829-6.

[12] C. Liu, Y. Yang, C. Chen, L. Li, J. Li, X. Wang, Q. Chu, L. Qiu, Q. Ba, X. Li, H. Wang, Environmental eustress modulates β-ARs/CCL2 axis to induce anti-tumor immunity and sensitize immunotherapy against liver cancer in mice, Nat. Commun. 12 (2021) 5725, https://doi.org/10.1038/s41467-021-25967-9.

[13] L.A. Grisanti, D.M. Perez, J.E. Porter, Modulation of immune cell function by α1-adrenergic receptor activation, Curr. Top. Membr. 67 (2011) 113–138, https://doi.org/10.1016/B978-0-12-384921-2.00006-9.

[14] D. Lorton, D.L. Bellinger, Molecular mechanisms underlying β-adrenergic receptor-mediated cross-talk between sympathetic neurons and immune cells, Int. J. Mol. Sci. 16 (2015), https://doi.org/10.3390/ijms16035635.

[15] R. Melamed, E. Rosenne, K. Shakhar, Y. Schwartz, N. Abudarham, S. Ben-Eliyahu, Marginating pulmonary-NK activity and resistance to experimental tumor metastasis: suppression by surgery and the prophylactic use of a beta-adrenergic antagonist and a prostaglandin synthesis inhibitor, Brain Behav. Immun. 19 (2005) 114–126, https://doi.org/10.1016/j.bbi.2004.07.004.

[16] S. Ben-Eliyahu, G. Shakhar, G.G. Page, V. Stefanski, K. Shakhar, Suppression of NK cell activity and of resistance to metastasis by stress: a role for adrenal catecholamines and beta-adrenoceptors, Neuroimmunomodulation 8 (2000) 154–164, https://doi.org/10.1159/000054276.

[17] E.K. Sloan, S.J. Priceman, B.F. Cox, S. Yu, M.A. Pimentel, V. Tangkanangnukul, J. M.G. Arevalo, K. Morizono, B.D.W. Karanikolas, L. Wu, A.K. Sood, S.W. Cole, The sympathetic nervous system induces a metastatic switch in primary breast cancer, Cancer Res. 70 (2010) 7042–7052, https://doi.org/10.1158/0008-5472.CAN-10-0522.

[18] H. Mohammadpour, C.R. MacDonald, P.L. McCarthy, S.I. Abrams, E.A. Repasky, β2-adrenergic receptor signaling regulates metabolic pathways critical to myeloid-derived suppressor cell function within the TME, Cell Rep. 37 (2021), https://doi.org/10.1016/j.celrep.2021.109883.

[19] A. Nakai, Y. Hayano, F. Furuta, M. Noda, K. Suzuki, Control of lymphocyte egress from lymph nodes through β2-adrenergic receptors, J. Exp. Med. 211 (2014) 2583–2598, https://doi.org/10.1084/jem.20141132.

[20] J.W. Eng, K.M. Kokolus, C.B. Reed, B.L. Hylander, W.W. Ma, E.A. Repasky, A nervous tumor microenvironment: the impact of adrenergic stress on cancer cells, immunosuppression, and immunotherapeutic response, Cancer Immunol Immunother 63 (2014), https://doi.org/10.1007/s00262-014-1617-9.

[21] M. Coelho, C. Soares-Silva, D. Brandão, F. Marino, M. Cosentino, L. Ribeiro, β-Adrenergic modulation of cancer cell proliferation: available evidence and clinical perspectives, J. Cancer Res. Clin. Oncol. 143 (2017) 275–291, https://doi.org/10.1007/s00432-016-2278-1.

[22] P.H. Thaker, L.Y. Han, A.A. Kamat, J.M. Arevalo, R. Takahashi, C. Lu, N. B. Jennings, G. Armaiz-Pena, J.A. Bankson, M. Ravoori, W.M. Merritt, Y.G. Lin, L. S. Mangala, T.J. Kim, R.L. Coleman, C.N. Landen, Y. Li, E. Felix, A.M. Sanguino, R.A. Newman, M. Lloyd, D.M. Gershenson, V. Kundra, G. Lopez-Berestein, S. K. Lutgendorf, S.W. Cole, A.K. Sood, Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma, Nat. Med. 12 (2006) 939–944, https://doi.org/10.1038/nm1447.

[23] B.M.R. Vilardi, D.M. Bravo-Calderón, D.G. Bernabé, S.H.P. Oliveira, D.T. Oliveira, VEGF-C expression in oral cancer by neurotransmitter-induced activation of beta-adrenergic receptors, Tumor Biol. 34 (2013) 139–143, https://doi.org/10.1007/s13277-012-0521-1.

[24] J.-W. Lee, M.M.K. Shahzad, Y.G. Lin, G. Armaiz-Pena, L.S. Mangala, H.-D. Han, H.-S. Kim, E.J. Nam, N.B. Jennings, J. Halder, A.M. Nick, R.L. Stone, C. Lu, S. K. Lutgendorf, S.W. Cole, A.E. Lokshin, A.K. Sood, Surgical stress promotes tumor growth in ovarian carcinoma, Clin. Cancer Res. 15 (2009) 2695–2702, https://doi.org/10.1158/1078-0432.CCR-08-2966.

[25] E.V. Yang, A.K. Sood, M. Chen, Y. Li, T.D. Eubank, C.B. Marsh, S. Jewell, N. A. Flavahan, C. Morrison, P.-E. Yeh, S. Lemeshow, R. Glaser, Norepinephrine up-regulates the expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in nasopharyngeal carcinoma tumor cells, Cancer Res. 66 (2006) 10357–10364, https://doi.org/10.1158/0008-5472.CAN-06-2496.

[26] L.M. Solernó, N.T. Sobol, M.F. Gottardo, C.S. Capobianco, M.R. Ferrero, L. Vásquez, D.F. Alonso, J. Garona, Propranolol blocks osteosarcoma cell cycle progression, inhibits angiogenesis and slows xenograft growth in combination with cisplatin-based chemotherapy, Sci. Rep. 12 (2022) 15058, https://doi.org/10.1038/s41598-022-18324-3.

[27] K.Y. Fjæstad, A.M.A. Rømer, V. Goitea, A.Z. Johansen, M.-L. Thorseth, M. Carretta, L.H. Engelholm, L. Grøntved, N. Junker, D.H. Madsen, Blockade of beta-adrenergic receptors reduces cancer growth and enhances the response to anti-CTLA4 therapy by modulating the tumor microenvironment, Oncogene 41 (2022) 1364–1375, https://doi.org/10.1038/s41388-021-02170-0.

[28] J.P. Hieble, W.E. Bondinell, R.R. Ruffolo, Alpha- and beta-adrenoceptors: from the gene to the clinic. 1. Molecular biology and adrenoceptor subclassification, J. Med. Chem. 38 (1995) 3415–3444, https://doi.org/10.1021/jm00018a001.

[29] S. Gandhi, M.R. Pandey, K.M. Attwood, W. Ji, A. Witkiewicz, E.S. Knudsen, C. Allen, J. Tario, P. Wallace, C. Cedeno, M. Levis, S. Stack, P. Funchain, J. Drabick, M. Bucsek, I. Puzanov, H. Mohammadpour, E.A. Repasky, M. S. Ernstoff, Phase I clinical trial of combination propranolol and pembrolizumab in locally advanced and metastatic melanoma: Safety, Tolerability, and Preliminary Evidence of Antitumor Activity, Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 27 (2021) 87, https://doi.org/10.1158/1078-0432.CCR-20-2381.

[30] P. Liao, K. Song, Z. Zhu, Z. Liu, W. Zhang, W. Li, J. Hu, Q. Hu, C. Chen, B. Chen, H.L. McLeod, H. Pei, L. Chen, Y. He, Propranolol Suppresses the Growth of Colorectal Cancer Through Simultaneously Activating Autologous CD8+ T Cells and Inhibiting Tumor AKT/MAPK Pathway, Clin. Pharmacol. Ther. 108 (2020), https://doi.org/10.1002/cpt.1894.

[31] W. Li, J. Wan, C. Chen, C. Zhou, P. Liao, Q. Hu, J. Hu, Y. Wang, Y. Zhang, C. Peng, Y. Huang, W. Huang, W. Zhang, H.L. Mcleod, Y. He, Dissecting the role of cell signaling versus CD8+ T cell modulation in propranolol antitumor activity, J. Mol. Med. (Berl.) 100 (2022) 1299–1306, https://doi.org/10.1007/s00109-022-02238-8.

[32] E. Pasquier, J. Ciccolini, M. Carre, S. Giacometti, R. Fanciullino, C. Pouchy, M.-P. Montero, C. Serdjebi, M. Kavallaris, N. André, Propranolol potentiates the anti-angiogenic effects and anti-tumor efficacy of chemotherapy agents: implication in breast cancer treatment, Oncotarget 2 (2011) 797–809.

[33] L.J. Wrobel, L. Bod, R. Lengagne, M. Kato, A. Prévost-Blondel, F.-A.L. Gal, Propranolol induces a favourable shift of anti-tumor immunity in a murine spontaneous model of melanoma, Oncotarget 7 (2016) 77825, https://doi.org/10.18632/oncotarget.12833.

[34] J.T. Nevin, M. Moussa, W.L. Corwin, I.I. Mandoiu, P.K. Srivastava, Sympathetic nervous tone limits the development of myeloid-derived suppressor cells, Sci. Immunol. 5 (2020) eaay9368, https://doi.org/10.1126/sciimmunol.aay9368.

[35] J. Zhu, S. Naulaerts, L. Boudhan, M. Martin, L. Gatto, B.J. Van den Eynde, Tumour immune rejection triggered by activation of α2-adrenergic receptors, Nature 618 (2023) 607–615, https://doi.org/10.1038/s41586-023-06110-8.

[36] M.H. Antoni, F.S. Dhabhar, Impact of psychosocial stress and stress management on immune responses in cancer patients, Cancer 125 (2019) 1417–1431, https://doi.org/10.1002/cncr.31943.

[37] A. Eckerling, I. Ricon-Becker, L. Sorski, E. Sandbank, S. Ben-Eliyahu, Stress and cancer: mechanisms, significance and future directions, Nat. Rev. Cancer 21 (2021) 767–785, https://doi.org/10.1038/s41568-021-00395-5.

[38] C. Fiuza-Luces, P.L. Valenzuela, B.G. Gálvez, M. Ramírez, A. López-Soto, R. J. Simpson, A. Lucia, The effect of physical exercise on anticancer immunity, Nat. Rev. Immunol. (2023), https://doi.org/10.1038/s41577-023-00943-0.

[39] H. Haykin, A. Rolls, The neuroimmune response during stress: a physiological perspective, Immunity 54 (2021) 1933–1947, https://doi.org/10.1016/j.immuni.2021.08.023.

[40] N. Schneiderman, G. Ironson, S.D. Siegel, Stress and health: psychological, behavioral, and biological determinants, Annu. Rev. Clin. Psychol. 1 (2005) 607–628, https://doi.org/10.1146/annurev.clinpsy.1.102803.144141.

[41] F.S. Dhabhar, B.S. McEwen, Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: a potential role for leukocyte trafficking, Brain Behav. Immun. 11 (1997) 286–306, https://doi.org/10.1006/brbi.1997.0508.

[42] F.S. Dhabhar, A.H. Miller, M. Stein, B.S. McEwen, R.L. Spencer, Diurnal and acute stress-induced changes in distribution of peripheral blood leukocyte

