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Review

A primer on global molecular responses to exercise in skeletal muscle: Omics in focus

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Highlights

- This study presents a history of omics approaches applied to skeletal muscle exercise research.
- Skeletal muscle epigenome, transcriptome, and proteome/phosphoproteome are altered with acute and chronic resistance and endurance exercise.
- Gain/loss of function preclinical studies reveal mechanisms from human omic findings and provide insights into exercise response heterogeneity and the effects of aging and biological sex.
- Future studies on global molecular wiring in muscle using multi-omics methods will help researchers and clinicians understand and improve skeletal muscle health and performance.
- Integration of omics layers with advanced computational approaches—including information from single cell and nucleus omics technologies—will provide new insights into the molecular regulation of exercise in skeletal muscle.

Abstract

Advances in skeletal muscle omics has expanded our understanding of exercise-induced adaptations at the molecular level. Over the past 2 decades, transcriptome studies in muscle have detailed acute and chronic responses to resistance, endurance, and concurrent exercise, focusing on variables such as training status, nutrition, age, sex, and metabolic health profile. Multi-omics approaches, such as the integration of transcriptomic and epigenetic data, along with emerging ribosomal RNA sequencing advancements, have further provided insights into how skeletal muscle adapts to exercise across the lifespan. Downstream of the transcriptome, proteomic and phosphoproteomic studies have identified novel regulators of exercise adaptations, while single-cell/nucleus and spatial sequencing technologies promise to evolve our understanding of cellular specialization and communication in and around skeletal muscle cells. This narrative review highlights (a) the historical foundations of exercise omics in skeletal muscle, (b) current research at 3 layers of the omics cascade (DNA, RNA, and protein), and (c) applications of single-cell omics and spatial sequencing technologies to study skeletal muscle adaptation to exercise. Further elaboration of muscle's global molecular footprint using multi-omics methods will help researchers and practitioners develop more effective and targeted approaches to improve skeletal muscle health as well as athletic performance.

Keywords: Single cell; Epigenomics; Transcriptomics; Proteomics; Phosphoproteomics

1. Introduction

Omics encompasses the comprehensive analysis of various molecules within cells, providing a broad and powerful way to understand complex biological systems. Omics technologies enable the study of thousands of molecules simultaneously while determining how these molecules influence each other.[1] Advances in technology encourage the study of omics across molecular layers, including at the DNA (epigenomic), mRNA (transcriptomic), and protein (proteome and phosphoproteome) levels. Studying a combination of these or others (e.g., genome, metabolome, microbiome, lipidome) is known as a multi-omics approach. This holistic view of physiological processes can be valuable for understanding the complexities of skeletal muscle adaptations. Identifying the molecular wiring of skeletal muscle in response to exercise may help develop more effective and targeted strategies to improve human health and performance. The current review highlights (a) the foundations of exercise omics in skeletal muscle, (b) current omics research at 3 layers (DNA, RNA, and protein), and (c) applications of single-cell omics and spatial sequencing technologies to study skeletal muscle adaptations to exercise (Fig. 1). We also provide perspectives and directions for future skeletal muscle omics research as it relates to exercise.

2. The foundations of exercise omics in human skeletal muscle

Over 20 years have passed since the first observation of altered gene expression with endurance or resistance exercise in human skeletal muscle.[2–4] This work in humans was predated and stimulated by seminal pre-clinical studies done in the mid-1980s to mid-1990s, which provided proof-of-concept evidence for acute and chronic muscle contractile activity stimulating gene expression changes *in vivo*.[5–12] The earliest studies in humans and animals used targeted techniques that, while cutting edge at the time, are now considered rudimentary by contemporary

muscle research laboratories. Nevertheless, these foundational experiments birthed a revolution in "molecular exercise physiology".[13] Muscle contractions causing transient changes in mRNA levels of exercise-responsive genes, leading to protein accumulation and ultimately adaptation in human skeletal muscle has since become doctrinal.[14–16]

Expanding on the classic targeted gene expression work in muscle with exercise, the initial human muscle transcriptome studies with exercise involved array technology.[17–20] These studies evaluated protein-coding mRNAs with limited genomic coverage.[21] For example, the first human exercise study to apply "low-density" arrays to muscle samples assayed ~600 of the ~20,000 protein coding genes.[3] Even with this low coverage, the arrays captured several gene classes and established that the transcriptional response to a bout of resistance exercise is blunted in the muscle of older *vs.* younger men.[3] The observation of age-dependency for gene expression provided an initial molecular explanation for why aged skeletal muscle is less plastic during exercise training. Molecular impairments to exercise with age are still appreciated and studied to this day using more advanced molecular techniques. Initial surveys of gene expression with exercise in muscle laid the foundation for what has become an explosion of "exercise omics" research, which is rapidly accelerating due to technological advancements.

