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Review

Regulation of skeletal muscle development and homeostasis by gene imprinting, histone acetylation and microRNA

Viviana Moresi *, Nicoletta Marroncelli, Dario Coletti, Sergio Adamo

Dept. of Anat., Histol., Forens. & Orthop. Sciences, Section of Histology and Medical Embryology, Sapienza University of Rome, Via Scarpa, 14, 00161 Rome, Italy

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ABSTRACT

Epigenetics is defined as heritable information other than the DNA sequence itself. The concept implies that the regulation of gene expression is a highly complex process in which epigenetics plays a major role that ranges from fine-tuning to permanent gene activation/deactivation. Skeletal muscle is the main tissue involved in locomotion and energy metabolism in the body, accounting for at least 40% of the body mass. Body mass and function vary according to age but also quickly adapt to both physiological and pathological cues. Besides transcriptional mechanisms that control muscle differentiation, postnatal growth and remodeling, there are numerous epigenetic mechanisms of regulation that modulate muscle gene expression. In this review, we describe and discuss only some of the mechanisms underlying epigenetic regulation, such as DNA methylation, histone modifications and microRNAs, which we believe are crucial to skeletal muscle development and disease.

1. Introduction

By combining the words "epi-" and "genetics", the term epigenetics originally suggested the idea that phenotypes arise from genotype through programmed changes induced by the environment [1]. Nowadays epigenetics is used to define changes in gene expression or cellular phenotype caused by mechanisms other than modifications in the DNA sequence. One example of such mechanisms is chromatin modifications, such as DNA methylation and histone modifications. Generally, DNA methylation confers long-term epigenetic silencing of transposons or imprinted genes in somatic cells, while histone marks confer short-term, flexible, epigenetic silencing of genes that are required later in development [2,3]. More recent findings have identified additional epigenetic mechanisms responsible for cellular diversity via small regulatory non-coding RNAs [4,5]. These molecules modulate translation of mRNAs by acting in a sequence-specific fashion. Epigenetic changes are preserved when cells divide. When epigenetic changes occur in sperm or egg cells that lead to fertilization, epigenetic changes are inherited by the offspring.

Interest in epigenetic mechanisms has grown considerably in recent years. As occurred with the Genome Project for widespread mapping of the genome, major efforts have been invested into shedding light on the epigenome and into defining where epigenetic modifications are located within the genome. For instance, about 15 billion sites in the human genome that may be modified by DNA methylation have been identified; in addition, more than 1600 sense-anti-sense gene pairs are believed to be transcribed, indicating that more than 8% of the estimated 40,000 human genes have an antisense partner [6]. These findings have laid the bases for studies on the post-transcriptional modulation of gene expression via epigenetic regulation.

2. DNA methylation and gene imprinting

DNA methylation is an epigenetic mechanism that controls gene expression and is associated with a number of key processes including genomic imprinting and X-chromosome inactivation. DNA methylation mainly occurs on CpG dinucleotides in mammals, although recent studies have highlighted the presence of DNA methylation at non-CpG sites, which is capable of regulating gene expression in adult mammalian somatic cells, including skeletal muscle cells [7]. DNA methylation distinguishes the paternal from the maternal gene copy in genomic imprinting. The repressed allele is methylated, whereas the active allele is unmethylated [8] (Fig. 1). Imprinted genes do not rely on Mendelian laws, according to which both parental copies are equally likely to contribute to the outcome. An established hypothesis for the evolution of gene imprinting is that the choice of which single allele of the gene is expressed, i.e. the maternal or the paternal one, is fully beneficial to the offspring when derived from one parent but has an inherent fitness cost, in terms of ability to survive and reproduce, when derived from the other parent [9]. According to this hypothesis, paternally expressed genes tend to promote growth, whereas maternally imprinted genes tend to be growth limiting because the mother needs to conserve resources for her own survival and for that of her litter [10]. Intriguingly,

* Corresponding author at: DAHFMO section of Histology and Medical Embryology, Sapienza University of Rome, Via Antonio Scarpa, 14, 00161 Rome, Italy. Tel.: +39 06 49766577.
E-mail address: viviana.moresi@uniroma1.it (V. Moresi).

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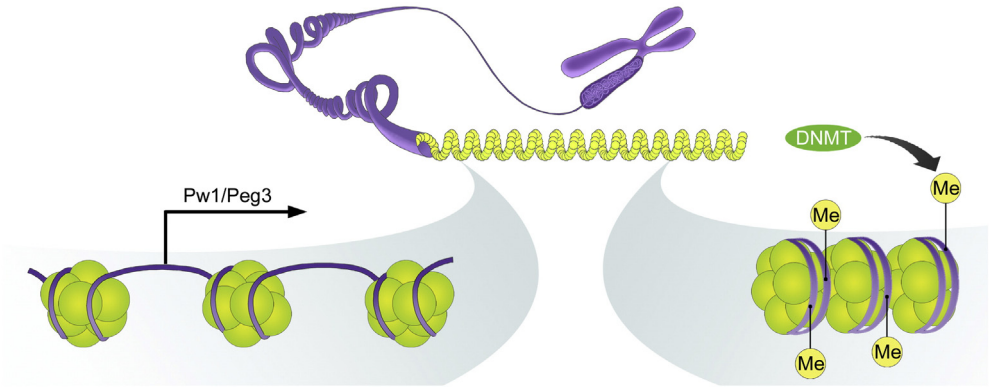