subpopulations, Brain Behav. Immun. 8 (1994) 66–79, https://doi.org/10.1006/brbi.1994.1006.
[43] F.S. Dhabhar, Effects of stress on immune function: the good, the bad, and the beautiful, Immunol. Res. 58 (2014) 193–210, https://doi.org/10.1007/s12026-014-8517-0.
[44] F.S. Dhabhar, A.H. Miller, B.S. McEwen, R.L. Spencer, Effects of stress on immune cell distribution. Dynamics and hormonal mechanisms, J. Immunol. 154 (1995) 5511–5527.
[45] N. Schneiderman, G. Ironson, S.D. Siegel, Stress and health: psychological, behavioral, and biological determinants, Annu Rev. Clin. Psychol. 1 (2005) 607–628, https://doi.org/10.1146/annurev.clinpsy.1.102803.144141.
[46] P. Xu, H. He, Y. Gu, Y. Wang, Z. Sun, L. Yang, C. Miao, Surgical trauma contributes to progression of colon cancer by downregulating CXCL4 and recruiting MDSCs, Exp. Cell Res. 16 (2015), https://doi.org/10.1016/j.yexcr.2018.07.035.
[47] E. Rosenne, L. Sorski, L. Shaashua, E. Neeman, P. Matzner, B. Levi, S. Ben-Eliyahu, In vivo suppression of NK cell cytotoxicity by stress and surgery: glucocorticoids have a minor role compared to catecholamines and prostaglandins, Brain Behav. Immun. 37 (2014), https://doi.org/10.1016/j.bbi.2013.12.007.
[48] S. Inbar, E. Neeman, R. Avraham, M. Benish, E. Rosenne, S. Ben-Eliyahu, Do stress responses promote leukemia progression? An animal study suggesting a role for epinephrine and prostaglandin-E2 through reduced NK activity, PLoS One 6 (2011), https://doi.org/10.1371/journal.pone.0019246.
[49] S. Ben-Eliyahu, G. Shakhar, G.G. Page, V. Stefanski, K. Shakhar, Suppression of NK cell activity and of resistance to metastasis by stress: a role for adrenal catecholamines and beta-adrenoceptors, Neuroimmunomodulation 8 (3) (2000) 154–164, https://doi.org/10.1159/000054276.
[50] E. Rosenne, G. Shakhar, R. Melamed, Y. Schwartz, A. Erdreich-Epstein, S. Ben-Eliyahu, Inducing a mode of NK-resistance to suppression by stress and surgery: a potential approach based on low dose of poly I-C to reduce postoperative cancer metastasis, Brain Behav. Immun. 21 (2007), https://doi.org/10.1016/j.bbi.2006.12.002.
[51] F.S. Dhabhar, A.N. Saul, C. Daugherty, T.H. Holmes, D.M. Bouley, T. M. Oberyszyn, Short-term stress enhances cellular immunity and increases early resistance to squamous cell carcinoma,Brain Behav, Immun 24 (2010), https://doi.org/10.1016/j.bbi.2009.09.004.
[52] N. Benaroya-Milshtein, N. Hollander, A. Apter, I. Yaniv, C.G. Pick, Stress conditioning in mice: alterations in immunity and tumor growth, Stress 14 (2011), https://doi.org/10.3109/10253890.2010.545845.
[53] M.H. Antoni, S.K. Lutgendorf, S.W. Cole, F.S. Dhabhar, S.E. Sephton, P. G. McDonald, M. Stefanek, A.K. Sood, The influence of bio-behavioural factors on tumour biology: pathways and mechanisms, Nat. Rev. Cancer 6 (2006) 240–248, https://doi.org/10.1038/nrc1820.
[54] A. Agorastos, G.P. Chrousos, The neuroendocrinology of stress: the stress-related continuum of chronic disease development, Mol. Psychiatry 27 (2022) 502–513, https://doi.org/10.1038/s41380-021-01224-9.
[55] K.L. Chan, W.C. Poller, F.K. Swirski, S.J. Russo, Central regulation of stress-evoked peripheral immune responses, Nat. Rev. Neurosci. 24 (2023) 591–604, https://doi.org/10.1038/s41583-023-00729-2.
[56] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, CA: A Cancer J. Clin. 71 (2021) 209–249, https://doi.org/10.3322/caac.21660.
[57] S. Gao, Z. Sha, J. Zhou, Y. Wu, Y. Song, C. Li, X. Liu, T. Zhang, R. Yu, BYSL contributes to tumor growth by cooperating with the mTORC2 complex in gliomas, Cancer Biol. Med. 18 (2021) 88–104, https://doi.org/10.20892/j.issn.2095-3941.2020.0096.
[58] O. Forkosh, S. Karamihalev, S. Roeh, U. Alon, S. Anpilov, C. Touma, M. Nussbaumer, C. Flachskamm, P.M. Kaplick, Y. Shemesh, A. Chen, Identity domains capture individual differences from across the behavioral repertoire, Nat. Neurosci. 22 (2019) 2023–2028, https://doi.org/10.1038/s41593-019-0516-y.
[59] S. Kreitler, D. Peleg, M. Ehrenfeld, Stress, self-efficacy and quality of life in cancer patients, Psychooncology 16 (2007) 329–341, https://doi.org/10.1002/pon.1063.
[60] S. Galić, Ž. Glavić, M. Cesarik, Stress and quality of life in patients with gastrointestinal cancer, Acta Clin. Croat. 53 (2014) 279–290.
[61] N. Nikbakhsh, S. Moudi, S. Abbasian, S. Khafri, Prevalence of depression and anxiety among cancer patients, Casp. J. Intern Med 5 (2014) 167–170.
[62] D.-H. Kang, N.-J. Park, T. McArdle, Cancer-specific stress and mood disturbance: implications for symptom perception, quality of life, and immune response in women shortly after diagnosis of breast cancer, ISRN Nurs. 2012 (2012) 608039, https://doi.org/10.5402/2012/608039.
[63] F. Gil, G. Costa, I. Hilker, L. Benito, First anxiety, afterwards depression: psychological distress in cancer patients at diagnosis and after medical treatment, Stress Health 28 (2012) 362–367, https://doi.org/10.1002/smi.2445.
[64] D.Y.M. El Kheir, A.H.M. Ibrahim, Epidemiological assessment of distress during chemotherapy: who is affected? J. Taibah Univ. Med Sci. 14 (2019) 448–453, https://doi.org/10.1016/j.jtumed.2019.08.004.
[65] Z. Chen, P. Zhang, Y. Xu, J. Yan, Z. Liu, W.B. Lau, B. Lau, Y. Li, X. Zhao, Y. Wei, S. Zhou, Surgical stress and cancer progression: the twisted tango, Mol. Cancer 18 (2019) 132, https://doi.org/10.1186/s12943-019-1058-3.
[66] M.H.J. van den Beuken-van Everdingen, J.M. de Rijke, A.G. Kessels, H. C. Schouten, M. van Kleef, J. Patijn, Prevalence of pain in patients with cancer: a systematic review of the past 40 years, Ann. Oncol. 18 (2007) 1437–1449, https://doi.org/10.1093/annonc/mdm056.
[67] W. Breitbart, B. Rosenfeld, H. Pessin, M. Kaim, J. Funesti-Esch, M. Galietta, C. J. Nelson, R. Brescia, Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer, JAMA 284 (2000) 2907–2911, https://doi.org/10.1001/jama.284.22.2907.
[68] S. Lebel, G. Ozakinci, G. Humphris, B. Mutsaers, B. Thewes, J. Prins, A. Dinkel, P. Butow, University of Ottawa Fear of Cancer Recurrence Colloquium attendees, From normal response to clinical problem: definition and clinical features of fear of cancer recurrence, Support Care Cancer 24 (2016) 3265–3268, https://doi.org/10.1007/s00520-016-3272-5.
[69] R. Gordan, J.K. Gwathmey, L.-H. Xie, Autonomic and endocrine control of cardiovascular function, World J. Cardiol. 7 (2015) 204–214, https://doi.org/10.4330/wjc.v7.i4.204.
[70] A.M.A. Berends, G. Eisenhofer, L. Fishbein, A.N.A. van der Horst-Schrivers, I. P. Kema, T.P. Links, J.W.M. Lenders, M.N. Kerstens, Intricacies of the molecular machinery of catecholamine biosynthesis and secretion by chromaffin cells of the normal adrenal medulla and in pheochromocytoma and paraganglioma, Cancers 11 (2019) 1121, https://doi.org/10.3390/cancers11081121.
[71] J.P. Herman, J.M. McKlveen, S. Ghosal, B. Kopp, A. Wulsin, R. Makinson, J. Scheimann, B. Myers, Regulation of the hypothalamic-pituitary-adrenocortical stress response, Compr. Physiol. 6 (2016) 603, https://doi.org/10.1002/cphy.c150015.
[72] S.M. Smith, W.W. Vale, The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress, Dialog-. Clin. Neurosci. 8 (2006) 383, https://doi.org/10.31887/DCNS.2006.8.4/ssmith.
[73] A.H. Zahalka, P.S. Frenette, Nerves in cancer, Nat. Rev. Cancer 20 (2020) 143–157, https://doi.org/10.1038/s41568-019-0237-2.
[74] A.H. Zahalka, A. Arnal-Estapé, M. Maryanovich, F. Nakahara, C.D. Cruz, L.W. S. Finley, P.S. Frenette, Adrenergic nerves activate an angio-metabolic switch in prostate cancer, Science 358 (2017) 321–326, https://doi.org/10.1126/science.aah5072.
[75] Y. Wu, L. Zeng, S. Zhao, Ligands of adrenergic receptors: a structural point of view, Biomolecules 11 (2021) 936, https://doi.org/10.3390/biom11070936.
[76] W.I. Weis, B.K. Kobilka, The molecular basis of g protein–coupled receptor activation, Annu. Rev. Biochem. 87 (2018) 897–919, https://doi.org/10.1146/annurev-biochem-060614-033910.
[77] T.D. O'Connell, B.C. Jensen, A.J. Baker, P.C. Simpson, Cardiac alpha1-adrenergic receptors: novel aspects of expression, signaling mechanisms, physiologic function, and clinical importance, Pharmacol. Rev. 66 (2014) 308–333, https://doi.org/10.1124/pr.112.007203.
[78] A. Scanzano, M. Cosentino, Adrenergic regulation of innate immunity: a review, Front. Pharmacol. 6 (2015), https://doi.org/10.3389/fphar.2015.00171.
[79] M. Johnson, Molecular mechanisms of beta(2)-adrenergic receptor function, response, and regulation, quiz 25, J. Allergy Clin. Immunol. 117 (2006) 18–24, https://doi.org/10.1016/j.jaci.2005.11.012.
[80] M. Johnson, The beta-adrenoceptor, Am. J. Respir. Crit. Care Med. 158 (1998) S146–S153, https://doi.org/10.1164/ajrccm.158.supplement_2.13tac110.
[81] G.A. Robison, R.W. Butcher, E.W. Sutherland, Adenyl cyclase as an adrenergic receptor, Ann. N. Y. Acad. Sci. 139 (1967) 703–723, https://doi.org/10.1111/j.1749-6632.1967.tb41239.
[82] M. Johnson, Mechanisms of Action of β2-Adrenoceptor Agonists. in: Asthma and Rhinitis, John Wiley & Sons, Ltd, 2000, pp. 1541–1557, https://doi.org/10.1002/9780470694923.ch30.
[83] Y. Daaka, L.M. Luttrell, R.J. Lefkowitz, Switching of the coupling of the beta2-adrenergic receptor to different G proteins by protein kinase A, Nature 390 (1997) 88–91, https://doi.org/10.1038/36362.
[84] S.W. Cole, A.K. Sood, Molecular pathways: beta-adrenergic signaling in cancer, Clin. Cancer Res 18 (2012) 1201–1206, https://doi.org/10.1158/1078-0432.CCR-11-0641.
[85] M.J. Lohse, J.L. Benovic, J. Codina, M.G. Caron, R.J. Lefkowitz, beta-Arrestin: a protein that regulates beta-adrenergic receptor function, Science 248 (1990) 1547–1550, https://doi.org/10.1126/science.2163110.
[86] K.N. Nobles, K. Xiao, S. Ahn, A.K. Shukla, C.M. Lam, S. Rajagopal, R.T. Strachan, T.-Y. Huang, E.A. Bressler, M.R. Hara, S.K. Shenoy, S.P. Gygi, R.J. Lefkowitz, Distinct phosphorylation sites on the β(2)-adrenergic receptor establish a barcode that encodes differential functions of β-arrestin, Sci. Signal. 4 (2011) ra51, https://doi.org/10.1126/scisignal.2001707.
[87] S. Chhatar, G. Lal, Role of adrenergic receptor signalling in neuroimmune communication, Curr. Res. Immunol. 2 (2021) 202–217, https://doi.org/10.1016/j.crimmu.2021.11.001.
[88] K.S.R. Sastry, Y. Karpova, S. Prokopovich, A.J. Smith, B. Essau, A. Gersappe, J. P. Carson, M.J. Weber, T.C. Register, Y.Q. Chen, R.B. Penn, G. Kulik, Epinephrine protects cancer cells from apoptosis via activation of cAMP-dependent protein kinase and BAD phosphorylation, J. Biol. Chem. 282 (2007) 14094–14100, https://doi.org/10.1074/jbc.M611370200.
[89] J. de Rooij, F.J. Zwartkruis, M.H. Verheijen, R.H. Cool, S.M. Nijman, A. Wittinghofer, J.L. Bos, Epac is a Rap1 guanine-nucleotide-exchange factor directly activated by cyclic AMP, Nature 396 (1998) 474–477, https://doi.org/10.1038/24884.
[90] M.T. Branham, M.A. Bustos, G.A. De Blas, H. Rehmann, V.E.P. Zarelli, C. L. Treviño, A. Darszon, L.S. Mayorga, C.N. Tomes, Epac activates the small G Proteins Rap1 and Rab3A to achieve exocytosis, J. Biol. Chem. 284 (2009) 24825–24839, https://doi.org/10.1074/jbc.M109.015362.

