Transcriptional memory in skeletal muscle. Don't forget (to) exercise

Thomas Beiter1 | Andreas M. Nieß1 | Dirk Moser2

1Department of Sports Medicine, University Hospital Tübingen, Tübingen, Germany
2Department of Genetic Psychology, Faculty of Psychology, Ruhr-University Bochum, Bochum, Germany

Correspondence
Thomas Beiter, Department of Sports Medicine, University Hospital Tübingen, Hoppe-Seyler-Str. 6, 72076 Tuebingen, Germany.
Email: thomas.beiter@med.uni-tuebingen.de

Abstract
Transcriptional memory describes an ancient and highly conserved form of cellular learning that enables cells to benefit from recent experience by retaining a mitotically inheritable but reversible memory of the initial transcriptional response when encountering an environmental or physiological stimulus. Herein, we will review recent progress made in the understanding of how cells can make use of diverse constituents of the epigenetic toolbox to retain a transcriptional memory of past states and perturbations. Specifically, we will outline how these mechanisms will help to improve our understanding of skeletal muscle plasticity in health and disease. We describe the epigenetic road map that allows skeletal muscle fibers to navigate through training-induced adaptation processes, and how epigenetic memory marks can preserve an autobiographical history of lifestyle behavior changes, pathological challenges, and aging. We will further consider some key findings in the field of exercise epigenomics to emphasize major challenges when interpreting dynamic changes in the chromatin landscape in response to acute exercise and training.

KEYWORDS
chromatin, DNA methylation, skeletal, DNA methylation, epigenomics, exercise, histones, microRNA, muscle, nuclear pore, skeletal

1 INTRODUCTION

The mammalian skeletal muscle is a peculiar tissue that is composed of bundles of multinucleated, post-mitotic myofibers with distinct contractile and metabolic properties, each endowed with a pool of resident progenitor cells, termed satellite cells (SCs), that confer powerful capability for regeneration (Egan & Zierath, 2013). Skeletal muscles provide locomotion and physical activity, maintain body posture, protect our skeleton and internal organs, regulate whole-body energy metabolism, and support immune homeostasis. Loss of muscle mass, strength, and metabolic capacity due to physical inactivity, overnutrition, pathological challenges, or aging inevitably promotes and is accompanied by the development of chronic diseases (including diabetes, cardiovascular disease, autoimmune diseases, cancer, and mental disorders) that threaten to become an escalating social, clinical, and economic burden of the 21st century (Alwan et al., 2010). At the same time, the unique capability of our muscles to adapt and change its mass, structural composition, and metabolic properties offers enormous potential to prevent and fight chronic inflammatory disease states by prescribing physical training programs.

Skeletal muscle adaptation to training results from the cumulative effects of frequently repeated bouts of exercise that transiently challenge whole-body homeostasis, and that acutely induce myofibrillar stress at the metabolic, inflammatory, and structural level. To better cope with recurrent exercise stress and to gain balanced improvements in biomechanical and metabolic economy/efficiency, skeletal muscle has to process multiple signaling inputs that have to be perceived, integrated and weighed against each other (Egan & Zierath, 2013).
The functional interplay of regulatory circuits that orchestrate and transduce this information to the level of gene expression is only partly understood (Hoppeler, 2016). Likewise, there is still no comprehensive understanding of how single-exercise stimuli are memorized, and when and how myofibrillar “decision-making” for stable changes in adaptive gene expression pattern is achieved.

A better understanding of the molecular mechanisms that govern skeletal muscle plasticity, however, is necessary to provide a fundamental basis for the development of individually tailored exercise training programs, not only to improve athletic performance but also to establish exercise-based prevention, rehabilitation, and therapy concepts to counteract deregulated skeletal muscle physiology in conditions of muscle wasting and chronic disease. In recent years, innovative methodological approaches in the fields of transcriptomics, proteomics and metabolomics have been exploited to study large-scale biological processes that participate in metabolic and structural remodeling of human skeletal muscle, both in response to acute exercise and long-term training stimulation (Catoire et al., 2012; Hoffman et al., 2015; Lindholm et al., 2016; Nader et al., 2014; Neubauer et al., 2014; Raue et al., 2012; Schild et al., 2015; Vissing & Schjerling, 2014). In combination, such studies have revealed a complex interplay between a myriad of signaling cascades that are physically and functionally interconnected to build up a continuous framework where each step from gene transcription to active protein feeds back to, depends on, and is influenced by regulatory input from diverse intracellular and extracellular pathways. If there is one protein feeds back to, depends on, and is influenced by regulatory input continuous framework where each step from gene transcription to active protein feeds back to, depends on, and is influenced by regulatory input from diverse intracellular and extracellular pathways. If there is one protein feeds back to, depends on, and is influenced by regulatory input from diverse intracellular and extracellular pathways.

A better understanding of the molecular mechanisms that govern skeletal muscle plasticity, however, is necessary to provide a fundamental basis for the development of individually tailored exercise training programs, not only to improve athletic performance but also to establish exercise-based prevention, rehabilitation, and therapy concepts to counteract deregulated skeletal muscle physiology in conditions of muscle wasting and chronic disease. In recent years, innovative methodological approaches in the fields of transcriptomics, proteomics and metabolomics have been exploited to study large-scale biological processes that participate in metabolic and structural remodeling of human skeletal muscle, both in response to acute exercise and long-term training stimulation (Catoire et al., 2012; Hoffman et al., 2015; Lindholm et al., 2016; Nader et al., 2014; Neubauer et al., 2014; Raue et al., 2012; Schild et al., 2015; Vissing & Schjerling, 2014). In combination, such studies have revealed a complex interplay between a myriad of signaling cascades that are physically and functionally interconnected to build up a continuous framework where each step from gene transcription to active protein feeds back to, depends on, and is influenced by regulatory input from diverse intracellular and extracellular pathways. If there is one protein feeds back to, depends on, and is influenced by regulatory input continuous framework where each step from gene transcription to active protein feeds back to, depends on, and is influenced by regulatory input from diverse intracellular and extracellular pathways. If there is one protein feeds back to, depends on, and is influenced by regulatory input from diverse intracellular and extracellular pathways.

2 | TRANSCRIPTIONAL MEMORY ENABLES LEARNING FROM EXPERIENCE

Intuitively, we link exercise training-induced skeletal muscle adaptation to beneficial effects, like enhanced performance, overall wellbeing, and healthy longevity. Viewed from a biochemical perspective, skeletal muscle adaptation is a cost-intensive process that consumes considerable amounts of energy and resources. Biological systems function on a maximum economy basis. Technically speaking, the metabolic costs that arise from functional, structural, and metabolic remodeling of skeletal muscle groups must somehow get weighed against the potential benefits to better cope with recurrent exercise. To get the optimal trade-off, skeletal muscle biochemical networks have to integrate mode, duration, and intensity of single-exercise bouts, and somehow have to develop a strategy based on the frequency of recurrent exercise regimes. Thus, skeletal muscle adaptation processes must at least partly rely on a system of adaptive thresholds to integrate the experience of previous bouts of exercise into its decision-making networks, or, simply spoken, skeletal muscle must retain a “memory” of its exercise history.