Considerable effort has been directed toward understanding exercise adaptation in skeletal muscle at the molecular level. Skeletal muscle is at the center of whole body function[22] and maintenance of a healthy lifespan, or "healthspan" (i.e., time lived in a healthy state). Understanding the molecular circuitry of muscle adaptation to exercise can reveal therapeutic targets to improve the human condition and enhance athletic performance. The coordinated attempts of ongoing large-scale multi-center trials are using multi-omics approaches to generate a comprehensive "omics map" of the molecular transducers of physical activity in muscle. The

National Institutes of Health (NIH) Molecular Transducers of Physical Activity Consortium (MoTrPAC) is one such effort aimed at providing comprehensive exercise omics across numerous tissues, including skeletal muscle.[23] The first major MoTrPAC research publication—which utilized endurance type exercise in rats—identified regulation of heat shock proteins as a conserved exercise response across numerous tissues.[24] This observation reinforced and expanded on what was observed by the first targeted gene expression studies evaluating the muscle response to contractile activity in animals[25,26] and the transcriptome response to exercise in humans.[3] Large "atlases" of omic responses to exercise in muscle coupled with open access data availability will help with the identification of novel regulators of mitochondrial biogenesis, metabolic health, fiber-type transitioning, muscle mass, contractile function, circadian rhythmicity, and tissue crosstalk that is known to occur with structured muscular activity.[16]

3. Transcriptomics—proliferation of exercise transcriptome studies in human skeletal muscle

The number of studies exploring the exercise transcriptome in skeletal muscle has increased steadily since the early 2000s. This trajectory is due primarily to rapid advancements in technology, including the emergence of high-coverage arrays and RNA-sequencing (RNA-seq).[21] A PubMed search for "skeletal muscle and transcriptome and exercise" returns 1 study published in 2001 and 74 studies in 2023.

At the present time, well-powered meta-analytical work has begun to decode the transcriptional underpinnings of exercise adaptation in human skeletal muscle.[27,28] A meta-analysis of 66 published exercise transcriptome studies (>1000 individuals, mostly human vastus lateralis muscle samples) reported that *nuclear receptor subfamily 4 group A member 3* (*NR4A3*) is highly responsive to both acute endurance and resistance exercise in muscle of young healthy

individuals.[27] NR4A3 protein was reported to regulate the metabolic response to muscle cell exercise *in vitro*,[27] which is consistent with gain and loss of function studies in muscle *in vivo*.[29–32] Recent human muscle transcriptome studies in unique populations reveal mRNAs associated with very long-term endurance[33] and resistance training adaptations,[34] the response to acute exercise in elite endurance athletes,[35] and the gene networks mediating muscle mass regulation under different loading conditions, which includes chronic resistance exercise.[36]

Literature on the transcriptome in muscle with exercise is now vast and has broadly focused on: global gene expression after acute resistance,[18,37–39] concurrent,[40] and endurance exercise featuring different time points across the recovery period;[18,19,41] how acute responses to a bout of exercise are altered by training status,[38,42,43] biological sex,[44] and nutrition;[45] chronic endurance[20,46–48] and resistance training adaptations[17,38] while factoring for age,[17,38,49–51] biological sex,[17,28,47] and metabolic health status;[52–54] response heterogeneity to resistance training;[55] gene expression profiles of athletes from divergent disciplines;[34,56] the effect of exercise on circadian rhythm;[18,57] divergent responses between oxidative and glycolytic fiber types after resistance and high-intensity interval exercise;[38,58] and differential responses to disparate exercise modes.[59] Key findings from some of these studies are elaborated in a recent review by Smith et al.[16] Three recent studies worth highlighting are those by Pataky et al.,[60] Edman et al.,[57] and Lavin et al.[55] Pataky et al.[60] reported that sex hormones are upstream regulators of the transcriptome response to different exercise training modes in men and women, and that this divergence is affected by age. Edman et al.[57] temporally resolved the 24-h time course of transcriptional responses to resistance exercise in human skeletal muscle and found that changes to protein-coding genes peak 8 h into recovery. They also showed that *MYC* is one of the most influential transcription factors directing the resistance exercise transcriptome, and that pulses of *MYC* are sufficient for hypertrophy in adult murine skeletal muscle.[60] Lavin et al.[55]

found that baseline skeletal muscle gene expression may be a more powerful predictor of the hypertrophy resulting from resistance exercise training than the training-induced transcriptome response. All these observations have implications with respect to exercise training response heterogeneity, where personalized exercise prescriptions for low responders could be directed by molecular attributes. Collectively, the web of protein-coding genes that are responsive to different types of exercise under different conditions is being unraveled at an accelerating rate.