[91] D. Matallanas, M. Birtwistle, D. Romano, A. Zebisch, J. Rauch, A. von Kriegsheim, W. Kolch, Raf Family Kinases, Genes Cancer 2 (2011) 232–260, https://doi.org/10.1177/1947601911407323.
[92] A.V. Maltsev, Y.M. Kokoz, E.V. Evdokimovskii, O.Y. Pimenov, S. Reyes, A. E. Alekseev, Alpha-2 adrenoceptors and imidazoline receptors in cardiomyocytes mediate counterbalancing effect of agmatine on NO synthesis and intracellular calcium handling, J. Mol. Cell. Cardiol. 68 (2014) 66–74, https://doi.org/10.1016/j.yjmcc.2013.12.030.
[93] F. Cattaneo, G. Guerra, M. Parisi, M. De Marinis, D. Tafuri, M. Cinelli, R. Ammendola, Cell-surface receptors transactivation mediated by G protein-coupled receptors, Int. J. Mol. Sci. 15 (2014) 19700–19728, https://doi.org/10.3390/ijms151119700.
[94] S. Cotecchia, C.D. del Vescovo, M. Colella, S. Caso, D. Diviani, The alpha1-adrenergic receptors in cardiac hypertrophy: Signaling mechanisms and functional implications, Cell. Signal. 27 (2015) 1984–1993, https://doi.org/10.1016/j.cellsig.2015.06.009.
[95] Y.M. Ulrich-Lai, J.P. Herman, Neural regulation of endocrine and autonomic stress responses, Nat. Rev. Neurosci. 10 (2009) 397–409, https://doi.org/10.1038/nrn2647.
[96] F. Marino, M. Cosentino, Adrenergic modulation of immune cells: an update, Amino Acids 45 (2013) 55–71, https://doi.org/10.1007/s00726-011-1186-6.
[97] V.M. Sanders, R.A. Baker, D.S. Ramer-Quinn, D.J. Kasprowicz, B.A. Fuchs, N. E. Street, Differential expression of the beta2-adrenergic receptor by Th1 and Th2 clones: implications for cytokine production and B cell help, J. Immunol. 158 (1997) 4200–4210.
[98] C.L. Lubahn, D. Lorton, J.A. Schaller, S.J. Sweeney, D.L. Bellinger, Targeting α- and β-adrenergic receptors differentially shifts Th1, Th2, and inflammatory cytokine profiles in immune organs to attenuate adjuvant arthritis, Front Immunol. 5 (2014) 346, https://doi.org/10.3389/fimmu.2014.00346.
[99] K. Suzuki, Y. Hayano, A. Nakai, F. Furuta, M. Noda, Adrenergic control of the adaptive immune response by diurnal lymphocyte recirculation through lymph nodes, J. Exp. Med. 213 (2016) 2567–2574, https://doi.org/10.1084/jem.20160723.
[100] S. Ostrand-Rosenberg, CD4+ T lymphocytes: a critical component of antitumor immunity, Cancer Invest 23 (2005) 413–419.
[101] K.T. Byrne, R.H. Vonderheide, CD40 therapy and surgery: a potential immunologic partnership, J. Immunother. 36 (2013) 359–361, https://doi.org/10.1097/CJI.0b013e31829fb871.
[102] C. Pfirschke, C. Engblom, S. Rickelt, V. Cortez-Retamozo, C. Garris, F. Pucci, T. Yamazaki, V. Poirier-Colame, A. Newton, Y. Redouane, Y.-J. Lin, G. Wojtkiewicz, Y. Iwamoto, M. Mino-Kenudson, T.G. Huynh, R.O. Hynes, G. J. Freeman, G. Kroemer, L. Zitvogel, R. Weissleder, M.J. Pittet, Immunogenic chemotherapy sensitizes tumors to checkpoint blockade therapy, Immunity 44 (2016) 343–354, https://doi.org/10.1016/j.immuni.2015.11.024.
[103] A.B. Sharabi, M. Lim, T.L. DeWeese, C.G. Drake, Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy, Lancet Oncol. 16 (2015) e498–e509, https://doi.org/10.1016/S1470-2045(15)00007-8.
[104] M.D. LaJevic, S. Suleiman, R.L. Cohen, D.A. Chambers, Activation of p38 mitogen-activated protein kinase by norepinephrine in T-lineage cells, Immunology 132 (2011) 197–208, https://doi.org/10.1111/j.1365-2567.2010.03354.x.
[105] L.R. Frick, M.L. Barreiro Arcos, M. Rapanelli, M.P. Zappia, M. Brocco, C. Mongini, A.M. Genaro, G.A. Cremaschi, Chronic restraint stress impairs T-cell immunity and promotes tumor progression in mice, Stress 12 (2009) 134–143, https://doi.org/10.1080/10253890802137437.
[106] D. Schmidt, D. Peterlik, S.O. Reber, A. Lechner, D.N. Männel, Induction of Suppressor Cells and Increased Tumor Growth following Chronic Psychosocial Stress in Male Mice, PLoS One 11 (2016) e0159059, https://doi.org/10.1371/journal.pone.0159059.
[107] G. Mg, A. Lp, M. Jt, T. Mc, N. Vm, V. Bc, R. Vo, K. Ac, B. Pc, B. As, Beta2-adrenergic receptor signaling in CD4+ Foxp3+ regulatory T cells enhances their suppressive function in a PKA-dependent manner, Eur. J. Immunol. 43 (2013), https://doi.org/10.1002/eji.201243005.
[108] I.J. Elenkov, R.L. Wilder, G.P. Chrousos, E.S. Vizi, The sympathetic nerve–an integrative interface between two supersystems: the brain and the immune system, Pharm. Rev. 52 (2000) 595–638.
[109] C. Slota, A. Shi, G. Chen, M. Bevans, N. Weng, Norepinephrine preferentially modulates memory CD8 T cell function inducing inflammatory cytokine production and reducing proliferation in response to activation, Brain Behav. Immun. 46 (2015) 168–179, https://doi.org/10.1016/j.bbi.2015.01.015.
[110] M. Wahle, U. Stachetzki, A. Krause, M. Pierer, H. Häntzschel, C.G. Baerwald, Regulation of beta2-adrenergic receptors on CD4 and CD8 positive lymphocytes by cytokines in vitro, Cytokine 16 (2001) 205–209, https://doi.org/10.1006/cyto.2001.0965.
[111] Q. G, B. Mj, W. Nm, C. M, G. T, O. Sh, H. Bl, R. Ea, β-Adrenergic signaling blocks murine CD8+ T-cell metabolic reprogramming during activation: a mechanism for immunosuppression by adrenergic stress, Cancer Immunol., Immunother.: CII 68 (2019), https://doi.org/10.1007/s00262-018-2243-8.
[112] G. Qiao, M. Chen, H. Mohammadpour, C.R. MacDonald, M.J. Bucsek, B. L. Hylander, J.J. Barbi, E.A. Repasky, Chronic adrenergic stress contributes to metabolic dysfunction and an exhausted phenotype in T cells in the tumor microenvironment, Cancer Immunol. Res 9 (2021) 651–664, https://doi.org/10.1158/2326-6066.CIR-20-0445.
[113] F.S. Dhabhar, A.N. Saul, T.H. Holmes, C. Daugherty, E. Neri, J.M. Tillie, D. Kusewitt, T.M. Oberyszyn, High-anxious individuals show increased chronic stress burden, decreased protective immunity, and increased cancer progression in a mouse model of squamous cell carcinoma, PLoS One 7 (2012) e33069, https://doi.org/10.1371/journal.pone.0033069.
[114] B. Mj, G Q., Cr M., T G., L E., B N., H L., Km K., Jw E., Mn M., K A., Si A., Bl H., Ea R, β-adrenergic signaling in mice housed at standard temperatures suppresses an effector phenotype in CD8+ T cells and undermines checkpoint inhibitor therapy, Cancer Res. 77 (2017), https://doi.org/10.1158/0008-5472.CAN-17-0546.
[115] J.-Y. Bao, Y. Huang, F. Wang, Y.-P. Peng, Y.-H. Qiu, Expression of α-AR subtypes in T lymphocytes and role of the α-ARs in mediating modulation of T cell function, Neuroimmunomodulation 14 (2008) 344–353, https://doi.org/10.1159/000129670.
[116] V.M. Sanders, The beta2-adrenergic receptor on T and B lymphocytes: Do we understand it yet? Brain, Behav., Immun. 26 (2012) 195–200, https://doi.org/10.1016/j.bbi.2011.08.001.
[117] F.S. Dhabhar, W.B. Malarkey, E. Neri, B.S. McEwen, Stress-induced redistribution of immune cells–from barracks to boulevards to battlefields: a tale of three hormones–Curt Richter Award winner, Psychoneuroendocrinology 37 (2012) 1345–1368, https://doi.org/10.1016/j.psyneuen.2012.05.008.
[118] H. Engler, L. Dawils, S. Hoves, S. Kurth, J.R. Stevenson, K. Schauenstein, V. Stefanski, Effects of social stress on blood leukocyte distribution: the role of alpha- and beta-adrenergic mechanisms, J. Neuroimmunol. 156 (2004) 153–162, https://doi.org/10.1016/j.jneuroim.2004.08.005.
[119] C.M. Laumont, A.C. Banville, M. Gilardi, D.P. Hollern, B.H. Nelson, Tumour-infiltrating B cells: immunological mechanisms, clinical impact and therapeutic opportunities, Nat. Rev. Cancer 22 (2022) 414–430, https://doi.org/10.1038/s41568-022-00466-1.
[120] A.P. Kohm, A. Mozaffarian, V.M. Sanders, B cell receptor- and beta 2-adrenergic receptor-induced regulation of B7-2 (CD86) expression in B cells, J. Immunol. 168 (2002) 6314–6322, https://doi.org/10.4049/jimmunol.168.12.6314.
[121] J.R. Podojil, V.M. Sanders, Selective regulation of mature IgG1 transcription by CD86 and beta 2-adrenergic receptor stimulation, J. Immunol. 170 (2003) 5143–5151, https://doi.org/10.4049/jimmunol.170.10.5143.
[122] G. Pongratz, J.W. McAlees, D.H. Conrad, R.S. Erbe, K.M. Haas, V.M. Sanders, The level of IgE produced by a B cell is regulated by norepinephrine in a p38 MAPK- and CD23-dependent manner, J. Immunol. 177 (2006) 2926–2938, https://doi.org/10.4049/jimmunol.177.5.2926.
[123] V.M. Sanders, The Beta2-Adrenergic receptor on T and B lymphocytes: do we understand it yet? Brain Behav. Immun. 26 (2012) 195–200, https://doi.org/10.1016/j.bbi.2011.08.001.
[124] L. Shaashua, M. Shabat-Simon, R. Haldar, P. Matzner, O. Zmora, M. Shabtai, E. Sharon, T. Allweis, I. Barshack, L. Hayman, J. Arevalo, J. Ma, M. Horowitz, S. Cole, S. Ben-Eliyahu, Perioperative COX-2 and β-adrenergic blockade improves metastatic biomarkers in breast cancer patients in a phase-II randomized trial, Clin. Cancer Res. 23 (2017) 4651–4661, https://doi.org/10.1158/1078-0432.CCR-17-0152.
[125] C.M. Laumont, A.C. Banville, M. Gilardi, D.P. Hollern, B.H. Nelson, Tumour-infiltrating B cells: immunological mechanisms, clinical impact and therapeutic opportunities, Nat. Rev. Cancer 22 (2022) 414–430, https://doi.org/10.1038/s41568-022-00466-1.
[126] C. Shi, E.G. Pamer, Monocyte recruitment during infection and inflammation, Nat. Rev. Immunol. 11 (2011) 762–774, https://doi.org/10.1038/nri3070.
[127] J. Yang, L. Zhang, C. Yu, X.-F. Yang, H. Wang, Monocyte and macrophage differentiation: circulation inflammatory monocyte as biomarker for inflammatory diseases, Biomark. Res. 2 (2014) 1, https://doi.org/10.1186/2050-7771-2-1.
[128] X. Guirao, A. Kumar, J. Katz, M. Smith, E. Lin, C. Keogh, S.E. Calvano, S.F. Lowry, Catecholamines increase monocyte TNF receptors and inhibit TNF through beta 2-adrenoreceptor activation, Am. J. Physiol. 273 (1997) E1203–E1208, https://doi.org/10.1152/ajpendo.1997.273.6.E1203.
[129] K. Mizuno, H.K. Takahashi, H. Iwagaki, G. Katsuno, H.A.S.M. Kamurul, S. Ohtani, S. Mori, T. Yoshino, M. Nishibori, N. Tanaka, Beta2-adrenergic receptor stimulation inhibits LPS-induced IL-18 and IL-12 production in monocytes, Immunol. Lett. 101 (2005) 168–172, https://doi.org/10.1016/j.imlet.2005.05.008.
[130] H.K. Takahashi, T. Morichika, H. Iwagaki, T. Yoshino, R. Tamura, S. Saito, S. Mori, T. Akagi, N. Tanaka, M. Nishibori, Effect of beta 2-adrenergic receptor stimulation on interleukin-18-induced intercellular adhesion molecule-1 expression and cytokine production, J. Pharmacol. Exp. Ther. 304 (2003) 634–642, https://doi.org/10.1124/jpet.102.042622.
[131] N. Paul-Eugene, J.P. Kolb, A. Abadie, J. Gordon, G. Delespesse, M. Sarfati, J. M. Mencia-Huerta, P. Braquet, B. Dugas, Ligation of CD23 triggers cAMP generation and release of inflammatory mediators in human monocytes, J. Immunol. 149 (1992) 3066–3071.
[132] J.M. Mencia-Huerta, N. Paul-Eugène, B. Dugas, C. Petit-Frère, J. Gordon, V. Lagente, J. Cairns, P. Braquet, Beta-2-adrenoceptor agonists up-regulate the in vitro Fc epsilon receptor II/CD23 expression on, and release from, the promonocytic cell line U937 and human blood monocytes, Int. Arch. Allergy Appl. Immunol. 94 (1991) 91–92, https://doi.org/10.1159/000235334.
[133] C. Rouppe van der Voort, A. Kavelaars, M. van de Pol, C.J. Heijnen, Neuroendocrine mediators up-regulate alpha1b- and alpha1d-adrenergic receptor subtypes in human monocytes, J. Neuroimmunol. 95 (1999) 165–173, https://doi.org/10.1016/s0165-5728(99)00011-9.
[134] C.I. Ezeamuzie, P.K. Shihab, R. Al-Radwan, Loss of surface beta-2 adrenoceptors accounts for the insensitivity of cultured human monocytes to beta-2 adrenoceptor agonists, Int. Immunopharmacol. 11 (2011) 1189–1194, https://doi.org/10.1016/j.intimp.2011.03.017.