Retaining an epigenetic memory of past incidents is an efficient strategy of eukaryotic organisms to quantitatively and qualitatively adapt transcriptional responses after repeated encounters with the initial stimulus (D’Urso & Brickner, 2017). This “transcriptional memory” was initially described in yeast cells that, once fed with galactose instead of glucose, can remember this metabolic challenge and reactivate genes for galactose conversion more rapidly when encountering galactose again (Kundu, Horn, & Peterson, 2007). Reciprocally, genes that transiently become repressed during the first encounter with galactose show stronger and more rapid suppression in subsequent rounds of carbon-source shifts (B. B. Lee, Choi, et al., 2018). Intriguingly, these acquired traits become transmitted across cell generations and are maintained through multiple cell divisions. Similar mechanisms are exploited by plants to “remember” abiotic and biotic stresses, as evidenced by modified transcriptional responses, enhanced tolerance, or improved defense capacity when facing the same stressor again (Crisp, Ganguly, Eichten, Borevitz, & Pogson, 2016). In view of the fact that many epigenetic mechanisms and strategies are highly conserved between species, it is hardly surprising that also mammalian cells make use of transcriptional/epigenetic memory to recall past incidents and to use this stored knowledge for flexible adaptation of gene expression programs. Recent studies have provided evidence that transcriptional memory plays an important role in mammalian immunity, allowing innate immune cells to remember and to adaptively respond when challenged by repeated exposure to pathogenic and inflammatory stimuli, a phenomenon known as “trained innate immunity” (Dunn, McCuaig, Tu, Hardy, & Rao, 2015; Hamon & Quintin, 2016). The concept of “trained immunity” lead to a paradigm shift in immunology, since innate immune cells have traditionally been thought incapable to adapt or to preserve an active memory of prior exposure. Importantly, trained immunity responses have...
further been shown to become circumstantially readjusted to accommodate changing environmental conditions and challenges (Kamada et al., 2018).

As comprehensively reviewed by Adam Sharples and colleagues, there is ample evidence that also SCs can retain a mitotically inheritable "epi"-memory of prior physical activity, metabolic challenges, as well as of prior maladaptive states (Sharples, Stewart, & Seaborne, 2016). SCs are indispensable to promote muscle repair and regeneration, but their actual role(s) in adult skeletal muscle homeostasis and exercise adaptation is not comprehensively understood. It is commonly acknowledged that exercise-induced hypertrophy of skeletal muscle fibers is initiated/accompanied by SC activation and proliferation, and/or acquisition of extra fiber nuclei (myonuclei) from SC fusion (Blauw & Reggiani, 2014; Snijders et al., 2015). Experimental studies in rodents revealed that muscle fibers can acquire myonuclei from SCs during a period of resistance exercise or overload, and these extra nuclei can be maintained even during prolonged periods of detraining and atrophy, providing a long-lasting "muscle memory" that confers improved hypertrophic capacity when muscle mass and metabolic properties are reestablished (Bruusgaard, Johansen, Egner, Rana, & Gundersen, 2010; H. Lee, Kim, et al., 2018). It should, however, be mentioned that, in experimental models, hypotrophic responses in skeletal muscle have reportedly been observed without myonuclear accretion (Blauw et al., 2009; McCarthy et al., 2011). Similarly, a recent human study found no increase in myonuclear number that would accompany gains in muscle mass and force in the course of 10 weeks of leg strength training (Psilander et al., 2019). Further complication arises from a recent murine study that reported training-induced increases in myonuclear density but found no evidence for a retention of these newly recruited myonuclei that would last over a subsequent period of detraining (Dungan et al., 2019). Therefore it does not surprise that the question as to the overall contribution of SC fusion in resistance exercise adaptation is a matter of ongoing debate (Gundersen, 2016; Murach et al., 2018).

Far less questionable is the general notion that skeletal muscle is somehow capable of remembering hypertrophic exercise, even over prolonged periods of subsequent inactivity. One session of maximal eccentric exercise has been shown sufficient to imprint a "lasting impression" in the skeletal muscles of untrained individuals, as evidenced by a modified acute inflammatory response when challenged by a second bout of exercise 4 weeks later (Deyhle et al., 2015). Long-term protective memory effects that provide improved recovery from acute eccentric exercise could be demonstrated to last for up to 9 months when untrained males were initially challenged by a single bout of repeated maximal isometric contractions (Nosaka, Sakamoto, Newton, & Sacco, 2001). At the molecular level, 7 weeks of resistance exercise training have recently been proposed to leave distinct memory marks in the chromatin landscape that persisted over a 7-week period of complete detraining, becoming manifest in an improved capacity to regain muscle mass and strength when training was resumed (Seaborne et al., 2018). In contrast, long-term or lasting memory effects of endurance exercise and training are less well-studied and, due to the multilevel impact of endurance exercise adaptation on whole-body physiology, also less straightforward to assess. In a recent study using a within-subject design with single- and double-leg endurance exercise, no coherent evidence of a skeletal muscle memory at the functional level or global transcriptome level from 3 months of endurance training was found retained after 9 months of detraining, albeit the authors could not altogether exclude residual memory patterns when analyzing the skeletal muscle transcriptome after a second subsequent training period (Lindholm et al., 2016). Due to lack of studies focusing on this topic, it remains to be established whether endurance and resistance exercise are equally remembered, or whether there are differences in the length of memory (or the degree of memory dissipation) that is inflicted in our muscles by different training modes.

Over the course of prolonged exercise training, untrained skeletal muscles develop progressive adjustments in mechanic and energetic characteristics, affecting mitochondrial function and biogenesis, vascular supply, enzymatic equipment, activation patterning, structural composition of the contractile apparatus, and even complete reprogramming of fiber types (Egan & Zierath, 2013; Talbot & Maves, 2016), albeit the extent to which the latter occurs is not entirely clear (Wilson et al., 2012). Analogous to long-term and short-term epigenetic memory effects from previous experience of exercise stress or training, it seems conceivable that during the initiation phase of skeletal muscle adaptation, each exercise regime should leave distinct epigenetic/transcriptional memory marks to accumulate retrospective information that navigates subsequent phenotypic adaptations. Such transcriptional memory effects were recently illustrated for key genes involved in mitochondrial biogenesis, including the most versatile transcriptional coactivator in the control of energy metabolism, named peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α). During a 2-week period of high-intensity interval training, acute transcriptional response kinetics progressively changed after each successive training session, with gene-specific gradual adjustments in activation and resolution patterns (Perry et al., 2010).

In the following section, we will outline how skeletal muscle can make use of the epigenetic toolbox to retain a recollection of previous experience of exercise and training, enabling muscle fibers to respond differentially to subsequent bouts of exercise, thereby setting the scene for short-term and long-term adaptation processes. We have to emphasize that these mechanisms do not act in isolation but are part of a closely interconnected network of endogenous and exogenous signaling pathways, equally complex and fascinating, but still a long way from comprehensive understanding.

3 | EPIGENETIC FOUNDATIONS OF TRANSCRIPTIONAL MEMORY

3.1 | Chromatin modifications

The basic units of chromatin are the nucleosomes consisting of an octamer, formed by two copies each of the core histones H2A, H2B,
H3, and H4, around which ~146 bp of DNA are wrapped in almost two turns (Luger, Mader, Richmond, Sargent, & Richmond, 1997). Active transcription depends on and is associated with major changes in chromatin organization to modulate the accessibility of the DNA template for TFs, regulatory factors, and RNA Polymerase II (Pol II), and to facilitate passage of Pol II along the gene body (Venkatesh & Workman, 2015). Alterations of chromatin structure are commonly associated with covalent modifications of DNA and histones which may alter the physical properties of the nucleosome, and serve to recruit downstream effectors that promote, retard or modulate transcriptional activity. For instance, active genes generally are characterized by a lack of DNA methylation at their promoters and carry high levels of acetylated lysines on the tails of core histones H3 and H4 (H3/4Kac). In addition, transcriptional active genomic regions often show histones with di- or trimethylated lysine residues on H3 (H3K4me2/3) at their core promoters, and H3K36me3 along the gene body, whereas active enhancers often are enriched in H3K27ac and H3K4me1. Repressed loci typically show hypoacetylation of both H3 and H4, di- and trimethylation of H3 at K9 and K27 (H3K9me2/3, H3K27me3), and/or contain 5′-methylated DNA cytosine residues (5mC) at CG dinucleotides (CpG sites) in promoter or enhancer regions (Chen & Dent, 2014; Venkatesh & Workman, 2015). Intriguingly, hypomethylated CpG sites within regulatory regions may circumstantially be associated with “bivalent domains” of histone modifications, harboring both repressive marks, such as H3K27me3, and active marks, such as H3K4me3 (Jadhav et al., 2016; Kinkley et al., 2016; Sodersten et al., 2018; Weiner et al., 2016). Such seemingly “undecided” chromatin states preserve a higher rate of adaptive flexibility, allowing rapid changes in either direction (Figure 1).