Transcriptome studies are informative but not without limitations. One such limitation is that transcriptome techniques will not capture the influence of exercise on ribosome biogenesis. Ribosomal RNA (rRNA) is > 80% of the total RNA pool in skeletal muscle,[61] so rRNA is excluded from transcriptional profiling to enrich for mRNAs and other RNA species. However, an emerging area of interest is how the transcription of rRNA (i.e., ribosome biogenesis), which controls translational capacity and is highly sensitive to exercise in muscle,[62] contributes to different forms of training adaptation (e.g., endurance *vs.* resistance exercise).[63] There is also a growing appreciation for the role of ribosome specialization in skeletal muscle in response to exercise—that is, changes to ribosomes that allow for preferential translation of specific transcripts dependent on the condition.[64] Ribosome methylation sequencing (RiboMeth-seq), which analyzes the methylation status of rRNA, was recently leveraged to show that the rRNA methylome shifts in response to an acute hypertrophic stimulus in murine skeletal muscle.[65] Changes in rRNA methylation could represent a new form of ribosome specialization that contributes to muscle adaptation. Sequencing technologies such as RiboMeth-seq applied to muscle lays the groundwork for future studies evaluating the mechanistic role of rRNA methylation (and the epitranscriptome at large) during exercise. RiboMeth-seq findings can now be validated in humans and expanded on using novel techniques such as long-read RNA-seq,[66] which allows for the detection of RNA modifications at single molecule resolution.[67] Other

forms of RNA-seq, such as global run-on sequencing (GRO-seq) to identify real-time transcription and transcriptional regulatory elements,[68,69] may be informative for identifying the most transcriptionally active genes with exercise in human skeletal muscle. A recent study in mice used a related approach (i.e., sequencing of 5-ethenyl uridine labeled mRNA) to explore the contribution of nascent *vs.* stable mRNAs to global gene expression during hypertrophy in mice.[70] This approach identified key genes and pathways contributing to rapid muscle growth that are more influenced by active transcription *vs.* altered stability,[70] thereby providing insights into which regulatory processes could be targeted for interventions.

All exercise-responsive genes are now being characterized and catalogued across contexts and conditions.[27,28] With this information, differentially expressed gene lists can be cross-referenced with genes whose gain or loss of function are known to affect muscle biology in a fashion consistent with exercise adaptation. This type of analysis is what ultimately leads to effective interventions due to a knowledge of mechanism-of-action *vs.* simply evaluating correlations and relationships. Meta-analyses of *in vivo* rodent models found that at least 31 genes are mechanistically linked to improved endurance performance, and numerous are associated with muscle phenotypes.[71] Twenty-five muscle genes were implicated in the determination of fiber type.[72] At least 47 genes are causal for muscle hypertrophy.[73] Several of these gene products converge on mammalian target of rapamycin complex 1 (mTORC1), a central regulator of muscle growth,[74,75] or are linked to peroxisome proliferator-activated receptor γ coactivator-1 (PGC1), a driver of mitochondrial biogenesis and oxidative fiber type transitioning.[76–78] Many of the genes that were identified are endurance or resistance exercise-responsive in human skeletal muscle.[27,28,71,73] It is worth pointing out that preclinical models testing the necessity and/or sufficiency of genes for exercise adaptation typically involve a constitutive (or permanent) approach for knockdown or overexpression, which has limitations. As an example, it is well-

established that mTORC1 is central to the hypertrophic response to resistance training in skeletal muscle[75,79]; however, sustained induction in muscle fibers leads to pathology.[80,81] Murine genetic approaches for transiently inducing a gene or genes of interest in the absence of recombination specifically in skeletal muscle, as was recently done for *MYC,*[57] will become increasingly important for replicating the "pulsatile" nature of transcription after exercise and exploring the temporal contribution of exercise-mediated gene expression during adaptation. New knowledge from such approaches may help inform drug discovery for conditions of impaired muscle health or provide new targets for improving exercise performance. Characterizing the exercise transcriptome has shaped our understanding of muscle adaptation; however, mRNA levels are only a single readout of a multi-faceted and coordinated molecular interplay controlling muscle phenotype with exercise.