[135] A.J. Baker, R.W. Fuller, Loss of response to beta-adrenoceptor agonists during the maturation of human monocytes to macrophages in vitro, J. Leukoc. Biol. 57 (1995) 395–400, https://doi.org/10.1002/jlb.57.3.395.
[136] H. Chen, D. Liu, L. Guo, X. Cheng, N. Guo, M. Shi, Chronic psychological stress promotes lung metastatic colonization of circulating breast cancer cells by decorating a pre-metastatic niche through activating β-adrenergic signaling, J. Pathol. 244 (2018) 49–60, https://doi.org/10.1002/path.4988.
[137] L. Dm, H. Hy, O. Th, K. Ck, S. Vl, A. N, M. Jcy, A. Jmg, C. Sw, S. Ek, β-Adrenergic-stimulated macrophages: Comprehensive localization in the M1-M2 spectrum, Brain Behav., Immun. 57 (2016), https://doi.org/10.1016/j.bbi.2016.07.162.
[138] Y. Cheng, X.Y. Tang, Y.X. Li, D.D. Zhao, Q.H. Cao, H.X. Wu, H.B. Yang, K. Hao, Y. Yang, Depression-Induced Neuropeptide Y Secretion Promotes Prostate Cancer Growth by Recruiting Myeloid Cells, Clin Cancer Res. 25 (2019), https://doi.org/10.1158/1078-0432.CCR-18-2912.
[139] A. Gosain, K. Muthu, R.L. Gamelli, L.A. DiPietro, Norepinephrine suppresses wound macrophage phagocytic efficiency through alpha- and beta-adrenoreceptor dependent pathways, Surgery 142 (2007) 170–179, https://doi.org/10.1016/j.surg.2007.04.015.
[140] P.H. Black, Stress and the inflammatory response: a review of neurogenic inflammation, Brain Behav. Immun. 16 (2002) 622–653, https://doi.org/10.1016/s0889-1591(02)00021-1.
[141] J.-L. Huang, Y.-L. Zhang, C.-C. Wang, J.-R. Zhou, Q. Ma, X. Wang, X.-H. Shen, C.-L. Jiang, Enhanced phosphorylation of MAPKs by NE promotes TNF-α production by macrophage through α adrenergic receptor, Inflammation 35 (2012) 527–534, https://doi.org/10.1007/s10753-011-9342-4.
[142] L.A. Grisanti, A.P. Woster, J. Dahlman, E.R. Sauter, C.K. Combs, J.E. Porter, α1-Adrenergic Receptors Positively Regulate Toll-Like Receptor Cytokine Production from Human Monocytes and Macrophages, J. Pharm. Exp. Ther. 338 (2011) 648–657, https://doi.org/10.1124/jpet.110.178012.
[143] K.M. Kokolus, H.M. Spangler, B.J. Povinelli, M.R. Farren, K.P. Lee, E.A. Repasky, Stressful presentations: mild cold stress in laboratory mice influences phenotype of dendritic cells in naïve and tumor-bearing mice, Front Immunol. 5 (2014) 23, https://doi.org/10.3389/fimmu.2014.00023.
[144] G.J.M. Maestroni, P. Mazzola, Langerhans cells beta 2-adrenoceptors: role in migration, cytokine production, Th priming and contact hypersensitivity, J. Neuroimmunol. 144 (2003) 91–99, https://doi.org/10.1016/j.jneuroim.2003.08.039.
[145] G.J. Maestroni, Dendritic cell migration controlled by alpha 1b-adrenergic receptors, J Immunol 165 (2000) 6743–6747, https://doi.org/10.4049/jimmunol.165.12.6743.
[146] P. Panina-Bordignon, D. Mazzeo, P.D. Lucia, D. D'Ambrosio, R. Lang, L. Fabbri, C. Self, F. Sinigaglia, Beta2-agonists prevent Th1 development by selective inhibition of interleukin 12, J. Clin. Invest 100 (1997) 1513–1519, https://doi.org/10.1172/JCI119674.
[147] Y. Yanagawa, M. Matsumoto, H. Togashi, Adrenoceptor-mediated enhancement of interleukin-33 production by dendritic cells, Brain, Behav., Immun. 25 (2011) 1427–1433, https://doi.org/10.1016/j.bbi.2011.04.012.
[148] K. Bj, J. Hp, Epinephrine-primed murine bone marrow-derived dendritic cells facilitate production of IL-17A and IL-4 but not IFN-γ by CD4+ T cells, Brain, Behav., Immun. 24 (2010), https://doi.org/10.1016/j.bbi.2010.05.003.
[149] J. Hervé, L. Dubreil, V. Tardif, M. Terme, S. Pogu, I. Anegon, B. Rozec, C. Gauthier, J.-M. Bach, P. Blancou, β2-Adrenoreceptor agonist inhibits antigen cross-presentation by dendritic cells, J. Immunol. 190 (2013) 3163–3171, https://doi.org/10.4049/jimmunol.1201391.
[150] J H., L D., V T., M T., S P., I A., B R., C G., Jm B., P B, β2-Adrenoreceptor agonist inhibits antigen cross-presentation by dendritic cells, J. Immunol. (Baltim., Md.: 1950) 190 (2013), https://doi.org/10.4049/jimmunol.1201391.
[151] H. Ueshima, T. Inada, K. Shingu, Suppression of phagosome proteolysis and Matrigel migration with the α2-adrenergic receptor agonist dexmedetomidine in murine dendritic cells, Immunopharmacol. Immunotoxicol. 35 (2013) 558–566, https://doi.org/10.3109/08923973.2013.822509.
[152] F. Botta, G.J.M. Maestroni, Adrenergic Modulation of Dendritic Cell Cancer Vaccine in a Mouse Model: Role of Dendritic Cell Maturation, J. Immunother. 31 (2008) 263, https://doi.org/10.1097/CJI.0b013e318160995e.
[153] D.I. Gabrilovich, H.L. Chen, K.R. Girgis, H.T. Cunningham, G.M. Meny, S. Nadaf, D. Kavanaugh, D.P. Carbone, Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells, Nat. Med 2 (1996) 1096–1103, https://doi.org/10.1038/nm1096-1096.
[154] P.M. Santos, L.H. Butterfield, Dendritic-cell-based therapeutic cancer vaccines, Immunity 39 (2013), https://doi.org/10.4049/jimmunol.1701024.
[155] S.K. Lutgendorf, A.K. Sood, B. Anderson, S. McGinn, H. Maiseri, M. Dao, J. I. Sorosky, K. De Geest, J. Ritchie, D.M. Lubaroff, Social support, psychological distress, and natural killer cell activity in ovarian cancer, J. Clin. Oncol. 23 (2005) 7105–7113, https://doi.org/10.1200/JCO.2005.10.015.
[156] M.M. Whalen, A.D. Bankhurst, Effects of beta-adrenergic receptor activation, cholera toxin and forskolin on human natural killer cell function, Biochem J. 272 (1990) 327–331, https://doi.org/10.1042/bj2720327.
[157] T. Takamoto, Y. Hori, Y. Koga, H. Toshima, A. Hara, M.M. Yokoyama, Norepinephrine inhibits human natural killer cell activity in vitro, Int J. Neurosci. 58 (1991) 127–131, https://doi.org/10.3109/00207459108987189.
[158] G.G. Page, S. Ben-Eliyahu, Natural killer cell activity and resistance to tumor metastasis in prepubescent rats: deficient baselines, but invulnerability to stress and beta-adrenergic stimulation, Neuroimmunomodulation 7 (2000) 160–168, https://doi.org/10.1159/000026434.
[159] G. Shakhar, S. Ben-Eliyahu, In vivo beta-adrenergic stimulation suppresses natural killer activity and compromises resistance to tumor metastasis in rats, J. Immunol. 160 (1998) 3251–3258.
[160] K. Hellstrand, S. Hermodsson, O. Strannegård, Evidence for a beta-adrenoceptor-mediated regulation of human natural killer cells, J. Immunol. 134 (1985) 4095–4099.
[161] J. Xiao, H.W. Huang, Y.P. Peng, J.Y. Bao, Y. Huang, Y.H. Qiu, Modulation of natural killer cell function by alpha-adrenoreceptor-coupled signalling, Neuro Endocrinol. Lett. 31 (2010). ⟨https://pubmed.ncbi.nlm.nih.gov/21173746/⟩.
[162] B.L. Andersen, W.B. Farrar, D. Golden-Kreutz, L.A. Kutz, R. MacCallum, M. E. Courtney, R. Glaser, Stress and immune responses after surgical treatment for regional breast cancer, J. Natl. Cancer Inst. 90 (1998) 30–36, https://doi.org/10.1093/jnci/90.1.30.
[163] K.A. Varker, C.E. Terrell, M. Welt, S. Suleiman, L. Thornton, B.L. Andersen, W. E. Carson, Impaired natural killer cell lysis in breast cancer patients with high levels of psychological stress is associated with altered expression of killer immunoglobin-like receptors, J. Surg. Res. 139 (2007) 36–44, https://doi.org/10.1016/j.jss.2006.08.037.
[164] R.J. Benschop, F.P. Nijkamp, R.E. Ballieux, C.J. Heijnen, The effects of beta-adrenoceptor stimulation on adhesion of human natural killer cells to cultured endothelium, Br. J. Pharmacol. 113 (1994) 1311–1316, https://doi.org/10.1111/j.1476-5381.1994.tb17141.x.
[165] R.J. Benschop, M. Schedlowski, H. Wienecke, R. Jacobs, R.E. Schmidt, Adrenergic control of natural killer cell circulation and adhesion, Brain Behav. Immun. 11 (1997) 321–332, https://doi.org/10.1006/brbi.1997.0499.
[166] A. Glasner, R. Avraham, E. Rosenne, M. Benish, O. Zmora, S. Shemer, H. Meiboom, S. Ben-Eliyahu, Improving survival rates in two models of spontaneous postoperative metastasis in mice by combined administration of a beta-adrenergic antagonist and a cyclooxygenase-2 inhibitor, J. Immunol. 184 (2010) 2449–2457, https://doi.org/10.4049/jimmunol.0903301.
[167] O. Kanemi, X. Zhang, Y. Sakamoto, M. Ebina, R. Nagatomi, Acute stress reduces intraparenchymal lung natural killer cells via beta-adrenergic stimulation, Clin. Exp. Immunol. 139 (2005) 25–34, https://doi.org/10.1111/j.1365-2249.2005.02672.x.
[168] R.M. Graff, H.E. Kunz, N.H. Agha, F.L. Baker, M. Laughlin, A.B. Bigley, M. M. Markofski, E.C. LaVoy, E. Katsanis, R.A. Bond, C.M. Bollard, R.J. Simpson, β2-Adrenergic receptor signaling mediates the preferential mobilization of differentiated subsets of CD8+ T-cells, NK-cells and non-classical monocytes in response to acute exercise in humans, Brain Behav. Immun. 74 (2018) 143–153, https://doi.org/10.1016/j.bbi.2018.08.017.
[169] E. Kenne Sarenmalm, L.B. Mårtensson, B.A. Andersson, P. Karlsson, I. Bergh, Mindfulness and its efficacy for psychological and biological responses in women with breast cancer, Cancer Med. 6 (2017) 1108–1122, https://doi.org/10.1002/cam4.1052.
[170] E. Wieduwild, M.J. Girard-Madoux, L. Quatrini, C. Laprie, L. Chasson, R. Rossignol, C. Bernat, S. Guia, S. Ugolini, β2-adrenergic signals downregulate the innate immune response and reduce host resistance to viral infection, J. Exp. Med. 217 (2020) e20190554, https://doi.org/10.1084/jem.20190554.
[171] C. Diaz-Salazar, R. Bou-Puerto, A.M. Mujal, C.M. Lau, M. von Hoesslin, D. Zehn, J. C. Sun, Cell-intrinsic adrenergic signaling controls the adaptive NK cell response to viral infection, J. Exp. Med. 217 (2020) e20190549, https://doi.org/10.1084/jem.20190549.
[172] W.M. Yokoyama, Natural killer cell immune responses, Immunol. Res 32 (2005) 317–325, https://doi.org/10.1385/IR:32:1-3:317.
[173] A. Cerwenka, L.L. Lanier, Natural killer cells, viruses and cancer, Nat. Rev. Immunol. 1 (2001) 41–49, https://doi.org/10.1038/35095564.
[174] D.B. McKim, W. Yin, Y. Wang, S.W. Cole, J.P. Godbout, J.F. Sheridan, Social stress mobilizes hematopoietic stem cells to establish persistent splenic myelopoiesis, Cell Rep. 25 (2018) 2552–2562.e3, https://doi.org/10.1016/j.celrep.2018.10.102.
[175] H. Mohammadpour, C.R. MacDonald, G. Qiao, M. Chen, B. Dong, B.L. Hylander, P.L. McCarthy, S.I. Abrams, E.A. Repasky, β2 adrenergic receptor-mediated signaling regulates the immunosuppressive potential of myeloid-derived suppressor cells, J. Clin. Invest 129 (2019) 5537–5552, https://doi.org/10.1172/JCI129502.
[176] T.L. Ben-Shaanan, M. Schiller, H. Azulay-Debby, B. Korin, N. Boshnak, T. Koren, M. Krot, J. Shakya, M.A. Rahat, F. Hakim, A. Rolls, Modulation of anti-tumor immunity by the brain's reward system, Nat. Commun. 9 (2018) 2723, https://doi.org/10.1038/s41467-018-05283-5.
[177] B.L. Mundy-Bosse, L.M. Thornton, H.-C. Yang, B.L. Andersen, W.E. Carson, Psychological stress is associated with altered levels of myeloid-derived suppressor cells in breast cancer patients, Cell Immunol. 270 (2011) 80–87, https://doi.org/10.1016/j.cellimm.2011.04.003.
[178] J. Jin, X. Wang, Q. Wang, X. Guo, J. Cao, X. Zhang, T. Zhu, D. Zhang, W. Wang, J. Wang, B. Shen, X. Gao, Y. Shi, J. Zhang, Chronic psychological stress induces the accumulation of myeloid-derived suppressor cells in mice, PLoS One 8 (2013) e74497, https://doi.org/10.1371/journal.pone.0074497.
[179] P. Xu, H. He, Y. Gu, Y. Wang, Z. Sun, L. Yang, C. Miao, Surgical trauma contributes to progression of colon cancer by downregulating CXCL4 and recruiting MDSCs, Exp. Cell Res. 370 (2018) 692–698, https://doi.org/10.1016/j.yexcr.2018.07.035.
[180] X. Ma, M. Wang, T. Yin, Y. Zhao, X. Wei, Myeloid-derived suppressor cells promote metastasis in breast cancer after the stress of operative removal of the primary cancer, Front. Oncol. 9 (2019) 855, https://doi.org/10.3389/fonc.2019.00855.