DNA methylation and specific histone modifications appear to reciprocally influence each other at multiple levels, albeit the complexity of the underlying mechanisms has yet to be fully characterized (Du, Johnson, Jacobsen, & Patel, 2015). CpG dinucleotides are statistically underrepresented in mammalian genomes but spottily occur in dense clusters, so-called “CpG islands” that are typically defined as CG-rich regions with length greater than 200 bps, GC content greater than 50%, and an observed to expected CpG ratio greater than 0.6 (Illingworth & Bird, 2009). CpG islands commonly colocalize with promoters and transcriptional start sites (TSSs) and thus have been the focus of research in seminal studies on the function of DNA methylation. In contrast to the vast majority of CpGs located in intergenic regions and repetitive elements, CpG islands typically are not methylated, irrespective of the transcriptional activity of the adjacent gene, but promote gene silencing when becoming hypermethylated. While CpG methylation at TSSs generally (but not necessarily) is associated with gene silencing, recent studies have demonstrated that DNA methylation, when found in the gene body, can be positively correlated with gene transcription, and may have impact on alternative splicing events (reviewed in Jones, 2012). To complicate matters further, results from genome-wide studies of the DNA methyleome revealed that instructive methylation marks that define cell populations, as well as aberrant methylation patterns in disease states, often are not found in CpG islands but occur more frequently in distal regulatory regions such as enhancers and insulators, and in so-called “shore” regions that flank both sides of CpG islands (up to 2 kb in distance; Edgar, Tan, Portales-Casamar, & Pavlidis, 2014; Ziller et al., 2013).

DNA methylation at CpG sites has long been thought to represent a rather static epigenetic mark that is established during early development to define lineage-restriction, genomic imprinting, X-chromosome inactivation, and to silence repetitive regions. In contrast to this prevailing view, a number of recent studies provided hints for dynamic switching of DNA methylation in response to environmental cues, internal signals, and stressors (Emeny et al., 2018; Hartley et al., 2013; Magnusson et al., 2015; Sauderson et al., 2016). This suggests that differential methylation of CpG sites not only serves to establish epigenetic memory during lineage commitment and cell differentiation but might also contribute to adaptive transcriptional memory mechanisms.

While the predictive relationship between specific chromatin modifications and different states of transcriptional activity has been widely described in large-scale profiling studies, whether and in which ways distinct marks are instructive or permissive, cause or consequence of transcriptional activity is still a matter of ongoing debate. Some chromatin marks are lineage-specific or reflect cell-type-specific states that are inherited within the cell lineage, allowing the cells of our body to always remember what cell they are and from which cell they derive (Atlasi & Stunnenberg, 2017). Other chromatin

![FIGURE 1](image_url)
modifications are dynamically associated with acute transcriptional activity and do not persist after the initial stimulus that drives the modification has ceased (Katan-Khaykovich & Struhl, 2002). However, some marks can be retained as a memory of recent transcriptional activity and thereby preserve information for future transcriptional events. Memory-responsive genes can either remain in an activated or repressed state for more rapid expression or can be blunted to provide differential responsiveness when the initial stimulus is encountered again (Figure 1).

As reviewed previously, there is ample evidence from human studies and animal models that exercise sustainably alters the chromatin landscape in skeletal muscle, both acutely as well as in the long term (Jacques et al., 2019; Widmann, Niess, & Munz, 2019). As we will exemplify below, one of the most challenging tasks will be to disentangle which chromatin alterations arise from homeostatic perturbation, reflect random fluctuations, are mere passive bystanders of acutely increased or repressed transcription, and which are true epigenetic marks that prelude, establish, or maintain adaptive gene expression programs.

### 3.2 Nuclear pore proteins

How distal regulatory elements (like enhancers or repressors) identify, recognize, and interact with their target promoters in the three-dimensional nuclear space as yet is not fully understood. Recent studies indicate that enhancer–promoter contacts can be facilitated and stabilized by components of the nuclear pore complex (NPC) to establish a memory system for signal-dependent transcription (Pascual-Garcia et al., 2017). The NPCs, doughnut-shaped structures that penetrate the nuclear envelope membranes to provide a gateway between the nucleus and the cytoplasm, are modularly assembled from ~30 different proteins, termed nucleoporins (Nups), which are broadly conserved among eukaryotes (Grossman, Medalia, & Zwerger, 2012). Early studies in yeast demonstrated that many active genes physically interact with the NPC. Some of the inducible genes that relocate from the nucleoplasm to the NPC upon activation remain at the nuclear periphery after repression and thereby retain a spatial memory of prior exposure that promotes future reactivation when cells re-encounter the initial stimulus (Figure 2; Brickner & Walter, 2004; Brickner et al., 2007; Taddei et al., 2006). Similarly, hundreds of genes in human HeLa cells have been shown to exhibit interferon γ (IFN-γ)-induced transcriptional memory that persists over several rounds of cell division and requires the interaction of genes with the nucleoporin Nup98, leading to H3K4 dimethylation and binding of poised Pol II to the promoter (Gialitakis, Arampatzis, Makatounakis, & Papamatheakis, 2010; Light et al., 2013). Cells with poised genes react more rapidly and more strongly to IFN-γ than cells that have no memory of IFN-γ exposure. Remarkably, some Nups are not spatially restricted to the NPC but dynamically shuttle on and off the NPC (Rabut, Doye, & Ellenberg, 2004). These mobile Nups retain the ability to regulate gene activity in the nucleoplasm and actively participate in transcriptional control also at genomic loci that do not become positioned at the nuclear periphery (Capelson et al., 2010; Griffis, Craige, Dimaano, Ullman, & Powers, 2004; Kalverda, Pickersgill, Shiroma, & Fornerod, 2010; Liang, Franks, Marchetto, Gage, & Hetzer, 2013).

In mammalian cardiomyocytes, Nups have emerged to participate in controlling the cardiac hypertrophic growth program. Here, the nucleoporin Nup155 can interconnect with the repressive chromatin modifier histone deacetylase 4 (HDAC4) to keep sarcomeric genes and Ca2+-handling genes in a poised state that can rapidly be resolved by removal of HDAC4 in response to mitogenic signaling (Kehat, Accornero, Aronow, & Molkentin, 2011). Similarly, Nup-chromatin interactions are also crucial for temporal and spatial regulation of structural gene expression programs in skeletal muscle. During skeletal muscle differentiation, the muscle-specific Nup210 has been shown to become integrated into the NPC to scaffold the TF myocyte-specific enhancer factor 2C (Mef2C) at the NPC, promoting activation of target genes involved in sarcomere assembly, myofiber maturation, and muscle growth (Raices et al., 2017). Remarkably, this muscle-specific NPC-tethered gene expression network not only encompasses protein-coding genes but also distinct species of muscle-specific microRNAs.