4. Epigenomics—insights into the epigenetic regulation of exercise adaptation

Upstream of transcription, epigenetic factors such as DNA methylation of promoter region CpGs control gene expression and contribute to exercise adaptation in muscle (Fig. 1). It was first reported in 2012 that DNA methylation of the promoter region of *PGC1α* is dynamically modified by acute endurance exercise in human skeletal muscle, thereby controlling *PGC1α* gene expression.[82] Efforts toward understanding the role of epigenetic regulation of exercise adaptation have since intensified.[51,83,84] Subsequent studies reported widespread methylome changes to DNA in promoters, enhancers, ribosomal DNA, and other regions with acute and chronic resistance[63,85,86] and endurance exercise[48,87,88] in human skeletal muscle tissue. Technologies such as reduced representation bisulfite sequencing (RRBS) and methylation arrays have made these types of discoveries possible, facilitating the analysis of thousands to millions of CpGs across different genomic contexts with high throughput and relatively low cost. These methods are tractable but still limited relative to whole genome bisulfite sequencing

(WGBS). WGBS is currently expensive and difficult to analyze due to the volume of data, but computational limitations will likely change in the immediate future, making such comprehensive analyses more accessible.

Corroborating and expanding on the human data, recent murine studies show that global DNA methylation specifically within muscle fiber nuclei (myonuclei) are dynamically modified by acute muscle loading[63,89,90] and high volume resistive run training.[91,92] Long-lasting changes to the DNA methylome resulting from hypertrophic exercise may facilitate future adaptations[91]; this emerging concept is known as epigenetic "muscle memory".[85,91] High-volume resistive exercise late in life can also decelerate the skeletal muscle DNA methylation aging "clock",[93,94] referred to as "biological age deceleration". The consequences of this deceleration may be improved healthspan. The muscle transcriptomic response to exercise, even late in life, overlaps with the transcriptome response to a known epigenetic reprogramming stimulus—Yamanaka Factor induction[95–97]—which may in part be due to methylome alterations by the exercise-responsive transcription factor MYC.[94] The precise mechanisms controlling DNA methylation in skeletal muscle with exercise are contentious and not well-understood,[98,99] but a role for MYC is emerging as a possible key factor.[100]

Accessibility of epigenetic profiling technologies has also paved the way for the multi-omics integration of DNA methylation with the transcriptome to infer epigenetic-transcriptional regulation in response to exercise in humans and rodents.[85,101,102] Ismaeel et al.[90] integrated the myonuclear transcriptome and methylome after an acute muscle growth stimulus (resistance exercise analogue) using a technique called binding and expression target analysis (BETA)[103] that was adapted for the methylome. This technique uses distance from transcription start sites and magnitude of methylation differences irrespective of direction (hypo- or hypermethylation)

to calculate a regulatory potential score for DNA methylation controlling transcription. BETA exposed a coordinated myonuclear molecular program that corresponded with the muscle metabolic response to muscle loading.[90] BETA was then applied to human muscle after a bout of resistance exercise and showed that methylome changes 30 min into recovery significantly corresponded with gene expression at 3 h, but not later time points of recovery.[57] A combined approach highlights the strength of integrating omics layers for understanding the molecular underpinning of exercise adaptation (Fig. 1). Histone modifications on DNA are also dynamic with acute and chronic resistance exercise[104,105] and after an endurance exercise bout[106] in human skeletal muscle. Changes to histones with exercise have recently been linked mechanistically to aspects of muscle adaptation.[107,108] These collective findings provide additional evidence for epigenetic regulation of exercise adaptation that deserves further exploration.

Other epigenetic regulators in skeletal muscle such as microRNAs (miRNAs), which affect mRNA levels and protein abundance without influencing the genetic code, have emerged as contributors to exercise adaptation. Muscle-enriched miRNAs, or myomiRs,[109] are sensitive to acute and chronic endurance exercise[110–112] and bouts of resistance exercise[113] in human skeletal muscle. Small RNA profiling (miRNome) identified miRNA-1 (miR-1) as the most abundant myomiR in skeletal muscle.[90,114] Studies show that miR-1 is exercise-responsive and a presumed negative regulator of muscle mass[115] that may act via regulation of the pentose phosphate pathway for biomass accumulation.[116,117] Upon contraction, miR-1 is released from muscle fibers in extracellular vesicles coinciding with muscle growth while promoting lipolysis in distant fat depots; data from exercising humans supports these observations.[118,119] In addition to the mature muscle fiber, miRNome analysis revealed that the myomiR miR-206 is the most abundant miRNA in activated myogenic progenitor cells.[120,121] In response to muscle loading, evidence suggests that miR-206 is communicated from muscle stem cells (satellite cells) to muscle fibers