[181] W. Li, K. Wu, E. Zhao, L. Shi, R. Li, P. Zhang, Y. Yin, X. Shuai, G. Wang, K. Tao, HMGB1 recruits myeloid derived suppressor cells to promote peritoneal dissemination of colon cancer after resection, Biochem. Biophys. Res. Commun. 436 (2013) 156–161, https://doi.org/10.1016/j.bbrc.2013.04.109.
[182] H. Mohammadpour, C.R. MacDonald, G. Qiao, M. Chen, B. Dong, B.L. Hylander, P.L. McCarthy, S.I. Abrams, E.A. Repasky, β2 adrenergic receptor–mediated signaling regulates the immunosuppressive potential of myeloid-derived suppressor cells, J Clin Invest 129 (2019) 5537–5552, https://doi.org/10.1172/JCI129502.
[183] B. Huang, P.-Y. Pan, Q. Li, A.I. Sato, D.E. Levy, J. Bromberg, C.M. Divino, S.-H. Chen, Gr-1+CD115+ immature myeloid suppressor cells mediate the development of tumor-induced T regulatory cells and T-cell anergy in tumor-bearing host, Cancer Res. 66 (2006) 1123–1131, https://doi.org/10.1158/0008-5472.CAN-05-1299.
[184] D.I. Gabrilovich, S. Nagaraj, Myeloid-derived-suppressor cells as regulators of the immune system, Nat. Rev. Immunol. 9 (2009) 162–174, https://doi.org/10.1038/nri2506.
[185] A.J. Nicholls, S.W. Wen, P. Hall, M.J. Hickey, C.H.Y. Wong, Activation of the sympathetic nervous system modulates neutrophil function, J. Leukoc. Biol. 103 (2018) 295–309, https://doi.org/10.1002/JLB.3MA0517-194RR.
[186] L. Corradi, F. Negri, A. Parini, N. Partesana, G. Finardi, Decreased beta-adrenoceptors in polymorphonucleates in essential hypertension, Boll. Soc. Ital. Biol. Sper. 57 (1981) 1766–1770.
[187] K.O. Schwab, H. Bartels, C. Martin, E.M. Leichtenschlag, Decreased beta 2-adrenoceptor density and decreased isoproterenol induced c-AMP increase in juvenile type I diabetes mellitus: an additional cause of severe hypoglycaemia in childhood diabetes? Eur. J. Pediatr. 152 (1993) 797–801, https://doi.org/10.1007/BF02073373.
[188] D. Ratge, A. Wiedemann, K.P. Kohse, H. Wisser, Alterations of beta-adrenoceptors on human leukocyte subsets induced by dynamic exercise: effect of prednisone, Clin. Exp. Pharmacol. Physiol. 15 (1988) 43–53, https://doi.org/10.1111/j.1440-1681.1988.tb01007.x.
[189] K.O. Schwab, H. Bartels, C. Martin, E.-M. Leichtenschlag, Decreased β2-adrenoceptor density and decreased isoproterenol induced c-AMP increase in juvenile type I diabetes mellitus: an additional cause of severe hypoglycaemia in childhood diabetes? Eur. J. Pediatr. 152 (1993) 797–801, https://doi.org/10.1007/BF02073373.
[190] M. Wahle, T. Greulich, C.G.O. Baerwald, H. Häntzschel, A. Kaufmann, Influence of catecholamines on cytokine production and expression of adhesion molecules of human neutrophils in vitro, Immunobiology 210 (2005) 43–52, https://doi.org/10.1016/j.imbio.2005.02.004.
[191] V.M. Sá-Rocha, L.C. Sá-Rocha, J. Palermo-Neto, Variations in behavior, innate immunity and host resistance to B16F10 melanoma growth in mice that present social stable hierarchical ranks, Physiol. Behav. 88 (2006) 108–115, https://doi.org/10.1016/j.physbeh.2006.03.015.
[192] M. Perego, V.A. Tyurin, Y.Y. Tyurina, J. Yellets, T. Nacarelli, C. Lin, Y. Nefedova, A. Kossenkov, Q. Liu, S. Sreedhar, H. Pass, J. Roth, T. Vogl, D. Feldser, R. Zhang, V.E. Kagan, D.I. Gabrilovich, Reactivation of dormant tumor cells by modified lipids derived from stress-activated neutrophils, Sci. Transl. Med. 12 (2020) eabb5817, https://doi.org/10.1126/scitranslmed.abb5817.
[193] I. Brunskole Hummel, M.T. Reinartz, S. Kälble, H. Burhenne, F. Schwede, A. Buschauer, R. Seifert, Dissociations in the effects of β2-adrenergic receptor agonists on cAMP formation and superoxide production in human neutrophils: support for the concept of functional selectivity, PLoS One 8 (2013) e64556, https://doi.org/10.1371/journal.pone.0064556.
[194] B. Trabold, D. Lunz, M. Gruber, D. Fröhlich, B. Graf, Immunomodulation of neutrophil–endothelial interaction by inotropes, Injury 41 (2010) 1079–1083, https://doi.org/10.1016/j.injury.2010.05.034.
[195] D. Beis, R. von Känel, N. Heimgartner, C. Zuccarella-Hackl, A. Bürkle, U. Ehlert, P. H. Wirtz, The role of norepinephrine and α-adrenergic receptors in acute stress-induced changes in granulocytes and monocytes, Psychosom. Med. 80 (2018) 649–658, https://doi.org/10.1097/PSY.0000000000000620.
[196] L. Duan, J. Chen, M. Razavi, Y. Wei, Y. Tao, X. Rao, J. Zhong, Alpha2B-adrenergic receptor regulates neutrophil recruitment in msu-induced peritoneal inflammation, Front. Immunol. 10 (2019) 501, https://doi.org/10.3389/fimmu.2019.00501.
[197] M.H. Kim, F. Gorouhi, S. Ramirez, J.L. Granick, B.A. Byrne, A.M. Soulika, S. I. Simon, RR Isseroff, Catecholamine Stress Alters Neutrophil Trafficking and Impairs Wound Healing by β2-Adrenergic Receptor–Mediated Upregulation of IL-6, Journal of Investigative Dermatology 134 (2014) 809–817, https://doi.org/10.1038/jid.2013.415.
[198] J Koch-Weser, Beta adrenergic blockade and circulating eosinophils, Archives of internal medicine. 121, doi:1968),10.1001/archinte.1968.03640030047007.
[199] B. Jj, I.S. Dm M, Inhibition of neutrophil and eosinophil adhesion to venules of rat trachea by beta 2-adrenergic agonist formoterol, J. Appl. Physiol. (Bethesda, Md) 1985 (1994) 77, https://doi.org/10.1152/jappl.1994.77.1.397.
[200] P.J. Barnes, Effect of β agonists on inflammatory cells, J. Allergy Clin. Immunol. 104 (1999) S10–S17, https://doi.org/10.1016/S0091-6749(99)70269-1.
[201] A. Miadonna, A. Tedeschi, E. Leggieri, P. Parravicini, M. Lorini, C. Zanussi, Clonidine inhibits IgE-mediated and IgE-independent in vitro histamine release from human basophil leukocytes, Int. J. Immunopharmacol. 11 (1989) 473–477, https://doi.org/10.1016/0192-0561(89)90176-8.
[202] P.F. Mannaioni, R. Mastroianni, D. Mastrangelo, Adrenaline inhibits the immunological activation of human basophils at pharmacological and ultra-low doses, Med. Sci. Monit. 16 (2010) BR227–BR232.
[203] X.S. Wang, H.Y.A. Lau, Beta-adrenoceptor-mediated inhibition of mediator release from human peripheral blood-derived mast cells, Clin. Exp. Pharmacol. Physiol. 33 (2006) 746–750, https://doi.org/10.1111/j.1440-1681.2006.04435.x.
[204] L.K. Chong, R. Chess-Williams, P.T. Peachell, Pharmacological characterisation of the beta-adrenoceptor expressed by human lung mast cells, Eur. J. Pharmacol. 437 (2002) 1–7, https://doi.org/10.1016/s0014-2999(02)01263-3.
[205] S.R. Carding, P.J. Egan, Gammadelta T cells: functional plasticity and heterogeneity, Nat. Rev. Immunol. 2 (2002) 336–345, https://doi.org/10.1038/nri797.
[206] L.H. Anane, K.M. Edwards, V.E. Burns, M.T. Drayson, N.E. Riddell, J.J.C.S.V. van Zanten, G.R. Wallace, P.J. Mills, J.A. Bosch, Mobilization of γδ T lymphocytes in response to psychological stress, exercise, and β-agonist infusion, Brain, Behav., Immun. 23 (2009) 823–829, https://doi.org/10.1016/j.bbi.2009.03.003.
[207] S. Dimitrov, T. Lange, J. Born, Selective mobilization of cytotoxic leukocytes by epinephrine, J. Immunol. 184 (2010) 503–511, https://doi.org/10.4049/jimmunol.0902189.
[208] M.H. Antoni, S.K. Lutgendorf, S.W. Cole, F.S. Dhabhar, S.E. Sephton, P. G. McDonald, M. Stefanek, A.K. Sood, The influence of bio-behavioural factors on tumour biology: pathways and mechanisms, Nat. Rev. Cancer 6 (2006) 240–248, https://doi.org/10.1038/nrc1820.
[209] M.S. Flint, A. Baum, W.H. Chambers, F.J. Jenkins, Induction of DNA damage, alteration of DNA repair and transcriptional activation by stress hormones, Psychoneuroendocrinology 32 (2007) 470–479, https://doi.org/10.1016/j.psyneuen.2007.02.013.
[210] M.R. Hara, J.J. Kovacs, E.J. Whalen, S. Rajagopal, R.T. Strachan, W. Grant, A. J. Towers, B. Williams, C.M. Lam, K. Xiao, S.K. Shenoy, S.G. Gregory, S. Ahn, D. R. Duckett, R.J. Lefkowitz, A stress response pathway regulates DNA damage through β2-adrenoreceptors and β-arrestin-1, Nature 477 (2011) 349–353, https://doi.org/10.1038/nature10368.
[211] S. Sengupta, C.C. Harris, p53: traffic cop at the crossroads of DNA repair and recombination, Nat. Rev. Mol. Cell Biol. 6 (2005) 44–55, https://doi.org/10.1038/nrm1546.
[212] M.R. Hara, B.D. Sachs, M.G. Caron, R.J. Lefkowitz, Pharmacological blockade of a β2AR-β-arrestin-1 signaling cascade prevents the accumulation of DNA damage in a behavioral stress model, Cell Cycle 12 (2013) 219–224, https://doi.org/10.4161/cc.23368.
[213] L. Yan, D.E. Vatner, J.P. O'Connor, A. Ivessa, H. Ge, W. Chen, S. Hirotani, Y. Ishikawa, J. Sadoshima, S.F. Vatner, Type 5 adenylyl cyclase disruption increases longevity and protects against stress, Cell 130 (2007) 247–258, https://doi.org/10.1016/j.cell.2007.05.038.
[214] G.N. Armaiz-Pena, J.K. Allen, A. Cruz, R.L. Stone, A.M. Nick, Y.G. Lin, L.Y. Han, L. S. Mangala, G.J. Villares, P. Vivas-Mejia, C. Rodriguez-Aquayo, A.S. Nagaraja, K. M. Gharpure, Z. Wu, R.D. English, K.V. Soman, M.M.K. Shazhad, M. Zigler, M. T. Deavers, A. Zien, T.G. Soldatos, D.B. Jackson, J.E. Wiktorowicz, M. Torres-Lugo, T. Young, K. De Geest, G.E. Gallick, M. Bar-Eli, G. Lopez-Berestein, S. W. Cole, G.E. Lopez, S.K. Lutgendorf, A.K. Sood, Src activation by β-adrenoreceptors is a key switch for tumor metastasis, Nat. Commun. 4 (2013) 1403, https://doi.org/10.1038/ncomms2413.
[215] M. Shi, D. Liu, H. Duan, L. Qian, L. Wang, L. Niu, H. Zhang, Z. Yong, Z. Gong, L. Song, M. Yu, M. Hu, Q. Xia, B. Shen, N. Guo, The β2-adrenergic receptor and Her2 comprise a positive feedback loop in human breast cancer cells, Breast Cancer Res. Treat. 125 (2011) 351–362, https://doi.org/10.1007/s10549-010-0822-2.
[216] A.K. Sood, G.N. Armaiz-Pena, J. Halder, A.M. Nick, R.L. Stone, W. Hu, A. R. Carroll, W.A. Spannuth, M.T. Deavers, J.K. Allen, L.Y. Han, A.A. Kamat, M.M. K. Shahzad, B.W. McIntyre, C.M. Diaz-Montero, N.B. Jennings, Y.G. Lin, W. M. Merritt, K. DeGeest, P.E. Vivas-Mejia, G. Lopez-Berestein, M.D. Schaller, S. W. Cole, S.K. Lutgendorf, Adrenergic modulation of focal adhesion kinase protects human ovarian cancer cells from anoikis, J. Clin. Invest 120 (2010) 1515–1523, https://doi.org/10.1172/JCI40802.
[217] J.W.-L. Eng, C.B. Reed, K.M. Kokolus, R. Pitoniak, A. Utley, M.J. Bucsek, W. W. Ma, E.A. Repasky, B.L. Hylander, Housing temperature-induced stress drives therapeutic resistance in murine tumour models through β2-adrenergic receptor activation, Nat. Commun. 6 (2015) 6426,, https://doi.org/10.1038/ncomms7426.
[218] S. Hassan, Y. Karpova, D. Baiz, D. Yancey, A. Pullikuth, A. Flores, T. Register, J. M. Cline, R. D'Agostino, N. Danial, S.R. Datta, G. Kulik, Behavioral stress accelerates prostate cancer development in mice, J. Clin. Invest 123 (2013) 874–886, https://doi.org/10.1172/JCI63324.
[219] T. Shan, Q. Ma, D. Zhang, K. Guo, H. Liu, F. Wang, E. Wu, β2-adrenoceptor blocker synergizes with gemcitabine to inhibit the proliferation of pancreatic cancer cells via apoptosis induction, Eur. J. Pharm. 665 (2011) 1–7, https://doi.org/10.1016/j.ejphar.2011.04.055.
[220] X. Lin, K. Luo, Z. Lv, J. Huang, Beta-adrenoceptor action on pancreatic cancer cell proliferation and tumor growth in mice, Hepatogastroenterology 59 (2012) 584–588, https://doi.org/10.5754/hge11271.
[221] M. Dal Monte, I. Fornaciari, G.P. Nicchia, M. Svelto, G. Casini, P. Bagnoli, β3-adrenergic receptor activity modulates melanoma cell proliferation and survival through nitric oxide signaling, Naunyn Schmiede Arch. Pharm. 387 (2014) 533–543, https://doi.org/10.1007/s00210-014-0969-1.
[222] M. Coelho, C. Soares-Silva, D. Brandão, F. Marino, M. Cosentino, L. Ribeiro, β-Adrenergic modulation of cancer cell proliferation: available evidence and clinical perspectives, J. Cancer Res Clin. Oncol. 143 (2017) 275–291, https://doi.org/10.1007/s00432-016-2278-1.