### 3.3 microRNAs

microRNAs (miRNAs) are small endogenous noncoding RNAs of ~22 nucleotides that are processed from the stem-loop structures of

---

**FIGURE 2** Dynamic associations of genomic loci and regulatory regions with the nuclear pore complex (NPC) provide an architectural framework for transcriptional memory responses. Initial gene activation leads to translocation of the genomic locus from the nucleoplasm to NPCs through association with nucleoporins (Nups) in a manner dependent upon transcription factor (TF) binding, promoter–enhancer interactions, and chromatin modifiers. After cessation of the transcriptional trigger, the gene remains at the nuclear periphery in a memory state that can be rapidly reactivated. This way, NPCs provide a scaffold for topological genome organization and memory function.
precursor transcripts by the concerted action of nuclear and cytoplasmic enzyme complexes, crucially involving two ribonuclease (RNase) III enzymes termed Drosha and Dicer (Figure 3; Ha & Kim, 2014). Mature miRNAs mediate posttranscriptional gene silencing (PTGS) by guiding Argonaute (AGO) family proteins to target transcripts in the cytoplasm. Target recognition is conferred by canonical and noncanonical base-pairing within partially complementary recognition sites, termed miRNA responsive elements (MREs), predominantly but not exclusively located in the 3′-untranslated region of the target mRNA. AGO and miRNA comprise the functional core of the so-called RNA-induced silencing complex (RISC) that mediates translational repression and/or targeted mRNA deadenylation, decapping, and decay (Jonas & Izaurralde, 2015).

In mammals, miRNA action has long been thought restricted to cytoplasmic PTGS. However, there is accumulating evidence that some fraction of mammalian miRNAs may also execute important nuclear regulatory functions by controlling gene expression in the nucleus at both transcriptional and posttranscriptional levels, as well as by affecting alternative splice site selection (Roberts, 2014). In a set of elegant experiments, a significant fraction of miRNAs and several RISC components, including AGOs, have been identified to become located and functionally operative within the nucleus of human cells (Avivi et al., 2017; Bottini et al., 2017; Castanotto et al., 2018; Gagnon, Li, Chu, Janowski, & Corey, 2014; Ohrt et al., 2008; Sarshad et al., 2018; Weinmann et al., 2009). Nuclear localized miRNAs were found capable both to suppress and to stimulate transcriptional expression at distinct gene loci, involving direct and indirect interference pathways. Target RNA levels in the nucleus can be reduced through site-specific cleavage by AGO slicer activity (Gagnon et al., 2014), enabling nuclear RISC not only to mediate degradation of mRNAs but also of diverse noncoding nuclear RNA species that serve gene regulatory functions (H. Liu et al., 2018). By repressing the repressors, specific nuclear miRNAs thus can indirectly promote transcriptional gene activation, for example, via

**FIGURE 3** Overview of microRNA (miRNA) processing, mode of action, and cellular localization. Mature miRNAs are generated from hairpin-containing primary miRNAs (pri-miRNA) transcripts that are initially processed into ∼70-nucleotide stem-loop precursor miRNAs (pre-miRNA) by the nuclear DROSHA complex. After cytoplasmic translocation, pre-miRNAs are further cleaved by the DICER complex into ∼21-nucleotide miRNA duplexes. Eventually, the miRNA duplex is loaded onto an Argonaute (AGO) protein to form the RNA-induced silencing complex (RISC). One strand of the duplex (passenger strand) becomes removed. The remaining RNA strand (guide strand) confers specificity to mature miRISC that now recognizes its mRNA targets and mediates posttranscriptional gene silencing by target-specific mRNA deadenylation/decapping and decay. Circumstantially, mRNA targets can specifically be protected from degradation by association with distinct RNA-binding proteins. Mature miRNAs localize in multiple subcellular locations in the cytoplasm. On the rough endoplasmic reticulum, miRISC can interfere with the translation initiation process. Complexes of miRISCs and polysome-bound mRNAs can shuttle to the early/late endosomes for storage and/or degradation. Under certain cellular conditions, miRISCs can be selectively incorporated into multivesicular bodies (MVB) that act as transport intermediates between early and late endosomes, but can also fuse with the plasma membrane to release their intraluminal vesicles into the extracellular milieu. AGO-associated miRNAs can also translocate to the mitochondrion to promote translational activation or mRNA translational inhibition and decay. Finally, AGO-associated miRNAs can relocate to the nucleus to influence alternate splicing decisions and to control gene expression, at both transcriptional and posttranscriptional levels.
miRNA-directed degradation of miRNA precursors, long noncoding RNAs, and natural antisense transcripts (NATs) that convey epigenetic silencing of distinct gene loci in either a cis or a trans manner (Beiter, Reich, Williams, & Simon, 2009; H. Liu et al., 2018; Roberts, 2014). However, it appears that the functions of miRNAs in the nucleus extend beyond RNA degradation pathways. Through base-pairing interactions with nascent transcripts, as well as with noncoding enhancer RNAs (eRNAs) and promoter-associated RNAs (paRNAs), miRNA-AGO complexes in the nucleus may serve as target guides for effector proteins, providing a molecular scaffold to attract chromatin remodelers and epigenetic enzymes towards destined genomic locations (Catalanotto, Cogoni, & Zardo, 2016; Holoch & Moazed, 2015; Weinberg & Morris, 2016). Reciprocally, availability of chromatin-modifying enzymes and DNA methyltransferases can be affected via PTGS in the cytoplasm, which in turn will also modulate specific downstream effects on the chromatin landscape (Singh & Campbell, 2013). This complex interplay has recently been found crucial in the functional reprogramming of macrophages that develop endotoxin tolerance after repeated or chronic exposure to endotoxin (Seeley et al., 2018). Here, immune memory is patterned via endotoxin-induced miRNAs that promote adaptive transcriptional silencing of a subset of inflammatory genes by repressing a chromatin remodeler that governs the reactivity of these genes.

Not surprisingly, miRNAs appear to be among the prime candidates to fine-tune the networks for transcriptional memory to past stimuli. Studies on the spatiotemporal distribution and functionality of miRNAs indicate that miRNAs and associated proteins can shuttle between different subcellular compartments with localized functionality, including cytoplasmic-processing bodies (P-bodies), endoplasmic reticulum (ER), endosomes, multivesicular bodies, mitochondria, and nucleus, and may differentially be stored for “on demand” use as needed (Leung, 2015; Pitchiaya, Heinicke, Park, Cameron, & Walter, 2017; Trabucchi, 2019). Moreover, reversible posttranslational modifications of RISC components allow flexible and context-specific regulation of miRNA activity and miRNA localization in response to endogenous and exogenous stimulation (Leung, 2015).

Several studies reported quantitative changes of skeletal muscle miRNA profiles in response to exercise and training, as well as in the wake of ageing and disease. Moreover, experimental approaches provided links for specific miRNAs species to be crucially involved in skeletal muscle differentiation, regulation of skeletal muscle growth, and fiber-type transformation. In these fields, the reader is referred to excellent reviews published recently (Domanska-Senderowska et al., 2019; Kirby, Chaillou, & McCarthy, 2015; Margolis & Rivas, 2018; Ultimo et al., 2018). At present, deciphering the true implications of miRNAs in skeletal muscle adaptation and memory modules is puzzling as each miRNA potentially targets a large number of genes, indicating substantial pleiotropic functional redundancy (Eichhorn et al., 2014; Liufu et al., 2017). Many miRNAs belong to multigene families, which are predicted to target the same (or overlapping) sets of genes, and multiple miRNAs may work as miRNA modules to synergistically regulate common target mRNAs (Ding, Li, & Hu, 2015). Moreover, in high-throughput quantitative studies, target prediction is primarily based on bioinformatic identification of phylogenetically conserved miRNA-binding sites, a methodological approach that is highly prone to produce false positive results (Pinzon et al., 2017).