and fibrogenic cells to influence the recipient cell transcriptome.[120–123] This communication can control extracellular matrix (ECM) remodeling to facilitate loading-induced muscle hypertrophy.[120–123] Alternative non-protein coding gene elements such as long non-coding RNAs (lncRNAs) are also responsive to endurance and resistance exercise in human muscle.[124] It has been shown that lncRNAs may influence aspects of muscle biology such as fiber type profile[125,126] and mass[127–129] via several avenues such as miRNA sponging and mRNA stabilization. The lncRNAs *cytoskeleton regulator RNA* (*CYTOR*; immune-related) and *myosin binding protein C2 Cis regulating lncRNA enhancer of myogenesis* (*MYREM*; muscle-fiber enriched), along with several others, have been linked to resistance exercise-induced skeletal muscle hypertrophic adaptation in humans.[130] Recently identified micropeptides can also originate from lncRNA transcripts and regulate muscle mass and performance.[131–133] Overall, the world of muscle epigenetics with exercise has been fostered by high-throughput omics approaches and is rapidly expanding to encompass several coordinated molecular layers and various RNA species.

5. Proteomics and phosphoproteomics—uncovering new regulators of exercise adaptation

Downstream of transcription, recent attention has deservingly been paid to proteomic and phosphoproteomic adaptations to exercise (Fig.1). Specific protein abundances and activation ultimately dictate phenotype in all cells. It is therefore important to comprehensively define the proteomic responses to acute and chronic exercise to better understand muscle plasticity. Advances in exploratory proteomic technology permit detailed characterization of specific skeletal muscle proteins at fiber type resolution in human biopsy samples.[134–136] Building on prior proteomic work in exercise-trained human muscle tissue[51,137–139] (which contains a variety of cell types beyond muscle fibers), proteins involved in transcription, mitochondrial function, calcium signaling, and fat and glucose metabolism were recently shown to be expressed in fiber

type-specific patterns using proteomics in human muscle after endurance exercise training.[140] The muscle fiber type-specific mitochondrial proteome with endurance training may be solely attributed to differences in total mitochondrial content.[141] Further interrogation of the mitochondrial proteome after high-intensity endurance training in human muscle revealed that enhancing electron flow to oxidative phosphorylation is more critical for increasing ATP generation than increasing oxidative phosphorylation machinery.[142] Alternatively, exercise that is too intense may elicit mitochondrial derangements.[143] Cross-sectional comparison to an age-matched control cohort also revealed a unique proteomic signature in the skeletal muscle of world-class master track and field athletes that is associated with superior muscle function.[144] Advances in protein detection technology have enabled a much deeper understanding of the complexities of exercise adaptation in muscle.

Together with advances in proteomic technologies, significant strides have been made in modeling exercise in pre-clinical settings.[145] Using a murine exercise approach called progressive weighted wheel running (PoWeR),[92,115,146] we recently leveraged BETA to link the late-life proteomic response to high-volume resistive exercise with the DNA methylome, suggesting coordinated regulation between these molecular layers.[147] Importantly, certain proteomic changes with exercise were correlated with muscle mass and function.[147] This type of analysis can provide guidance on potential therapeutic targets for improving muscle health. Numerous studies over the last few decades have broadly focused on the role of protein balance (i.e., rates of synthesis and breakdown) as well as mitochondrial turnover during adaptation to various forms of exercise; this work is reviewed elsewhere in great detail and will not be addressed here.[148–150] Combining high-coverage proteomic information with protein turnover information (i.e., dynamic or kinetic proteomics) using *in vivo* tracer technology may be the next frontier of proteomics in skeletal muscle exercise research.[151,152] Proteostasis is a process that is

disrupted by aging in skeletal muscle and may impair adaptive potential.[153] A combined "kinetic" approach to proteomics could reveal the mechanisms of proteostatic regulation with exercise and aging.

With respect to protein "activation", muscle phosphoproteomics after a single bout of high-intensity endurance exercise revealed widespread modifications in humans and rodents and uncovered unique regulation of adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) and store-operated calcium entry.[154] Phosphoproteomics of different exercise modalities unearthed the previously uncharacterized protein Chromosome 18 open reading frame 25 (C18ORF25) as an AMPK substrate and regulator of skeletal muscle contractile function.[155] In mice, phosphoproteomic profiling after maximal intensity contractions identified tripartite motif containing 28 (TRIM28) as a powerful but previously unrecognized regulator of muscle size and function.[156] In addition to the phosphoproteome, widespread changes to the protein acetylome (lysine acetyl sites on protein) are observed after high-intensity interval training and may influence muscle adaptation to exercise.[157] These initial studies reveal the discovery potential of characterizing post-translational modifications with exercise in skeletal muscle, leading to the identification of mechanisms.