[223] X. Huang, H. Wang, Z. Yuan, J. Huang, Q. Zheng, Norepinephrine stimulates pancreatic cancer cell proliferation, migration and invasion via β-adrenergic receptor-dependent activation of P38/MAPK pathway, Hepatogastroenterology 59 (2012) 889–893, https://doi.org/10.5754/hge11476.
[224] A.E. Carie, S.M. Sebti, A chemical biology approach identifies a beta-2 adrenergic receptor agonist that causes human tumor regression by blocking the Raf-1/Mek-1/Erk1/2 pathway, Oncogene 26 (2007) 3777–3788, https://doi.org/10.1038/sj.onc.1210172.
[225] C.P. Piñero, A. Bruzzone, M.G. Sarappa, L.F. Castillo, I.A. Lüthy, Involvement of α2- and β2-adrenoceptors on breast cancer cell proliferation and tumour growth regulation, Br. J. Pharmacol. 166 (2012) 721–736, https://doi.org/10.1111/j.1476-5381.2011.01791.x.
[226] M. Dal Monte, G. Casini, L. Filippi, G.P. Nicchia, M. Svelto, P. Bagnoli, Functional involvement of β3-adrenergic receptors in melanoma growth and vascularization, J. Mol. Med. (Berl.) 91 (2013) 1407–1419, https://doi.org/10.1007/s00109-013-1073-6.
[227] M. Dal Monte, I. Fornaciari, G.P. Nicchia, M. Svelto, G. Casini, P. Bagnoli, β3-adrenergic receptor activity modulates melanoma cell proliferation and survival through nitric oxide signaling, Naunyn Schmiede Arch. Pharmacol. 387 (2014) 533–543, https://doi.org/10.1007/s00210-014-0969-1.
[228] L. R. Gomes, L. F. Terra, M. C. Sogayar, L. Labriola, Epithelial-mesenchymal transition: implications in cancer progression and metastasis, Curr. Pharm. Biotechnol. 12 (2011) 1881–1890, https://doi.org/10.2174/138920111798377102.
[229] T. Shan, X. Cui, W. Li, W. Lin, Y. Li, X. Chen, T. Wu, Novel regulatory program for norepinephrine-induced epithelial-mesenchymal transition in gastric adenocarcinoma cell lines, Cancer Sci. 105 (2014) 847–856, https://doi.org/10.1111/cas.12438.
[230] J.P. Thiery, H. Acloque, R.Y.J. Huang, M.A. Nieto, Epithelial-mesenchymal transitions in development and disease, Cell 139 (2009) 871–890, https://doi.org/10.1016/j.cell.2009.11.007.
[231] J. Yu, Q. Cao, R. Mehra, B. Laxman, J. Yu, S.A. Tomlins, C.J. Creighton, S. M. Dhanasekaran, R. Shen, G. Chen, D.S. Morris, V.E. Marquez, R.B. Shah, D. Ghosh, S. Varambally, A.M. Chinnaiyan, Integrative genomics analysis reveals silencing of β-Adrenergic signaling by polycomb in prostate cancer, Cancer Cell 12 (2007) 419–431, https://doi.org/10.1016/j.ccr.2007.10.016.
[232] A. Jaśkiewicz, B. Pająk, A. Orzechowski, The Many Faces of Rap1 GTPase, Int. J. Mol. Sci. 19 (2018) 2848, https://doi.org/10.3390/ijms19102848.
[233] J. Folkman, K. Watson, D. Ingber, D. Hanahan, Induction of angiogenesis during the transition from hyperplasia to neoplasia, Nature 339 (1989) 58–61, https://doi.org/10.1038/339058a0.
[234] W. Li, H. Kohara, Y. Uchida, J.M. James, K. Soneji, D.G. Cronshaw, Y.-R. Zou, T. Nagasawa, Y.-S. Mukouyama, Peripheral nerve-derived CXCL12 and VEGF-A regulate the patterning of arterial vessel branching in developing limb skin, Dev. Cell 24 (2013) 359–371, https://doi.org/10.1016/j.devcel.2013.01.009.
[235] Y. Mukouyama, D. Shin, S. Britsch, M. Taniguchi, D.J. Anderson, Sensory nerves determine the pattern of arterial differentiation and blood vessel branching in the skin, Cell 109 (2002) 693–705, https://doi.org/10.1016/s0092-8674(02)00757-2.
[236] K.S. Madden, M.J. Szpunar, E.B. Brown, β-Adrenergic receptors (β-AR) regulate VEGF and IL-6 production by divergent pathways in high β-AR-expressing breast cancer cell lines, Breast Cancer Res. Treat. 130 (2011) 747–758, https://doi.org/10.1007/s10549-011-1348-y.
[237] S.K Lutgendorf, D.M. Lamkin, N.B. Jennings, J.M. Penedo, K. DeGeest, R. R. Langley, J.A. Lucci III, S.W. Cole, D.M. Lubaroff, A.K. Sood, Biobehavioral influences on matrix metalloproteinase expression in ovarian carcinoma, Cancer Res. 14 (2008), https://doi.org/10.1158/1078-0432.CCR-08-0230.
[238] E.V. Yang, S. Kim, E.L. Donovan, M. Chen, A.C. Gross, J.I. Webster Marketon, S. H. Barsky, R. Glaser, Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression, Brain Behav. Immun. 23 (2009) 267–275, https://doi.org/10.1016/j.bbi.2008.10.005.
[239] M. Hulsurkar, Z. Li, Y. Zhang, X. Li, D. Zheng, W. Li, Beta-adrenergic signaling promotes tumor angiogenesis and prostate cancer progression through HDAC2-mediated suppression of thrombospondin-1, Oncogene 36 (2017) 1525–1536, https://doi.org/10.1038/onc.2016.319.
[240] Z. Huang, G. Li, Z. Zhang, R. Gu, W. Wang, X. Lai, Z.-K. Cui, F. Zeng, S. Xu, F. Deng, β2AR-HIF-1α-CXCL12 signaling of osteoblasts activated by isoproterenol promotes migration and invasion of prostate cancer cells, BMC Cancer 19 (2019) 1142, https://doi.org/10.1186/s12885-019-6301-1.
[241] M. Calvani, F. Pelon, G. Comito, M.L. Taddei, S. Moretti, S. Innocenti, R. Nassini, G. Gerlini, L. Borgognoni, F. Bambi, E. Giannoni, L. Filippi, P. Chiarugi, Norepinephrine promotes tumor microenvironment reactivity through β3-adrenoreceptors during melanoma progression, Oncotarget 6 (2015) 4615–4632, https://doi.org/10.18632/oncotarget.2652.
[242] J. Lee, S.Y. Park, E.K. Lee, C.G. Park, H.C. Chung, S.Y. Rha, Y.K. Kim, G.-U. Bae, B. K. Kim, J.-W. Han, H.Y. Lee, Activation of hypoxia-inducible factor-1alpha is necessary for lysophosphatidic acid-induced vascular endothelial growth factor expression, Clin. Cancer Res. 12 (2006) 6351–6358, https://doi.org/10.1158/1078-0432.CCR-06-1252.
[243] L. Qi, F. Zhu, S.-H. Li, L.-B. Si, L.-K. Hu, H. Tian, Retinoblastoma binding protein 2 (RBP2) promotes HIF-1α-VEGF-induced angiogenesis of non-small cell lung cancer via the Akt pathway, PLoS One 9 (2014) e106032, https://doi.org/10.1371/journal.pone.0106032.
[244] G. Bergers, L.E. Benjamin, Tumorigenesis and the angiogenic switch, Nat. Rev. Cancer 3 (2003) 401–410, https://doi.org/10.1038/nrc1093.
[245] S.K. Lutgendorf, D.M. Lamkin, N.B. Jennings, J.M.G. Arevalo, F. Penedo, K. DeGeest, R.R. Langley, J.A. Lucci, S.W. Cole, D.M. Lubaroff, A.K. Sood, Biobehavioral influences on matrix metalloproteinase expression in ovarian carcinoma, Clin. Cancer Res. 14 (2008) 6839–6846, https://doi.org/10.1158/1078-0432.CCR-08-0230.
[246] J.W. Pollard, Tumour-educated macrophages promote tumour progression and metastasis, Nat. Rev. Cancer 4 (2004) 71–78, https://doi.org/10.1038/nrc1256.
[247] M.C. Vinci, L. Bellik, S. Filippi, F. Ledda, A. Parenti, Trophic effects induced by alpha1D-adrenoceptors on endothelial cells are potentiated by hypoxia, Am. J. Physiol. Heart Circ. Physiol. 293 (2007) H2140–H2147, https://doi.org/10.1152/ajpheart.00390.2007.
[248] J.C. Teeters, C. Erami, H. Zhang, J.E. Faber, Systemic α1A-adrenoceptor antagonist inhibits neointimal growth after balloon injury of rat carotid artery, Am. J. Physiol. -Heart Circ. Physiol. 284 (2003) H385–H392, https://doi.org/10.1152/ajpheart.00658.2002.
[249] M.B. Sporn, The war on cancer, Lancet 347 (1996) 1377–1381, https://doi.org/10.1016/s0140-6736(96)91015-6.
[250] S. Valastyan, R.A. Weinberg, Tumor metastasis: molecular insights and evolving paradigms, Cell 147 (2011) 275–292, https://doi.org/10.1016/j.cell.2011.09.024.
[251] D. Spano, C. Heck, P. De Antonellis, G. Christofori, M. Zollo, Molecular networks that regulate cancer metastasis, Semin. Cancer Biol. 22 (2012) 234–249, https://doi.org/10.1016/j.semcancer.2012.03.006.
[252] T.L. Drell, J. Joseph, K. Lang, B. Niggemann, K.S. Zaenker, F. Entschladen, Effects of neurotransmitters on the chemokinesis and chemotaxis of MDA-MB-468 human breast carcinoma cells, Breast Cancer Res Treat. 80 (2003) 63–70, https://doi.org/10.1023/A:1024491219366.
[253] K. Masur, B. Niggemann, K.S. Zanker, F. Entschladen, Norepinephrine-induced migration of SW 480 colon carcinoma cells is inhibited by beta-blockers, Cancer Res. 61 (2001) 2866–2869.
[254] K. Lang, T.L. Drell, A. Lindecke, B. Niggemann, C. Kaltschmidt, K.S. Zaenker, F. Entschladen, Induction of a metastatogenic tumor cell type by neurotransmitters and its pharmacological inhibition by established drugs, Int. J. Cancer 112 (2004) 231–238, https://doi.org/10.1002/ijc.20410.
[255] K. Guo, Q. Ma, L. Wang, H. Hu, J. Li, D. Zhang, M. Zhang, Norepinephrine-induced invasion by pancreatic cancer cells is inhibited by propranolol, Oncol. Rep. 22 (2009) 825–830, https://doi.org/10.3892/or_00000505.
[256] A.K. Sood, R. Bhatty, A.A. Kamat, C.N. Landen, L. Han, P.H. Thaker, Y. Li, D. M. Gershenson, S. Lutgendorf, S.W. Cole, Stress hormone-mediated invasion of ovarian cancer cells, Clin. Cancer Res 12 (2006) 369–375, https://doi.org/10.1158/1078-0432.CCR-05-1698.
[257] C. Strell, B. Niggemann, M.J. Voss, D.G. Powe, K.S. Zänker, F. Entschladen, Norepinephrine promotes the β1-integrin-mediated adhesion of MDA-MB-231 cells to vascular endothelium by the induction of a GROα release, Mol. Cancer Res 10 (2012) 197–207, https://doi.org/10.1158/1541-7786.MCR-11-0130.
[258] B. Cui, Y. Luo, P. Tian, F. Peng, J. Lu, Y. Yang, Q. Su, B. Liu, J. Yu, X. Luo, L. Yin, W. Cheng, F. An, B. He, D. Liang, S. Wu, P. Chu, L. Tian, X. Liu, H. Luo, J. Xu, Y. Pan, Y. Wang, D. Li, P. Huang, Q. Yang, L. Zhang, B.P. Zhou, S. Liu, G. Xu, E.W.-F. Lam, K.W. Kelley, Q. Liu, Stress-induced epinephrine enhances lactate dehydrogenase A and promotes breast cancer stem-like cells, J Clin Invest. 129 (2019) 1030–1046, https://doi.org/10.1172/JCI121685.
[259] H.-J. Jang, H.-J. Boo, H.J. Lee, H.-Y. Min, H.-Y. Lee, Chronic stress facilitates lung tumorigenesis by promoting exocytosis of IGF2 in lung epithelial cells, Cancer Res 76 (2016) 6607–6619, https://doi.org/10.1158/0008-5472.CAN-16-0990.
[260] W. Wang, X. Guo, H. Dan, α2A-adrenergic receptor inhibits the progression of cervical cancer through blocking PI3K/AKT/mTOR pathway, Onco Targets Ther. 13 (2020) 10535–10546, https://doi.org/10.2147/OTT.S264409.
[261] B.L. Andersen, W.B. Farrar, D.M. Golden-Kreutz, R. Glaser, C.F. Emery, T. R. Crespin, C.L. Shapiro, W.E. Carson, Psychological, behavioral, and immune changes after a psychological intervention: a clinical trial, J. Clin. Oncol. 22 (2004) 3570–3580, https://doi.org/10.1200/JCO.2004.06.030.
[262] B.L. Andersen, W.B. Farrar, D. Golden-Kreutz, C.F. Emery, R. Glaser, T. Crespin, W.E. Carson, Distress reduction from a psychological intervention contributes to improved health for cancer patients, Brain Behav. Immun. 21 (2007) 953–961, https://doi.org/10.1016/j.bbi.2007.03.005.
[263] C.R. Rouleau, S.N. Garland, L.E. Carlson, The impact of mindfulness-based interventions on symptom burden, positive psychological outcomes, and biomarkers in cancer patients, Cancer Manag. Res. 7 (2015) 121–131, https://doi.org/10.2147/CMAR.S64165.
[264] S. Poletti, G. Razzini, R. Ferrari, M.P. Ricchieri, G.A. Spedicato, A. Pasqualini, C. Buzzega, F. Artioli, K. Petropulacos, M. Luppi, E. Bandieri, Mindfulness-Based stress reduction in early palliative care for people with metastatic cancer: a mixed-method study, Complement Ther. Med. 47 (2019) 102218, https://doi.org/10.1016/j.ctim.2019.102218.
[265] J.E. Bower, A.D. Crosswell, A.L. Stanton, C.M. Crespi, D. Winston, J. Arevalo, J. Ma, S.W. Cole, P.A. Ganz, Mindfulness meditation for younger breast cancer survivors: a randomized controlled trial, Cancer 121 (2015) 1231–1240, https://doi.org/10.1002/cncr.29194.
[266] C.A. Lengacher, K.E. Kip, J. Post-White, S. Fitzgerald, C. Newton, M. Barta, P. B. Jacobsen, M.M. Shelton, M. Moscoso, V. Johnson-Mallard, E. Harris, L. Loftus, C. Cox, N. Le, M. Goodman, J. Djeu, R.H. Widen, B.B. Bercu, T.W. Klein, Lymphocyte recovery after breast cancer treatment and mindfulness-based stress reduction (MBSR) therapy, Biol. Res Nurs. 15 (2013) 37–47, https://doi.org/10.1177/1099800411419245.
[267] Y. Song, Y. Gan, Q. Wang, Z. Meng, G. Li, Y. Shen, Y. Wu, P. Li, M. Yao, J. Gu, H. Tu, Enriching the Housing Environment for Mice Enhances Their NK Cell