4 | SKELETAL MUSCLE, EXERCISE, AND FLEXIBLE EPIGENOME

In recent years, there is growing awareness that chromatin evolved with multiple functions that reach beyond the storage, propagation, and expression of genetic information. It has become evident that the cellular chromatin state is dynamically linked to metabolic and homeostatic perturbations, not only by providing a flexible platform for metabolic gene expression programs but also by acting as an intrinsic rheostat of carbon flux and cellular pH (van der Knaap & Verrijzer, 2016). As has been reviewed extensively elsewhere, the activity of histone- and nucleic acid-modifying enzymes relies on (and is influenced by) the availability of specific substrates, intermediates, and products from diverse metabolic pathways, including glycolysis, tricarboxylic acid cycle, fatty acid β-oxidation, methionine cycle, and glutamine metabolism (Etchegaray & Mostoslavsky, 2016; Li, Egervari, Wang, Berger, & Lu, 2018; Nieborak & Schneider, 2018; Reid, Dai, & Locasale, 2017; Schvartzman, Thompson, & Finley, 2018; Sharma & Rando, 2017; van der Knaap & Verrijzer, 2016). Consequently, shifts in substrate selection and energy provision in the exercising muscle may have multiple acute implications on chromatin dynamics and epigenetic modifications. An illustrative presentation of how metabolic activity can dynamically shape the overall chromatin landscape was recently provided by a comparative study of 11 non-tumorigenic and tumorigenic human cell lines, revealing that the cellular rate of glycolysis appeared strikingly reflected by the global level of histone acetylation (X. S. Liu, Little, & Yuan, 2015). There is emerging evidence that glycolytic flux directly feeds into histone acetylation, and the availability of acetyl-CoA, the preferred acetyl donor used by histone acetyltransferases (HATs), profoundly determines the abundance of histone lysine acetylation at a global scale (Cluntun et al., 2015; Simithy et al., 2017). Reciprocally, in cancer cells, global deacetylation of histones, mainly accomplished by HDACs, was found crucial to maintain intracellular pH homeostasis, mechanistically being coupled to the activity of monocarboxylate transporters that preserve physiological pH by pumping protons in a cotransport together with chromatin-derived acetate anions out of the cell (McBrian et al., 2013). It seems compelling to translate these findings to the exercising muscle when enhanced glycolytic flux becomes manifest in an accumulation of acetyl-CoA and a decrease of pH during energetically demanding contractile activity (Juel, 2008; Lundsgaard, Fritzen, & Kiens, 2018). Unfortunately, no experimental data are currently available concerning the kinetics and dynamics of global chromatin alterations during the course of prolonged contraction. What is evident is that exercise and skeletal muscle contraction provoke profound shifts in the balanced...
actions of HATs and HDACs, which have been conclusively linked to be involved in SC differentiation, metabolic adaptation, and regulation of muscle mass (Gaur et al., 2016; Hong et al., 2017; Mal, Sturmiolo, Schiltz, Ghosh, & Harter, 2001; McGee et al., 2008; McGee, Fairlie, Garnham, & Hargreaves, 2009; McKinsey, Zhang, & Olson, 2001; Moresi et al., 2010; Niu et al., 2017; Yang, Menconi, Wei, Petkova, & Hasselgren, 2005). Nuclear export of HDACs and temporarily increased global acetylation levels of H3K36 were detectable by western blot analysis immediately after a 60 min bout of intensive cycling exercise (McGee et al., 2009). Of note, acetylation of histones not only facilitates destabilization of DNA-nucleosome interactions for active transcription but, when provoked at a global scale, also promotes rearrangements in the three-dimensional genome architecture, thereby enabling extensive translocation of genomic loci and regulatory regions to the NPCs (Brown, Kennedy, Delmar, Forbes, & Silver, 2008). It remains yet to be deciphered how these multiple functional layers of chromatin conspire together, and how they can be integrated into current models of metabolic and adaptive programming in skeletal muscle.

In addition to global impacts on histone patterns, acute exercise also appears to affect the overall DNA methylation status in the contracting muscle. By the use of a methylation-sensitive restriction assay, a significant net decrease in whole-genome CpG methylation was observed in skeletal muscle samples from sedentary men and women after an acute bout of exhaustive cycling exercise (Barres et al., 2012). At the single-locus level, same authors reported acutely enhanced transcriptional activity and temporarily diminished methylation levels at the promoter regions of a selected set of known metabolic driver genes, including peroxisome proliferator-activated receptor γ (PPARG) and its “Jack of many trades” cofactor PGC-1α (PPARGC1A; Barres et al., 2012). Similarly, BeadChip profiling of bisulfite-converted DNA from skeletal muscle before and after an acute bout of resistance exercise revealed extensive changes in the DNA methylene, with a global trend towards acute hypomethylation of CpG sites (Seaborne et al., 2018). The same group analyzed differential basal methylation patterns provoked by chronic hypertrophy training, and deciphered several candidate genes that appear to become benchmarked at the start or in the course of resistance exercise training to become remembered in subsequent rounds of exercise (Seaborne et al., 2018). By comparing their differential methylation data with publicly available transcriptomic data sets, the authors further provided a list of putative “memory genes” that may exhibit differential responsiveness to recurrent resistance exercise stress (Turner, Seaborne, & Sharpe, 2019). Genome-wide DNA methylation profiles provided supportive evidence for DNA methylation/demethylation being also an integral part of the maintenance and memory programs that govern skeletal plasticity in response to endurance exercise training, revealing dynamic methylation signatures in enhancer regions that harbor putative binding motifs for several TFs known to control basic adaptive gene expression networks (Lindholm et al., 2016). Further, by use of methylated DNA immunoprecipitation method coupled with a promoter tiling array, altered methylation levels at promoter sites of several key genes attributed to skeletal muscle homeostasis have been reported to manifest after 6 week of endurance exercise (Nitert et al., 2012). A general trend towards reduced promoter methylation levels of genes involved in energy metabolism, myogenesis, contractile activity, and oxidative stress resistance became apparent when global methylation patterns in skeletal muscle of healthy aged men with a lifelong history of physical activity were compared to “couch potatoes” of the same age group (Sailani et al., 2019). Reciprocally, also “bad memories” inflicted by physical inactivity, unhealthy diet, and prenatal stress have been reported to become reflected by differential DNA methylation patterns in skeletal muscle tissue (Alibegovic et al., 2009; Jacobsen et al., 2012; Jacobsen et al., 2014; Nilsson & Ling, 2017; Nitert et al., 2012; Sharples, Polydorou et al., 2016; Sheppard et al., 2017).

A number of fascinating questions arise from these studies that will drive future work on skeletal muscle plasticity in health and disease. However, at present state, the overlap between published data sets is difficult to reconcile, and the establishment of causation in vivo is challenging. Issues that hamper data comparison include differences in study cohorts and study designs (mode, intensity, and duration of exercise and training), and a vast array of different methodological, analytical, and statistical approaches to detect, localize, and quantify physical activity-dependent methylation signatures. Data interpretation is further complicated by cell-type heterogeneity of biopsy material that may confound observed muscle-specific epigenetic patterns at variable degrees. This is specifically an issue when a huge mixed fiber-type muscle is represented by a small biopsy sample. Sample-to-sample variations may mimic or overshadow true methylation changes due to the differential contribution of fiber-type specific methylation marks (Begue, Raue, Jemiolo, & Trappe, 2017). To complicate matters further, distinct exercise regimes as well pathologies have distinct effects predominantly on particular fiber types, and the relative composition and size of muscle fibers can dramatically change in response to exercise, aging, or disease. Currently, it is even unclear whether all myonuclei in a muscle fiber share identical epigenetic signatures. But even within homogenous cell populations, the epigenome is known to exhibit stochastic cell-to-cell variation and also allelic variation between the two chromosomes within the same nucleus (Onuchic et al., 2018). Multiple patterns of methylation in regions of interest may simply arise from a dynamic equilibrium between constant gain and loss of methylation rather than reflecting meaningful biological differences (Edwards, Yarychkivska, Boulard, & Bestor, 2017; Lovkvist, Dodd, Sneppen, & Haerter, 2016). It is further crucial to distinguish changes on average methylation levels at a genomic locus from changes in methylation of specific individual CpGs that may instructively affect gene transcription function, that is when directly located within TF recognition sequences (Han, Shi, & Spivack, 2013; Lioznova et al., 2019; Maeder et al., 2013; Yin et al., 2017). Reciprocally, there is increasing evidence reinforcing the notion that DNA sequence polymorphisms that affect TF recognition seem to account for a substantial part of DNA methylation and chromatin pattern variability (Ball et al., 2009; Bell et al., 2011; Hellman & Chess, 2010; Kasowski et al., 2013; Onuchic et al., 2018). However, whether methylation at enhancers, promoters, and TSSs
generally controls or reacts to TF binding remains largely unexplored, and the ability to correctly assign a functional consequence to the local presence of DNA methylation so far has remained surprisingly limited (Luo, Hajkova, & Ecker, 2018; Schubeler, 2015). In the future, comprehensive screening approaches that integrate epigenetic, transcriptomic, and genotypic information (Birney, Smith, & Greally, 2016), as well as novel technologies for targeted methylome editing in experimental cell culture and animal models (Lei, Huang, & Greally, 2016), hold promise for a deeper understanding of exercise-dependent genomic methylation patterning and its contribution to adaptive skeletal muscle pathways.