Fig. 1. DNA methylation and gene imprinting. DNA methylation is a biochemical process whereby a methyl group is added to the cytosine or adenine DNA nucleotides by DNA methyltransferase (DNMT) enzyme. Upon DNA methylation, gene transcription is repressed. Some DNA methylations are heritable and cause genomic imprinting, as in the case of Pw1/Peg3 allele.

genomic imprinting is being considered a feature of mammalian stem cells [11]. Many parentally imprinted genes are expressed at high levels in fetal and newborn tissues and decline within weeks of birth in mice [12,13]. Others, such as Pw1/Peg3, are expressed in adult somatic stem cells though not in their differentiated progeny [14,15]. Dysregulation of the expression of Pw1/Peg3 in mice reveals the critical role of this gene in the maintenance of stem cells and skeletal muscle mass [15,16]. Pw1/Peg3 is a mediator of TNF-alpha and p53 pathways [17,18], which are crucial players in the regulation of skeletal muscle homeostasis. Transgenic mice for the dominant-negative form of Pw1/Peg3 are smaller, with atrophic skeletal muscles characterized by significantly fewer quiescent satellite cells but more activated euchromatic satellite cells than those of controls [18]. In addition to its role in satellite cell behavior, in vivo studies on tumor bearing mice have clarified the role of Pw1/Peg3 in mediating p53-dependent myofiber atrophy in response to cancer [18]. More recently, Pw1/Peg3 has been established as an invaluable marker for competent self-renewing stem cells in a wide range of adult tissues: from the intestine to the seminiferous tubules, from the bone to the central nervous system [14,19]. Thus, an incorrect genomic imprinting and expression pattern of a single, specific methylated gene, such as Pw1/Peg3, may have devastating consequences on tissue homeostasis. Indeed, many skeletal muscle diseases have been associated with defects in imprinted genes. Loss of methylation at several CpG dinucleotides on the maternal imprinted gene epsilon-sarcoglycan leads to biallelic expression of this gene and is associated with myoclonus-dystonia [20], a disorder characterized by rapid muscle contractions and repetitive movements. Loss of imprinting has also been demonstrated in rhabdomyosarcoma tumors, in which it may be involved in the onset and progression of the pathogenesis [21,22]. Hypermethylation of skeletal muscle ryanodine receptor gene reduces expression of this gene and has been associated with congenital myopathies, such as central core disease [23].

Besides influencing gene imprinting, DNA methylation also influences the expression of many genes that are critical to skeletal muscle development, such as the homeobox genes, T-box genes and sine oculis-related homeobox 1, which is strongly hypermethylated; whereas contractile fiber genes are hypomethylated [24–26]. DNA methylation is also involved in the promotion and the maintenance of muscle stem cell renewal via hypomethylation at intragenic or intergenic regions of the Notch receptors or Notch ligand genes in myoblasts but not in non-muscle cells [27]. Numerous external cues influence DNA methylation, which may determine disease onset or progression. For instance, a high fat diet given to pregnant mice induces hypermethylation of the peroxisome proliferative activated receptor, gamma, coactivator 1 alpha (PGC1α) promoter in the offspring; this epigenetic mark is maintained until 12 months of age in the offspring and correlates with reduced expression of PGC1α mRNA and increased metabolic dysfunctions with age [28]. Exercise during pregnancy prevents high fat diet-induced PGC1α methylation and increases PGC1α gene expression in the offspring, thereby reducing metabolic dysfunctions. DNA hypermethylation has also been observed in non-CpG sites at the PGC1α promoter in diabetic subjects and methylation levels negatively correlate with PGC1α mRNA levels, thereby indicating that increased promoter methylation at these loci in part regulates gene expression [29]. Besides PGC1α, exercise induces a whole genome hypomethylation in human skeletal muscle and dose-dependent expression of the pyruvate dehydrogenase kinase isozyme 4, of the peroxisome proliferator activator receptor delta and of the glucose transporter GLUT4 [30,31]. Unlike exercise, aging significantly increases DNA hypermethylation throughout the genome of skeletal muscle cells, although a direct correlation between DNA hypermethylation and the decline in skeletal muscle mass and function associated with aging has not been found [32]. When miss-regulated, DNA methylation may perturb the expression of genes involved in musculoskeletal diseases. Facioscapulohumeral muscular dystrophy (FSHD), for instance, is a disease caused by the stable expression of an alternative full-length mRNA form of the double homeobox 4 gene, which is sustained by two enhancers that are hypomethylated, i.e. in a permissive transcriptional state, in myoblasts of FSHD patients [33]. Abnormal levels of mitochondrial DNA methylation and mitochondrial DNA methyltransferase Dnmt3a have also been detected in skeletal muscle of presymptomatic amyotrophic lateral sclerosis (ALS) mice; these abnormalities occur concomitantly with loss of mitochondria in myofibers [34].