Antitumor Immunity via Sympathetic Nerve-Dependent Regulation of NKG2D and CCR5, Cancer Res. 77 (2017) 1611–1622, https://doi.org/10.1158/0008-5472.CAN-16-2143.
[268] C. Liu, Y. Yang, C. Chen, L. Li, J. Li, X. Wang, Q. Chu, L. Qiu, Q. Ba, X. Li, H. Wang, Environmental eustress modulates β-ARs/CCL2 axis to induce anti-tumor immunity and sensitize immunotherapy against liver cancer in mice, Nat. Commun. 12 (2021) 5725, https://doi.org/10.1038/s41467-021-25967-9.
[269] S.M. Zick, J. Colacino, M. Cornellier, T. Khabir, K. Surnow, Z. Djuric, Fatigue reduction diet in breast cancer survivors: a pilot randomized clinical trial, Breast Cancer Res Treat. 161 (2017) 299–310, https://doi.org/10.1007/s10549-016-4070-y.
[270] M. Hernandez-Reif, T. Field, G. Ironson, J. Beutler, Y. Vera, J. Hurley, M. A. Fletcher, S. Schanberg, C. Kuhn, M. Fraser, Natural killer cells and lymphocytes increase in women with breast cancer following massage therapy, Int J. Neurosci. 115 (2005) 495–510, https://doi.org/10.1080/00207450590523080.
[271] M.R. Irwin, R. Olmstead, E.C. Breen, T. Witarama, C. Carrillo, N. Sadeghi, J.M. G. Arevalo, J. Ma, P. Nicassio, P.A. Ganz, J.E. Bower, S. Cole, Tai chi, cellular inflammation, and transcriptome dynamics in breast cancer survivors with insomnia: a randomized controlled trial, J. Natl. Cancer Inst. Monogr. 2014 (2014) 295–301, https://doi.org/10.1093/jncimonographs/lgu028.
[272] G. Mp, W.-G. Cm, R. Ac, G. Da, K. E, J. Bd, S. Rj, , Exercise and the immune system: taking steps to improve responses to cancer immunotherapy, J. Immunother. Cancer 9 (2021), https://doi.org/10.1136/jitc-2020-001872.
[273] P.L. Valenzuela, G. Saco-Ledo, A. Santos-Lozano, J.S. Morales, A. Castillo-García, R.J. Simpson, A. Lucia, C. Fiuza-Luces, Exercise Training and Natural Killer Cells in Cancer Survivors: Current Evidence and Research Gaps Based on a Systematic Review and Meta-analysis, Sports Med. - Open 8 (2022), https://doi.org/10.1186/s40798-022-00419-w.
[274] T.M. Zúñiga, F.L. Baker, K.A. Smith, H. Batatinha, B. Lau, M.P. Gustafson, E. Katsanis, R.J. Simpson, Acute exercise mobilizes NKT-like cells with a cytotoxic transcriptomic profile but does not augment the potency of cytokine-induced killer (CIK) cells, Front. Immunol. 13 (2022), https://doi.org/10.3389/fimmu.2022.938106.
[275] A.B. Bigley, K. Rezvani, C. Chew, T. Sekine, M. Pistillo, B. Crucian, C.M. Bollard, R. Simpson, Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells, Brain, Behav., Immun. 39 (2014), https://doi.org/10.1016/j.bbi.2013.10.030.
[276] T. Schauer, S.S. Djurhuus, C. Simonsen, K. Brasso, J.F. Christensen, The effects of acute exercise and inflammation on immune function in early-stage prostate cancer, Brain, Behav., Immun. - Health 25 (2022), https://doi.org/10.1016/j.bbih.2022.100508.
[277] R.M. Graff, H.E. Kunz, N.H. Agha, F.L. Baker, M. Laughlin, A.B. Bigley, M. M. Markofski, E.C. LaVoy, E Katsanis, R.A. Bond, C.M. Bollard, R.J. Simpson, β2-Adrenergic receptor signaling mediates the preferential mobilization of differentiated subsets of CD8+ T-cells, NK-cells and non-classical monocytes in response to acute exercise in humans, Brain, Behav., Immun. 74 (2018), https://doi.org/10.1016/j.bbi.2018.08.017.
[278] S. Dimitrov, T. Lange, J. Born, Selective mobilization of cytotoxic leukocytes by epinephrine, J. Immunol. 184 (2010), https://doi.org/10.4049/jimmunol.0902189.
[279] K. Krüger, A. Lechtermann, M. Fobker, K. Völker, F.C. Mooren, Exercise-induced redistribution of T lymphocytes is regulated by adrenergic mechanisms, Brain, Behav., Immun. 22 (2008), https://doi.org/10.1016/j.bbi.2007.08.008.
[280] F.L. Baker, A.B. Bigley, N.H. Agha, C.R. Pedlar, D.P. O'Connor, R.A. Bond, C. M. Bollard, E. Katsanis, R.J. Simpson, Systemic β-Adrenergic Receptor Activation Augments the ex vivo Expansion and Anti-Tumor Activity of Vγ9Vδ2 T-Cells, Front. Immunol. 10 (2019), https://doi.org/10.3389/fimmu.2019.03082.
[281] K Krüger, FC Mooren, T cell homing and exercise, Exerc Immunol Rev 13 (2007).
[282] B.K. Clifford, N.O. Kaakoush, N. Tedla, D. Goldstein, D. Simar, The effect of exercise intensity on the inflammatory profile of cancer survivors: A randomised crossover study, Eur. J. Clin. Investig. 53 (2023), https://doi.org/10.1111/eci.13984.
[283] Dufresne S, Guéritat J, Chiavassa S, Noblet C, Assi M, Rioux-Leclercq N, Rannou-Bekono F, Lefeuvre-Orfila L, Paris F, Rébillard A, Exercise training improves radiotherapy efficiency in a murine model of prostate cancer, FASEB J.34 (2020), doi: 10.1096/fj.201901728R.
[284] S.S. Djurhuus, C. Simonsen, B.G. Toft, S.N. Thomsen, S. Wielsøe, M.A. Røder, T. Hasselager, P.B. Østergren, H. Jakobsen, B.K. Pedersen, P. Hojman, K. Brasso, J.F. Christensen, Exercise training to increase tumour natural killer-cell infiltration in men with localised prostate cancer: a randomised controlled trial, BJU Int 131 (2023), https://doi.org/10.1111/bju.15842.
[285] L. Pedersen, M. Idorn, G.H. Olofsson, B. Lauenborg, I. Nookaew, R.H. Hansen, H. H. Johannesen, J.C. Becker, K.S. Pedersen, C. Dethlefsen, J. Nielsen, J. Gehl, B. K. Pedersen, Thor Straten P, Hojman P, Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution, Cell Metab 23 (2016), https://doi.org/10.1016/j.cmet.2016.01.011.
[286] E. Wennerberg, C. Lhuillier, M.D. Rybstein, K. Dannenberg, N.-P. Rudqvist, G. J. Koelwyn, L.W. Jones, S. Demaria, Exercise reduces immune suppression and breast cancer progression in a preclinical model, Oncotarget 11 (2020) 452, https://doi.org/10.18632/oncotarget.27464.
[287] D.M. Lamkin, K.P. Bradshaw, J. Chang, M. Epstein, J. Gomberg, K.P. Prajapati, V. H. Soliman, T. Sylviana, Y. Wong, K. Morizono, E.K. Sloan, S.W. Cole, Physical activity modulates mononuclear phagocytes in mammary tissue and inhibits tumor growth in mice, PeerJ 9 (2021), https://doi.org/10.7717/peerj.10725.
[288] Q. Feng, Z. Liu, X. Yu, T. Huang, J. Chen, J. Wang, J. Wilhelm, S. Li, J. Song, W. Li, Z. Sun, B.D. Sumer, B. Li, Y.X. Fu, J. Gao, Lactate increases stemness of CD8 + T cells to augment anti-tumor immunity, Nature Communications 13 (2022), https://doi.org/10.1038/s41467-022-32521-8.
[289] H. Rundqvist, P. Veliça, L. Barbieri, P.A. Gameiro, D. Bargiela, M. Gojkovic, S. Mijwel, S.M. Reitzner, D. Wulliman, E. Ahlstedt, J. Ule, A. Östman, R. S. Johnson, Cytotoxic T-cells mediate exercise-induced reductions in tumor growthz, eLife 9 (2020), https://doi.org/10.7554/eLife.59996.
[290] I.L. Gomes-Santos, Z. Amoozgar, A.S. Kumar, W.W. Ho, K. Roh, N.P. Talele, H. Curtis, K. Kawaguchi, R.K. Jain, D. Fukumura, Exercise Training Improves Tumor Control by Increasing CD8+ T-cell Infiltration via CXCR3 Signaling and Sensitizes Breast Cancer to Immune Checkpoint Blockade, Cancer Immunology Research 9 (2021), https://doi.org/10.1158/2326-6066.
[291] C. Rincón-Castanedo, A. Martín-Ruiz, S. Zazo, A.L. Luis Huertas, P.L. Valenzuela, M. Morán, S.J. Fleck, A. Santos-Lozano, M. Ramírez, F. Rojo, A. Lucia, Á. González-Murillo, C. Fiuza-Luces, Combined exercise intervention in a mouse model of high-risk neuroblastoma: effects on physical, immune, tumor and clinical outcomes, Exerc Immunol. Rev. 29 (2023) 86–110.
[292] E.C. LaVoy, C.M. Bollard, P.J. Hanley, J.W. Blaney, D.P. O'Connor, J.A. Bosch, R. J. Simpson, A single bout of dynamic exercise enhances the expansion of MAGE-A4 and PRAME-specific cytotoxic T-cells from healthy adults, Exerc. Immunol. Rev. 21 (2015).
[293] Z.-Y. Chen, Q.-N. Wang, Y.-H. Zhu, L.-Y. Zhou, T. Xu, Z.-Y. He, Y. Yang, Progress in the treatment of infantile hemangioma, Ann. Transl. Med 7 (2019) 692, https://doi.org/10.21037/atm.2019.10.47.
[294] D. Lee, E. Boscolo, J.T. Durham, J.B. Mulliken, I.M. Herman, J. Bischoff, Propranolol Targets Contractility of Infantile Hemangioma-derived Pericytes, Br. J. Dermatol. 171 (2014) 1129–1137, https://doi.org/10.1111/bjd.13048.
[295] B. Annabi, M.-P. Lachambre, K. Plouffe, R. Moumdjian, R. Béliveau, Propranolol adrenergic blockade inhibits human brain endothelial cells tubulogenesis and matrix metalloproteinase-9 secretion, Pharmacol. Res. 60 (2009) 438–445, https://doi.org/10.1016/j.phrs.2009.05.005.
[296] L. Zhang, H.-M. Mai, J. Zheng, J.-W. Zheng, Y.-A. Wang, Z.-P. Qin, K.-L. Li, Propranolol inhibits angiogenesis via down-regulating the expression of vascular endothelial growth factor in hemangioma derived stem cell, Int J. Clin. Exp. Pathol. 7 (2014) 48–55.
[297] M.D. Buck, D. O'Sullivan, E.L. Pearce, T cell metabolism drives immunity, J. Exp. Med. 212 (2015) 1345–1360, https://doi.org/10.1084/jem.20151159.
[298] A.O. Kamphorst, A. Wieland, T. Nasti, S. Yang, R. Zhang, D.L. Barber, B. T. Konieczny, C.Z. Daugherty, L. Koenig, K. Yu, G.L. Sica, A.H. Sharpe, G. J. Freeman, B.R. Blazar, L.A. Turka, T.K. Owonikoko, R.N. Pillai, S. S. Ramalingam, K. Araki, R. Ahmed, Rescue of exhausted CD8 T cells by PD-1-targeted therapies is CD28-dependent, Science 355 (2017) 1423–1427, https://doi.org/10.1126/science.aaf0683.
[299] T.L. Ben-Shaanan, M. Schiller, H. Azulay-Debby, B. Korin, N. Boshnak, T. Koren, M. Krot, J. Shakya, M.A. Rahat, F. Hakim, A. Rolls, Modulation of anti-tumor immunity by the brain's reward system, Nat. Commun. 9 (2018) 2723, https://doi.org/10.1038/s41467-018-05283-5.
[300] H. Mohammadpour, C.R. MacDonald, G. Qiao, M. Chen, B. Dong, B.L. Hylander, P.L. McCarthy, S.I. Abrams, E.A. Repasky, β2 adrenergic receptor-mediated signaling regulates the immunosuppressive potential of myeloid-derived suppressor cells, J. Clin. Investig. 129 (2019), https://doi.org/10.1172/JCI129502.
[301] M. Calvani, G. Bruno, M. Dal Monte, R. Nassini, F. Fontani, A. Casini, L. Cavallini, M. Becatti, F. Bianchini, F. De Logu, G. Forni, G. la Marca, L. Calorini, P. Bagnoli, P. Chiarugi, A. Pupi, C. Azzari, P. Geppetti, C. Favre, L. Filippi, β3 -Adrenoceptor as a potential immuno-suppressor agent in melanoma, Br. J. Pharmacol. 176 (2019) 2509–2524, https://doi.org/10.1111/bph.14660.
[302] R.P. Dawes, K.A. Burke, D.K. Byun, Z. Xu, P. Stastka, L. Chan, E.B. Brown, K. S. Madden, Chronic stress exposure suppresses mammary tumor growth and reduces circulating exosome TGF-β content via β-adrenergic receptor signaling in MMTV-PyMT Mice, 1178223420931511, Breast Cancer (Auckl.) 14 (2020), https://doi.org/10.1177/1178223420931511.
[303] E. Batlle, J. Massagué, Transforming growth factor-β signaling in immunity and cancer, Immunity 50 (2019) 924–940, https://doi.org/10.1016/j.immuni.2019.03.024.
[304] M. Yi, Y. Wu, M. Niu, S. Zhu, J. Zhang, Y. Yan, P. Zhou, Z. Dai, K. Wu, Anti-TGF-β/PD-L1 bispecific antibody promotes T cell infiltration and exhibits enhanced antitumor activity in triple-negative breast cancer, J. Immunother. Cancer 10 (2022) e005543, https://doi.org/10.1136/jitc-2022-005543.
[305] M. Yi, J. Zhang, A. Li, M. Niu, Y. Yan, Y. Jiao, S. Luo, P. Zhou, K. Wu, The construction, expression, and enhanced anti-tumor activity of YM101: a bispecific antibody simultaneously targeting TGF-β and PD-L1, J. Hematol. Oncol. 14 (2021) 27, https://doi.org/10.1186/s13045-021-01045-x.
[306] M. Yi, M. Niu, J. Zhang, S. Li, S. Zhu, Y. Yan, N. Li, P. Zhou, Q. Chu, K. Wu, Combine and conquer: manganese synergizing anti-TGF-β/PD-L1 bispecific antibody YM101 to overcome immunotherapy resistance in non-inflamed cancers, J. Hematol. Oncol. 14 (2021) 146, https://doi.org/10.1186/s13045-021-01155-6.
[307] M. Yi, M. Niu, Y. Wu, H. Ge, D. Jiao, S. Zhu, J. Zhang, Y. Yan, P. Zhou, Q. Chu, K. Wu, Combination of oral STING agonist MSA-2 and anti-TGF-β/PD-L1 bispecific antibody YM101: a novel immune cocktail therapy for non-inflamed tumors, J. Hematol. Oncol. 15 (2022) 142, https://doi.org/10.1186/s13045-022-01363-8.