5 | PERSPECTIVES

A better understanding of the molecular mechanisms involved in the control of skeletal muscle plasticity is fundamental to implement efficient and individually tailored exercise training programs that ameliorate or even restore disturbed energetics and metabolism in chronic disease states, and counteract diminished muscle strength and loss of muscle mass under physiological and pathophysiological conditions (including e.g. aging, malnutrition, disuse, obesity, diabetes, cancer, inflammation, neuromuscular disorders, and myopathies). Chromatin dynamics constitute a crucial part of the decision-making processes that enable the skeletal muscle to structurally and functionally adapt to variations in working demand, nutritional state, and environmental factors. By establishing epigenetic memory marks of recent and remote experience, muscles can preserve an autobiographical history that determines how an individual responds and adapts to lifestyle behavior changes, pathological challenges, and aging. Unquestionably, the reversible nature of epigenetic alterations provides novel opportunities and challenges for nonpharmacological and pharmacological intervention strategies in prophylaxis and therapy. In this context, one primary goal of exercise research will be to find suitable answers as to how targeted exercise regimes can be exploited to inflect good memories into our muscle and to erase bad memories from times of physical inactivity, overnutrition, or disease.

CONFLICT OF INTERESTS

No conflicts of interest, financial or otherwise, are declared by the authors.

ORCID

Thomas Beiter http://orcid.org/0000-0001-7299-7303

REFERENCES

Alibegovic, A. C., Hojbjerre, L., Sonne, M. P., van Hall, G., Stalknecht, B., Dela, F., & Vaag, A. (2009). Impact of 9 days of bed rest on hepatic and peripheral insulin action, insulin secretion, and whole-body lipolysis in healthy young male offspring of patients with type 2 diabetes. Diabetes, 58(12), 2749–2756. https://doi.org/10.2337/db09-0369

Allis, C. D., & Jenuwein, T. (2016). The molecular hallmarks of epigenetic control. Nature Reviews Genetics, 17(8), 487–500. https://doi.org/10.1038/nrg.2016.59

Alwan, A., Maclean, D. R., Riley, L. M., d’Espaignet, E. T., Mathers, C. D., Stevens, G. A., & Bettcher, D. (2010). Monitoring and surveillance of chronic non-communicable diseases: Progress and capacity in high-burden countries. Lancet, 376(9755), 1861–1868. https://doi.org/10.1016/S0140-6736(10)61853-3

Atias, Y., & Stunnenberg, H. G. (2017). The interplay of epigenetic marks during stem cell differentiation and development. Nature Reviews Genetics, 18(11), 643–658. https://doi.org/10.1038/nrg.2017.57

Avivi, S., Mor, A., Dotan, I., Tzadok, S., Kantor, I., Kinor, N., … Shav-Tal, Y. (2017). Visualizing nuclear RNAi activity in single living human cells. Proceedings of the National Academy of Sciences of the United States of America, 114(42), E8837–E8846. https://doi.org/10.1073/pnas.1707440114

Ball, M. P., Li, J. B., Gao, Y., Lee, J. H., LeProust, E. M., Park, I. H., … Lei, J. H. (2016). DNA methylation – making, breaking, and surveillance of cellular and long-term memory. Nature Biotechnology, 34(9), 851–858. https://doi.org/10.1038/nbt.3599

Barres, R., Yan, J., Egan, B., Treebak, J. T., Masmussen, M., Fritz, T., … Zierath, J. R. (2012). Acute exercise remodels promoter methylation in human skeletal muscle. Cell Metabolism, 15(3), 405–411. https://doi.org/10.1016/j.cmet.2012.01.001

Begue, G., Raue, U., Jemiolo, B., & Trappe, S. (2017). DNA methylation assessment from human slow- and fast-twitch skeletal muscle fibers. Journal of Applied Physiology, 122(4), 952–967. https://doi.org/10.1152/japplphysiol.00867.2016

Beiter, T., Reich, E., Williams, R. W., & Simon, P. (2009). Antisense transcription: A critical look in both directions. Cellular and Molecular Life Science, 66(1), 94–112. https://doi.org/10.1007/s00018-008-8831-y

Bell, J. T., Pai, A. A., Pickrell, J. K., Gaffney, D. J., Pique-Regi, R., Degner, J. F., … Pritchard, J. K. (2011). DNA methylation patterns associate with genetic and gene expression variation in HapMap cell lines. Genome Biology, 12(1), R10. https://doi.org/10.1186/gb-2011-12-1-r10

Birney, E., Smith, G. D., & Greally, J. M. (2016). Epigenome-wide association studies and the interpretation of disease-omics. PLOS Genetics, 12(6): e1006105. https://doi.org/10.1371/journal.pgen.1006105

Blaauw, B., Canato, M., Agatea, L., Toniolo, L., Mammucari, C., Masiero, E., … Reggiani, C. (2009). Inducible activation of Akt increases skeletal muscle mass and force without satellite cell activation. FASEB Journal, 23(11), 3896–3905. https://doi.org/10.1096/fj.09-131870

Blaauw, B., & Reggiani, C. (2014). The role of satellite cells in muscle hypertrophy. Journal of Muscle Research and Cell Motility, 35(1), 3–10. https://doi.org/10.1007/s10974-014-9376-y

Bottini, S., Hamouda-Tekaya, N., Mategot, R., Zaragosi, L. E., Audebert, S., Pisano, S., … Trabucchi, M. (2017). Post-transcriptional gene silencing mediated by microRNAs is controlled by nucleoplasmic Sfpq. Nature Communications, 8(1), 1189. https://doi.org/10.1038/s41467-017-01126-x

Brickner, D. G., Cajigas, I., Fondufe-Mittendorf, Y., Ahmed, S., Lee, P. C., Widom, J., & Brickner, J. H. (2007). H2A.Z-mediated localization of genes at the nuclear periphery confers epigenetic memory of previous transcriptional state. PLOS Biology, 5(4), e81. https://doi.org/10.1371/journal.pbio.0050081

Brickner, J. H., & Walter, P. (2004). Gene recruitment of the activated INO1 locus to the nuclear membrane. PLOS Biology, 2(11), e342. https://doi.org/10.1371/journal.pbio.0020342