The current recommended exercise prescription for health and wellbeing is a combination of endurance and resistance training (i.e., concurrent training).[158] Some evidence suggests that endurance training blunts adaptations to resistance training via "molecular interference" between activated AMPK and mTOR,[159] but this observation is not unanimous.[160] Recent phosphoproteomic work in human muscle has expanded our knowledge on the AMPK–mTOR axis with endurance exercise.[161] It will be illuminating to employ proteomic/phosphoproteomic approaches to concurrently trained muscle to provide clarity on the issue of "molecular

interference" and further refine optimal exercise prescriptions in different populations and conditions. Further advances in proteomic and phosphoproteomic detection technology as well as other protein modifications applied to human and rodent muscle tissue, combined with the development of translatable murine exercise training models within the last few years,[145,146,162] will facilitate further discovery of the mechanisms regulating acute exercise responses and chronic adaptations.

6. Exercise adaptation through the lens of single-cell omics

The application of RNA-seq to single cells (scRNA-seq) and nuclei (snRNA-seq) from muscle tissue[163–165] has provided a wealth of information on how diverse interstitial mononuclear cell populations and myonuclei behave and interact to support muscle adaptation.[166] This technology has also facilitated the discovery of novel and rare cell populations[164] and homeostatic states[167] in muscle. Computational algorithms such as RNAvelocity,[168] partition-based graph abstraction (PAGA),[169] Capybara,[170] CellChat,[168] and CellPhoneDB[171] are powerful tools that allow for the inference of cell fate and communication in these datasets.[172] When such tools are deployed in the study of severe injury-induced murine muscle regeneration and multiplexed with emerging techniques such as spatial transcriptomics, the complex but coordinated interactions between satellite cells, fibro-adipogenic progenitors (FAPs), immune cells such as macrophages and T-cells, endothelial cells, and other cell types to accomplish successful tissue reconstitution and restoration of function becomes apparent.[173,174] The effects of muscle injury are unique from exercise,[175,176] however, so applying these techniques and technologies in an exercise context in adult muscle is important for understanding adaptation in non-pathologic settings.

During surgical mechanical overload-induced hypertrophy in adult mice (an approach that typically does not involve catastrophic muscle injury and shares similarities with human

resistance exercise in several ways including omic responses[177,178]), scRNA-seq revealed a communication network connecting satellite cells to numerous cell types in muscle.[122] This same overload with single cell approach also revealed the diversity of macrophage populations and their influence on ECM regulation.[179] A combination of snRNA-seq during loading-induced muscle hypertrophy and recombination-independent satellite cell-specific lineage tracing in mice identified a subpopulation of satellite cells characterized by low levels of *Notch receptor 1* (*Notch1*), *nuclear factor erythroid 2-related factor 2* (*Nrf2*), and *glutamate–cysteine ligase modifier subunit* (*Gclm*) that fuse directly to muscle fibers without first proliferating.[180] Inducible cell-specific knockout experiments further emphasize how satellite cells and FAPs interact with each other and other cell types via various mechanisms to facilitate proper adaptation to loading.[120–122,181] Specifically, the cellular choreography that drives favorable remodeling of the ECM—a hallmark of well-trained endurance and/or resistance-trained muscle[91,182,183]—is of central importance. The successful remodeling of the ECM with exercise may be mediated by succinate released from the muscle fiber.[184] These data suggest ECM deposition is in part regulated by the muscle fiber itself. Further evidence for muscle fiber-specific ECM regulation is provided by significant enrichment of ECM transcripts specifically in myonuclei after an acute overload stimulus in mice as revealed by myonucleus-specific RNA-seq.[70]

Surgical mechanical overload in rodents is an informative tool for understanding hypertrophic skeletal muscle adaptation,[177,178] but non-surgical approaches may more closely reproduce the exercise response in humans.[145,162,185] Using our PoWeR approach in mice, snRNA-seq showed how satellite cells positively influence myonuclear transcriptional profiles following a bout of high-volume endurance/resistance exercise in trained mice.[186,187] This finding was corroborated and expanded on using mechanical overload and a genetically-inducible fusion-incompetent satellite cell model.[188] Non-hypertrophic unweighted wheel running in young and old mice