[308] M. Horowitz, E. Neeman, E. Sharon, S. Ben-Eliyahu, Exploiting the critical perioperative period to improve long-term cancer outcomes, Nat. Rev. Clin. Oncol. 12 (2015) 213–226, https://doi.org/10.1038/nrclinonc.2014.224.
[309] E. Neeman, S. Ben-Eliyahu, The perioperative period and promotion of cancer metastasis: new outlooks on mediating mechanisms and immune involvement, Brain Behav. Immun. 30 (2013) S32–S40, https://doi.org/10.1016/j.bbi.2012.03.006.
[310] L. Sorski, R. Melamed, P. Matzner, H. Lavon, L. Shaashua, E. Rosenne, S. Ben-Eliyahu, Reducing liver metastases of colon cancer in the context of extensive and minor surgeries through β-adrenoceptors blockade and COX2 inhibition, Brain Behav. Immun. 58 (2016) 91–98, https://doi.org/10.1016/j.bbi.2016.05.017.
[311] X. Jing, F. Yang, C. Shao, K. Wei, M. Xie, H. Shen, Y. Shu, Role of hypoxia in cancer therapy by regulating the tumor microenvironment, Mol. Cancer 18 (2019) 157, https://doi.org/10.1186/s12943-019-1089-9.
[312] L. Schito, G.L. Semenza, Hypoxia-inducible factors: master regulators of cancer progression, Trends Cancer 2 (2016) 758–770, https://doi.org/10.1016/j.trecan.2016.10.016.
[313] S. Rey, G.L. Semenza, Hypoxia-inducible factor-1-dependent mechanisms of vascularization and vascular remodelling, Cardiovasc Res 86 (2010) 236–242, https://doi.org/10.1093/cvr/cvq045.
[314] D. Samanta, G.L. Semenza, Maintenance of redox homeostasis by hypoxia-inducible factors, Redox Biol. 13 (2017) 331–335, https://doi.org/10.1016/j.redox.2017.05.022.
[315] V. Albiñana, K. Villar Gómez de las Heras, G. Serrano-Heras, T. Segura, A. B. Perona-Moratalla, M. Mota-Pérez, J.M. de Campos, L.M. Botella, Propranolol reduces viability and induces apoptosis in hemangioblastoma cells from von Hippel-Lindau patients, Orphanet J. Rare Dis. 10 (2015) 118, https://doi.org/10.1186/s13023-015-0343-5.
[316] F.-Q. Wu, T. Fang, L.-X. Yu, G.-S. Lv, H.-W. Lv, D. Liang, T. Li, C.-Z. Wang, Y.-X. Tan, J. Ding, Y. Chen, L. Tang, L.-N. Guo, S.-H. Tang, W. Yang, H.-Y. Wang, ADRB2 signaling promotes HCC progression and sorafenib resistance by inhibiting autophagic degradation of HIF1α, J. Hepatol. 65 (2016) 314–324, https://doi.org/10.1016/j.jhep.2016.04.019.
[317] H. Chim, B.S. Armijo, E. Miller, C. Gliniak, M.A. Serret, A.K. Gosain, Propranolol induces regression of hemangioma cells through HIF-1α-mediated inhibition of VEGF-A, Ann. Surg. 256 (2012) 146–156, https://doi.org/10.1097/SLA.0b013e318254ce7a.
[318] M. Barathova, K. Grossmannova, P. Belvoncikova, V. Kubasova, V. Simko, R. Skubla, L. Csaderova, J. Pastorek, Impairment of Hypoxia-Induced CA IX by beta-blocker propranolol—impact on progression and metastatic potential of colorectal cancer cells, Int. J. Mol. Sci. 21 (2020) 8760, https://doi.org/10.3390/ijms21228760.
[319] B. Puzderova, P. Belvoncikova, K. Grossmannova, L. Csaderova, M. Labudova, S. Fecikova, J. Pastorek, M. Barathova, Propranolol, promising chemosensitizer and candidate for the combined therapy through disruption of tumor microenvironment homeostasis by decreasing the level of carbonic anhydrase IX, Int. J. Mol. Sci. 24 (2023) 11094, https://doi.org/10.3390/ijms241311094.
[320] A.M. Harris, B.W. Warner, J.M. Wilson, A. Becker, R.G. Rowland, W. Conner, M. Lane, K. Kimbler, E.B. Durbin, A.T. Baron, N. Kyprianou, Effect of alpha1-adrenoceptor antagonist exposure on prostate cancer incidence: an observational cohort study, J. Urol. 178 (2007) 2176–2180, https://doi.org/10.1016/j.juro.2007.06.043.
[321] T.J. Murtola, T.L.J. Tammela, L. Määttänen, M. Ala-Opas, U.H. Stenman, A. Auvinen, Prostate cancer incidence among finasteride and alpha-blocker users in the Finnish Prostate Cancer Screening Trial, Br. J. Cancer 101 (2009) 843–848, https://doi.org/10.1038/sj.bjc.6605188.
[322] H. Kanda, K. Ishii, Y. Ogura, T. Imamura, M. Kanai, K. Arima, Y. Sugimura, Naftopidil, a selective alpha-1 adrenoceptor antagonist, inhibits growth of human prostate cancer cells by G1 cell cycle arrest, Int J. Cancer 122 (2008) 444–451, https://doi.org/10.1002/ijc.23095.
[323] D. Yamada, H. Nishimatsu, S. Kumano, Y. Hirano, M. Suzuki, T. Fujimura, H. Fukuhara, Y. Enomoto, H. Kume, Y. Homma, Reduction of prostate cancer incidence by naftopidil, an α1-adrenoceptor antagonist and transforming growth factor-β signaling inhibitor, Int. J. Urol. 20 (2013) 1220–1227, https://doi.org/10.1111/iju.12156.
[324] A. Nakamura, W. Matsunaga, A. Gotoh, Autophagy induced by naftopidil inhibits apoptosis of human gastric cancer cells, Anticancer Res. 38 (2018) 803–809.
[325] E. Masachika, T. Kanno, T. Nakano, A. Gotoh, T. Nishizaki, Naftopidil induces apoptosis in malignant mesothelioma cell lines independently of α1-adrenoceptor blocking, Anticancer Res. 33 (2013) 887–894.
[326] Y. Kaku, A. Tsuchiya, T. Shimizu, A. Tanaka, T. Nishizaki, HUHS1015 suppresses colonic cancer growth by inducing necrosis and apoptosis in association with mitochondrial damage, Anticancer Res. 36 (2016) 39–48.
[327] Y. Hori, K. Ishii, H. Kanda, Y. Iwamoto, K. Nishikawa, N. Soga, H. Kise, K. Arima, Y. Sugimura, Naftopidil, a selective {alpha}1-adrenoceptor antagonist, suppresses human prostate tumor growth by altering interactions between tumor cells and stroma, Cancer Prev. Res (Philos.) 4 (2011) 87–96, https://doi.org/10.1158/1940-6207.CAPR-10-0189.
[328] R. Florent, L.-B. Weiswald, B. Lambert, E. Brotin, E. Abeilard, M.-H. Louis, G. Babin, L. Poulain, M. N'Diaye, Bim, Puma and Noxa upregulation by Naftopidil sensitizes ovarian cancer to the BH3-mimetic ABT-737 and the MEK inhibitor Trametinib, Cell Death Dis. 11 (2020) 380, https://doi.org/10.1038/s41419-020-2588-8.
[329] A. Bruzzone, C.P. Piñero, P. Rojas, M. Romanato, H. Gass, C. Lanari, I.A. Lüthy, α(2)-Adrenoceptors enhance cell proliferation and mammary tumor growth acting through both the stroma and the tumor cells, Curr. Cancer Drug Targets 11 (2011) 763–774, https://doi.org/10.2174/156800911796191051.
[330] D.M. Lamkin, H.Y. Sung, G.S. Yang, J.M. David, J.C.Y. Ma, S.W. Cole, E.K. Sloan, α2-Adrenergic blockade mimics the enhancing effect of chronic stress on breast cancer progression, Psychoneuroendocrinology 51 (2015) 262–270, https://doi.org/10.1016/j.psyneuen.2014.10.004.
[331] L.F. Castillo, E.M. Rivero, V. Goffin, I.A. Lüthy, Alpha2-adrenoceptor agonists trigger prolactin signaling in breast cancer cells, Cell. Signal. 34 (2017), https://doi.org/10.1016/j.cellsig.2017.03.003.
[332] S. Maccari, M. Buoncervello, B. Ascione, T. Stati, D. Macchia, S. Fidanza, L. Catalano, P. Matarrese, L. Gabriele, G. Marano, α-Adrenoceptor stimulation attenuates melanoma growth in mice, British Journal of Pharmacology. 179 (2022), https://doi.org/10.1111/bph.15731.
[333] N Kanno, G Lesage, JL Phinizy, S Glaser, H Francis, G Alpini, Stimulation of alpha2-adrenergic receptor inhibits cholangiocarcinoma growth through modulation of Raf-1 and B-Raf activities, Hepatol. 35 (2002), https://doi.org/10.1053/jhep.2002.33330.
[334] L.E. Anselmino, M.V. Baglioni, G. Reynoso, V.R. Rozados, O.G. Scharovsky, M. J. Rico, M. Menacho-Márquez, Potential effect of chloroquine and propranolol combination to treat colorectal and triple-negative breast cancers, Sci. Rep. 13 (2023) 7923, https://doi.org/10.1038/s41598-023-34793-6.
[335] Y. Lin, Y. Liu, Z. Gao, D. Jing, R. Bi, X. Cui, Q. Cao, Q. Zhao, R. Gao, Y. Su, S. Liu, M. Zhao, Y. Yang, A. Chen, B. Dai, X. Gao, Beta-adrenergic receptor blocker propranolol triggers anti-tumor immunity and enhances irinotecan therapy in mice colorectal cancer, Eur. J. Pharmacol. 949 (2023), https://doi.org/10.1016/j.ejphar.2023.175718.
[336] J. Hu, C. Chen, R. Lu, Y. Zhang, Y. Wang, Q. Hu, W. Li, S. Wang, O. Jing, H. Yi, W. Zhang, L. Chen, W. Huang, J. Luo, H.L. McLeod, R. Xu, Y. He, β-adrenergic receptor inhibitor and oncolytic herpesvirus combination therapy shows enhanced antitumoral and antiangiogenic effects on colorectal cancer, Front. Pharmacol. 12 (2021), https://doi.org/10.3389/fphar.2021.735278.
[337] J. Hu, R. Lu, Y. Zhang, W. Li, Q. Hu, C. Chen, Z. Liu, W. Zhang, L. Chen, R. Xu, J. Luo, H.L. McLeod, Y. He, β-adrenergic receptor inhibition enhances oncolytic herpes virus propagation through STAT3 activation in gastric cancer, Cell Biosci. 11 (2021) 174, https://doi.org/10.1186/s13578-021-00687-1.
[338] M. Chen, G. Qiao, B.L. Hylander, H. Mohammadpour, X.-Y. Wang, J.R. Subjeck, A. K. Singh, E.A. Repasky, Adrenergic stress constrains the development of anti-tumor immunity and abscopal responses following local radiation, Nat. Commun. 11 (2020) 1821, https://doi.org/10.1038/s41467-020-15676-0.
[339] R. Di Fonte, S. Strippoli, M. Garofoli, G. Cormio, S. Serratì, V. Loizzi, R. Fasano, F. Arezzo, M. Volpicella, A. Derakhshani, M. Guida, L. Porcelli, A. Azzariti, Cervical cancer benefits from trabectedin combination with the β-blocker propranolol: in vitro and ex vivo evaluations in patient-derived organoids, Front Cell Dev. Biol. 11 (2023) 1178316, https://doi.org/10.3389/fcell.2023.1178316.
[340] H. Satilmis, E. Verheye, P. Vlummens, I. Oudaert, N. Vandewalle, R. Fan, J. M. Knight, N. De Beule, G. Ates, A. Massie, J. Moreaux, A. Maes, E. De Bruyne, K. Vanderkerken, E. Menu, E.K. Sloan, K. De Veirman, Targeting the β2 -adrenergic receptor increases chemosensitivity in multiple myeloma by induction of apoptosis and modulating cancer cell metabolism, J. Pathol. 259 (2023) 69–80, https://doi.org/10.1002/path.6020.
[341] B.L. Hylander, C.J. Gordon, E.A. Repasky, Manipulation of ambient housing temperature to study the impact of chronic stress on immunity and cancer in mice, J. Immunol. 202 (2019) 631–636, https://doi.org/10.4049/jimmunol.1800621.