Brown, C. R., Kennedy, C. J., Delmar, V. A., Forbes, D. J., & Silver, P. A. (2008). Global histone acetylation induces functional genomic reorganization at mammalian nuclear pore complexes. Genes and Development, 22(5), 627–639. https://doi.org/10.1101/gad.1632708
Holoch, D., & Moazed, D. (2015). RNA-mediated epigenetic regulation of gene expression. Nature Reviews Genetics, 16(2), 71–84. https://doi.org/10.1038/nrg3663

Hong, S., Zhou, W., Fang, B., Lu, W., Loro, E., Damle, M., Sun, Z. (2017). Dissociation of muscle insulin sensitivity from exercise endurance in mice by HDAC3 depletion. Nature Medicine, 23(2), 223–234. https://doi.org/10.1038/nmm4245

Hoppeler, H. (2016). Molecular networks in skeletal muscle plasticity. Journal of Experimental Biology, 219(Pt 2), 205–213. https://doi.org/10.1242/jeb.128207

Illingworth, R. S., & Bird, A. P. (2009). CpG islands—a rough guide. FEBS Letters, 583(11), 1713–1720. https://doi.org/10.1016/j.feblet.2009.04.012

Jacobsen, S. C., Brons, C., Bork-Jensen, J., Ribel-Madsen, R., Yang, B., Lara, E., Vaag, A. (2014). Effects of short-term high-fat feeding on genome-wide DNA methylation in the skeletal muscle of healthy young men. Diabetologia, 55(12), 3341–3349. https://doi.org/10.1007/s00125-012-2717-8

Jacobsen, S. C., Gillberg, L., Bork-Jensen, J., Ribel-Madsen, R., Lara, E., Calvanese, V., Vaag, A. (2014). Young men with low birthweight exhibit decreased plasticity of genome-wide DNA methylation by high-fat feeding. Diabetologia, 57(6), 1154–1158. https://doi.org/10.1007/s00125-014-3198-8

Jacques, M., Hiam, D., Craig, J., Barres, R., Eynon, N., & Voisin, S. (2019). Epigenetic changes in healthy human skeletal muscle following exercise: a systematic review. Epigenetics, 14(7), 633–648. https://doi.org/10.1080/15592294.2019.1614416

JadHAV, U., Nalapareddy, K., Saxena, M. O’, Neill, N. K., Pinello, L., Yuan, G. C., ... Shviddasani, R. A. (2016). Acquired tissue-specific promoter bivalency is a basis for PRC2 necessity in adult cells. Cell, 165(6), 1389–1400. https://doi.org/10.1016/j.cell.2016.04.031

Jonas, S., & Izaurrealde, E. (2015). Towards a molecular understanding of microRNA-mediated gene silencing. Nature Reviews Genetics, 16(7), 421–433. https://doi.org/10.1038/nrg3965

Jones, P. A. (2012). Functions of DNA methylation: Islands, start sites, Holoch, D., & Moazed, D. (2015). RNA transcriptional memory at the yeast GAL gene cluster. Genome Biology, 19(11), 187. https://doi.org/10.1186/s13059-018-1566-2

Leung, A. K. L. (2015). The whereabouts of microRNA actions: Cytoplasm and beyond. Trends in Cell Biology, 25(10), 601–610. https://doi.org/10.1016/j.tcb.2015.07.005

Li, X., Egervari, G., Wang, Y., Berger, S. L., & Lu, Z. (2018). Regulation of chromatin and gene expression by metabolic enzymes and metabolites. Nature Reviews Molecular Cell Biology, 19(9), 563–578. https://doi.org/10.1038/s41580-018-0029-7

Liang, Y., Frankis, T. M., Marchetto, M. C., Gage, F. H., & Hetzer, M. W. (2013). Dynamic association of NUP98 with the human genome. PLOS Genetics, 9(2), e1003308. https://doi.org/10.1371/journal.pgen.1003308

Light, W. H., Freaney, J., Sood, V., Thompson, A., D’Urso, A., Horvath, C. M., & Brickner, J. H. (2013). A conserved role for human Nup98 in altering chromatin structure and promoting epigenetic transcriptional memory. PLOS Biology, 11(3), e1001524. https://doi.org/10.1371/journal.pbio.1001524

Lindholm, M. E., Giacomello, S., Werne Solnestam, B., Fischer, H., Huss, M., Kjellqvist, S., & Sundberg, C. J. (2016). The impact of endurance training on human skeletal muscle memory, global isoform expression and resolution. Nature Communications, 7, 12514. https://doi.org/10.1038/ncomms12514

Kirby, T. J., Chailou, T., & McCarthy, J. J. (2015). The role of microRNAs in skeletal muscle health and disease. Frontiers in Bioscience, 20, 37–77. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25553440

Kundu, S., Horn, P. J., & Peterson, C. L. (2007). SWI/SNF is required for transcriptional memory at the yeast GAL gene cluster. Genes and Development, 21(8), 997–1004. https://doi.org/10.1101/gad.1506607

Lee, B. B., Choi, A., Kim, J. H., Jun, Y., Woo, H., Ha, S. D., ... Kim, T. (2018). Rpd3L HDAC links H3K4me3 to transcriptional repression memory. Nucleic Acids Research, 46(16), 8261–8274. https://doi.org/10.1093/nar/gky573

Lee, H., Kim, K., Kim, B., Shin, J., Rajan, S., Wu, J., ... Park, J. Y. (2018). A cellular mechanism of muscle memory facilitates mitochondrial remodelling following resistance training. Journal of Physiology, 596(18), 4413–4426. https://doi.org/10.1113/JP275308

Lei, Y., Huang, Y. H., & Goodell, M. A. (2018). DNA methylation and demethylation using hybrid site-targeting proteins. Genome Biology, 19(1), 187. https://doi.org/10.1186/s13059-018-1566-2

Liu, H., Lei, C., He, Q., Pan, Z., Xiao, D., & Tao, Y. (2018). Nuclear functions of mammalian MicroRNAs in gene regulation, immunity and cancer. Molecular Cancer, 17(1), 64. https://doi.org/10.1186/s12943-018-0765-5

Liu, X., Alarcon, J. B., & Yuan, Z. M. (2015). Glycolytic metabolism influences global chromatin structure. Oncotarget, 6(4), 4214–4225. https://doi.org/10.18632/oncotarget.2929

Liu, Z., Zhao, Y., Guo, L., Miao, G., Xiao, J., Lyu, Y., Wu, C. I. (2017). Redundant and incoherent regulations of multiple phenotypes suggest microRNAs’ role in stability control. Genome Research, 27(10), 1665–1673. https://doi.org/10.1101/gr.222505.117

Lokvist, C., Dodd, I. B., Sneppen, K., & Haertter, J. O. (2016). DNA methylation in human epigenomes depends on local topology of CpG sites. Nucleic Acids Research, 44(11), 5123–5132. https://doi.org/10.1093/nar/gkw124

Luger, K., Mader, A. W., Richmond, R. K., Sargent, D. F., & Richmond, T. J. (1997). Crystal structure of the nucleosome core particle at 2.8 A resolution. Nature, 389(6648), 251–260. https://doi.org/10.1038/38444

Lundsgaard, A. M., Fritzén, A. M., & Kiens, B. (2018). Molecular regulation of fatty acid oxidation in skeletal muscle during aerobic exercise.
young and old adults. Journal of Applied Physiology, 112(10), 1625–1636. https://doi.org/10.1152/japplphysiol.00435.2011

Reid, M. A., Dai, Z., & Locasale, J. W. (2017). The impact of cellular metabolism on chromatin dynamics and epigenetics. Nature Cell Biology, 19(11), 1298–1306. https://doi.org/10.1038/ncb3629

Robert, T. C. (2014). The microRNA biology of the mammalian nucleus. Molecular Therapy: Nucleic Acids, 3, e188. https://doi.org/10.1038/mtna.2014.40

Sailani, M. R., Halling, J. F., Moller, H. D., Lee, H., Plomgaard, P., Pilegaard, H., & Regen berg, B. (2019). Lifelong physical activity is associated with promoter hypomethylation of genes involved in metabolism, myogenesis, contractile properties and oxidative stress resistance in aged human skeletal muscle. Scientific Reports, 9(1), 3272. https://doi.org/10.1038/s41598-018-37985-8

Sharad, A. A., Juan, A. H., Muler, A. I. C., Anastasakis, D. G., Wang, X., Genzor, P., ... Hafner, M. (2018). Argonauta-miRNA complexes silence target mRNAs in the nucleus of mammalian stem cells. Molecular Cell, 71(6), 1040–1050. https://doi.org/10.1016/j.molcel.2018.07.020. e1048.