revealed a physical activity transcriptome signature in various immune cell populations at single cell resolution in muscle, as well as more youthful transcriptome and cell–cell communication profiles across all cell types.[189] Another study used scRNA-seq in muscle following wheel running in the context of healthy metabolism and diet-induced obesity.[190] In addition to identifying 7 discrete FAP populations in this study, ECM-related pathways in FAPs were upregulated by obesity but downregulated by unweighted wheel running. Circadian gene regulation in muscle with running was also enriched in FAPs. This study further emphasized the extent of intercellular communication that occurs in skeletal muscle with activity as several cell types were predicted to act upon FAPs via secreted factors. Finally, scRNA-seq provided evidence that long-term unweighted wheel running restores circadian gene expression in skeletal muscle FAPs and endothelial cells of aged animals.[191] Pre-clinical sc/snRNA-seq studies are emerging with respect to muscle loading, activity, and exercise that provide new insights on intercellular dynamics during adaptation, but the field is still in its infancy.

Currently, scRNA-seq studies involving exercise in human muscle are even more sparse than preclinical studies. One investigation revealed the heterogeneity of macrophages following acute resistance exercise[192]. A different study used scRNA-seq in muscle tissue after a bout of high-intensity interval exercise to reveal potentially unique myogenic cell responses.[193] Single cell and nucleus technology is still developing (albeit at a rapid pace), but it is worth mentioning that relatively low transcript coverage in sc/snRNAseq, variation introduced during extended cell/nuclear isolation and sample processing times, and a lack of consensus on the most robust analysis approaches are still shortcomings of these techniques at present. Nevertheless, advanced single cell and nucleus transcriptional analyses combined with methylome,[194,195] assay for transposase-accessible chromatin with high throughput sequencing (ATAC-Seq; chromatin accessibility),[163] and proteomics[196,197] at single cell and nucleus resolution will continue to

provide unprecedented information on the contributions of supporting cell types and myonuclei to muscle adaptations when combined with human exercise interventions.

7. Conclusion and future directions

The rapid advancement and expansion of omics technologies has revolutionized skeletal muscle exercise research. A multi-omics picture of several molecular layers (e.g., methylome, transcriptome, miRNome, proteome, phosphoproteome) in response to acute exercise and exercise training will not only help identify targets for therapy and performance enhancement but inform at which layer of regulation an intervention may be most effective. There are also numerous other omes (e.g., acetylome, ubiquitinome, glycosylome, lactylome, succinylome, palmitoylome, *etc*.) that quantify post-translational modifications—some of which also apply to histone proteins—that are likely influenced by exercise in skeletal muscle. There is significant crosstalk between these numerous different modifications.[198] It will be important to analyze these omes simultaneously, alongside technologies such as metabolomics, lipidomics, and others to understand how they influence one another during exercise in skeletal muscle, thereby providing a window into their contribution to known exercise-mediated phenotypes. With respect to study design, it will be important to move past "snapshot" analyses and perform omics studies with high temporal resolution. For example, it is generally believed that global molecular responses to an acute exercise bout at a given timepoint become smaller in magnitude as training progresses,[199] which is likely true in many instances. Recent evidence also indicates that peak molecular responses to a bout of exercise may "phase shift" to an earlier time point as training status improves.[200] Multi-omics time course studies will help to resolve which instance is most prevalent and explanatory across molecular layers. It will also be important to link omics to function outcomes in muscle such as muscle size, contractile performance, and metabolic health[90,147] to help guide therapeutic target discovery.

As the cost of omics analyses declines, single cell and nucleus RNA-seq and spatial transcriptomics in skeletal muscle with exercise will likely become more common. Single cell and nucleus omics (e.g., RNA-seq and ATAC-seq) will help unravel how exercise affects cell type proportions, cell state transitions, and myonuclear specialization. These techniques may resolve how myonuclei, which reside in syncytial muscle fibers, coordinate with one another during exercise adaptation to regulate myonuclear domains.[201] Spatial omics will also shed light on the molecular consequences of mononuclear cell type paracrine and physical interactions (e.g., satellite cells, endothelial cells, FAPs, macrophages) in muscle tissue with exercise. The successful adoption and integration of all omics mentioned will depend on advances in computational tools,[202] specifically those that leverage data mining, network-based integration, machine learning, and artificial intelligence. A timely example is a recent human exercise study that used RNA-seq combined with machine learning and *in silico* approaches to identify how adipose tissue metabolism is controlled by muscle-specific miRNA after resistance exercise;[119] traditional analyses were insufficient for identifying this connection.

Combining human omic discoveries with mechanistic gain- and loss-of-function insights from pre-clinical models will be a powerful approach for identifying new molecular players in exercise adaptation. Further understanding of the molecular circuitry of muscle adaptation across molecular layers and at cell and nucleus resolution will help with developing targeted approaches to improve muscle health and enhance athletic performance.