Saunderson, E. A., Spiers, H., Milfsud, K. R., Gutierrez-Mecinas, M., Trollope, A. F., Shaikh, A., ... Reul, J. M. (2016). Stress-induced gene expression and behavior are controlled by DNA methylation and methyl donor availability in the dentate gyrus. Proceedings of the National Academy of Sciences of the United States of America, 113(17), 4830–4835. https://doi.org/10.1073/pnas.1524857113

Schild, M., Ruhs, A., Beiter, T., Zugel, M., Hudemann, J., Reimer, A., ... Mooren, F. C. (2015). Basal and exercise induced label-free quantitative protein profiling of m. vastus lateralis in trained and untrained individuals. Journal of Proteomics, 122, 119–132. https://doi.org/10.1016/j.jprot.2015.03.028

Schubeler, D. (2015). Function and information content of DNA methylation. Nature, 517(7534), 321–326. https://doi.org/10.1038/nature14192

Schwartzman, J. M., Thompson, C. B., & Finley, L. W. S. (2018). Metabolic regulation of chromatin modifications and gene expression. Journal of Cell Biology, 217(7), 2247–2259. https://doi.org/10.1083/jcb.201803061

Seaborne, R. A., Strauss, J., Bakke, R. G., Mohamed, G., Bruns, T., Hayden, M. S., ... Workman, J. L. (2015). Histone exchange, chromatin structure and the regulation of transcription. Journal of Cell Biology, 263(3), 178–189. https://doi.org/10.1038/nrm3941

Singh, P. K., & Campbell, M. J. (2013). The interactions of microRNA and epigenetic modifications in prostate cancer. Cancers, 5(3), 998–1019. https://doi.org/10.3390/cancers5030998

Snedd, T., Nederveen, J. P., McKay, B. R., Joanisse, S., Verdijk, L. B., van Loon, L. J., & Parise, G. (2015). Satellite cells in human skeletal muscle plasticity. Frontiers in Physiology, 6, 283. https://doi.org/10.3389/fphys.2015.00283

Sodersten, E., Taskas, K., Ralikki, V., Tiklova, K., Bjorklund, A. K., Ringner, M., ... Holmberg, J. (2018). A comprehensive map coupling histone modifications with gene regulation in adult dopaminergic and serotonergic neurons. Nature Communications, 9(1), 1226. https://doi.org/10.1038/s41467-018-03538-9

Taddel, A., Van Houwe, G., Hediger, F., Kalck, V., Cubizolles, F., Schober, H., & Gasser, S. M. (2006). Nuclear pore association confers optimal expression levels for an inducible yeast gene. Nature, 441(7094), 774–778. https://doi.org/10.1038/nature04845

Telbot, J., & Maves, L. (2016). Skeletal muscle fibre type: Using insights from muscle developmental biology to dissect targets for susceptibility and resistance to muscle disease. Wiley Interdisciplinary Reviews: Developmental Biology, 5(4), 518–534. https://doi.org/10.1002/wdev.230

Trabucchi, M. (2019). Subcellular heterogeneity of the microRNA machinery. Trends in Genetics, 35(1), 15–28. https://doi.org/10.1016/j.tig.2018.10.006

Turner, D. C., Seaborne, R. A., & Sharples, A. P. (2019). Comparative transcriptome and methylome analysis in human skeletal muscle anabolism, hypertrophy and epigenetic memory. Scientific Reports, 9(1), 4251. https://doi.org/10.1038/s41598-019-40778-0

Ultimo, S., Zauli, G., Martelli, A. M., Vitale, M., McCubrey, J. A., Capitani, S., & Neri, L. M. (2018). Influence of physical exercise on microRNAs in skeletal muscle regeneration, aging and diseases. Oncotarget, 9(24), 17220–17237. https://doi.org/10.18632/oncotarget.24991

van der Kraap, J. A., & Verrijzer, C. P. (2016). Undercover: Gene control by metabolites and metabolic enzymes. Genes and Development, 30(21), 2345–2369. https://doi.org/10.1101/gad.289140.116

Venkatesh, S., & Workman, J. L. (2015). Histone exchange, chromatin structure and the regulation of transcription. Nature Reviews Molecular Cell Biology, 16(3), 178–189. https://doi.org/10.1038/nrm3941

Vissing, K., & Schjerling, P. (2014). Simplified data access on human skeletal muscle transcription responses to differentiated exercise. Scientific Data, 1, 140041. https://doi.org/10.1038/sdata.2014.41

Weinberg, M. S., & Morris, K. V. (2016). Transcriptional gene silencing in humans. Nucleic Acids Research, 44(44), 6505–6517. https://doi.org/10.1093/nar/gkw139

Weiner, A., Lara-Astiaso, D., Krupalnik, V., Gafni, O., David, E., Winter, D. R., ... Amit, I. (2016). Co-ChIP enables genome-wide mapping of histone mark co-occurrence at single-molecule resolution. Nature Biotechnology, 34(9), 953–961. https://doi.org/10.1038/nbt.3652

Weimann, L., Hock, J., Iavecic, T., Ohrt, T., Mutze, J., Schwille, P., ... Meister, G. (2009). Importin 8 is a gene silencing factor that targets argonauta proteins to distinct mRNAs. Cell, 136(3), 496–507. https://doi.org/10.1016/j.cell.2008.12.023

Widmann, M., Nick, A. M., & Munz, B. (2019). Physical exercise and epigenetic modifications in skeletal muscle. Sports Medicine, 49, 509–523. https://doi.org/10.1007/s40279-019-01070-4

Wilson, J. M., Loenneke, J. P., & Wilson, G. J., Zouroudis, M. C., & Kim, J. S. (2012). The effects of endurance, strength, and power training on muscle fiber type shifting. Journal of Strength and Conditioning Research, 26(6), 1724–1729. https://doi.org/10.1519/JSC.0b013e318234ebf

Yang, H., Menconi, M. J., Wei, W., Petkova, V., & Hasselgren, P. O. (2005). Dexamethasone upregulates the expression of the nuclear cofactor p300 and its interaction with CBP/p30 in cultured myotubes. Journal of Cellular Biochemistry, 94(5), 1058–1067. https://doi.org/10.1002/jcb.20371
Yin, Y., Morgunova, E., Jolma, A., Kaasinen, E., Sahu, B., Khund-Sayeed, S., … Taipale, J. (2017). Impact of cytosine methylation on DNA binding specificities of human transcription factors. Science, 356(6337), eaaj2239. https://doi.org/10.1126/science.aaj2239

Ziller, M. J., Gu, H., Muller, F., Donaghey, J., Tsai, L. T., Kohlbacher, O., … Meissner, A. (2013). Charting a dynamic DNA methylation landscape of the human genome. Nature, 500(7463), 477–481. https://doi.org/10.1038/nature12433

How to cite this article: Beiter T, Nieß AM, Moser D. Transcriptional memory in skeletal muscle. Don’t forget (to) exercise. J Cell Physiol. 2020;235:5476–5489. https://doi.org/10.1002/jcp.29535