Authors' contributions

KAM and JRB wrote and edited the manuscript and prepared the figure. Both authors read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

Both authors declare that they have no competing interests.

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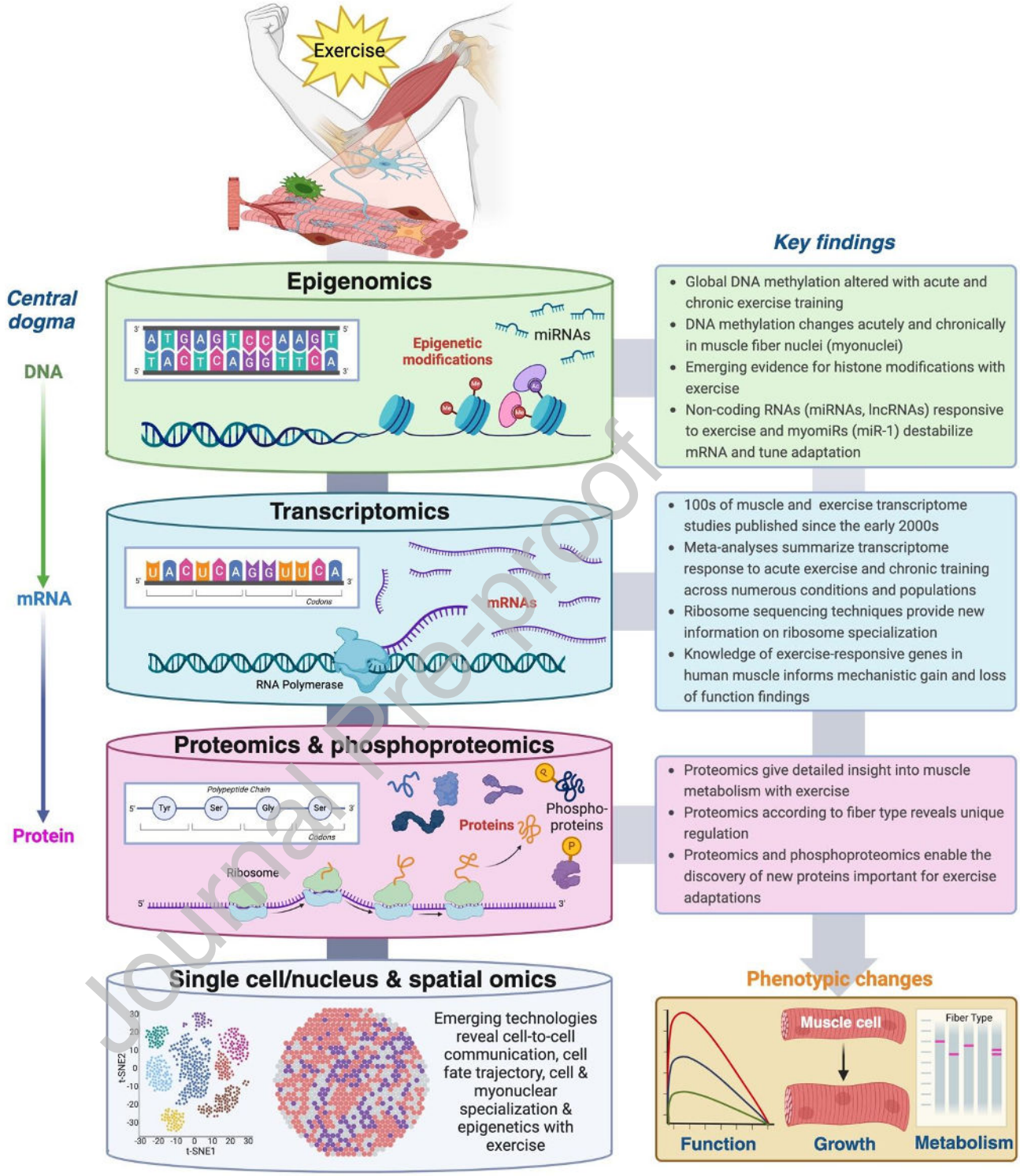

Fig. 1. Skeletal muscle omics cascade. Illustration of the global response to exercise in muscle cells, highlighting the "Central Dogma of molecular biology" with corresponding omics layers and key findings of skeletal muscle omics research. Gly = glycine; lncRNAs = long non-coding

RNAs; miRNA = microRNA; myomiRs = muscle-specific microRNAs; Ser = serine; Tyr = tyrosine.

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