Thus, further studies aimed at providing a better understanding of DNA methylation in muscle development and homeostasis may offer the opportunity to prevent and treat numerous muscle diseases.

3. Histone modifications

Gene activation or repression, as well as transcriptional initiation and elongation, are regulated by many epigenetic mechanisms. With regard to histone modifications alone, we should mention the existence of numerous epigenetic marks, such as histone methylation, ubiquitylation, phosphorylation, sumoylation, ribosylation, citrullination and acetylation, which affect chromatin structure and, consequently, gene expression.

In the last decade, many studies have focused on the role of histone methylation in modulating the pluripotency and lineage restriction of a number of cells [35]. While the Polycomb Repressive Complex 2 (PRC2) establishes gene silencing by trimethylation of histone 3 lysine 27 (H3K27me3) at developmentally regulated loci, the trithorax group, which mediate the trimethylation of histone 3 lysine 4 (H3K4me3), together with the lysine (K)-specific demethylase 6A and KDM1 lysine (K)-specific demethylase 6B family, antagonize PRC2 repressive activity and allow gene expression in specific cell types. In muscle stem cells,

the lack of the repressing H3K27me3 across the genome and the concomitant presence of H3K4me3 at the transcription start sites of a large number of genes determine and maintain the chromatin in a primed status, thus allowing such cells to respond readily to external stimuli [36]. Accordingly, mice lacking the enzymatic subunit of PRC2 in skeletal muscle display impaired muscle stem cell proliferation and inappropriate gene expression, which are normally absent in muscle cell lineages [37].

Ubiquitylation of histones influences both transcriptional initiation and elongation, as well as transcriptional silencing in vertebrates [38], at least in part through the promotion of H3K4me3 following histone ubiquitylation, and H3K36me3 tri-methylation following deubiquitylation [39]. Very little information is available on the role of histone ubiquitylation and skeletal muscle cells. During myogenic differentiation, histone H2B ubiquitylation levels decrease. Interestingly, this reduction is impaired in muscle cells derived from "Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia" patients [40], thus suggesting that histone ubiquitylation plays a role in this muscular disease.

Although histone phosphorylation was reported to occur in skeletal muscle cells by many laboratories several years ago [41,42], its functional role has not yet been described. Similarly, histone sumoylation has been associated with gene silencing through the recruitment of histone deacetylase and heterochromatin protein 1 [43], though its effect on skeletal muscle cells has yet to be addressed. Histone ADP-ribosylation directly destabilizes histone–DNA interactions in the nucleosome, therefore facilitating gene transcription in many cell types [44,45]. Many different cellular features may be influenced by histone ADP-ribosylation, such as cell cycle progression, DNA repair and activation of specific gene expression [46], though the role of this histone mark in skeletal muscle is still not yet clear. Histone citrullination, in which an arginine is converted into the amino acid citrulline, is a post-transcriptional modification involved in chromatin decondensation and gene regulation that has been associated with numerous disorders [47]. The functional role of histone citrullination in skeletal muscle cells has not yet been clarified either.

3.1. Histone acetylation

Acetylated histones represent a chromatin epigenetic tag [48]. By removing positive charges, acetylation reduces the interactions between histones and the DNA, thereby relaxing the DNA structure and allowing higher levels of gene transcription. Being an essential component of gene regulation, histone acetylation and deacetylation are a highly dynamic process, controlled by the balance between the antagonistic actions of the histone acetyltransferases (HATs) and the histone deacetylases (HDACs), that influence numerous cellular pathways [49,50]. Depending on their protein structure and function, HDAC proteins fall into four groups. The first two groups, i.e. class I and class II HDACs, are considered classical HDACs whose deacetylase activities are inhibited by the pan-HDAC inhibitor trichostatin A (TSA) or valproic acid (VPA); the third group, i.e. the sirtuins, is a family of NAD^+-dependent deacetylases, whereas the fourth group, i.e. HDAC11, is an atypical category that is considered to be HDAC-based only on account of its DNA sequence similarity to other HDACs. Biochemical analyses have revealed that the majority of HDAC activity is due to class I HDACs, whereas highly purified recombinant class II HDACs possess only minimal catalytic activity [51–53]. Therefore, class II HDACs recruit members of class I HDACs on specific targets to remove the acetyl groups from histones. Moreover, unlike class I HDACs, which are broadly expressed, class II HDACs display relatively restricted expression patterns [49]. Histone acetylation and deacetylation regulate many steps of myogenesis in vitro, controlling the temporal hierarchical transcription of myogenic genes, and allowing rapid transcriptional response upon extracellular stimuli. Moreover, histone deacetylation provides a possible explanation for the paradoxical finding that some transcription factors are expressed in myoblasts when their target genes have not yet been activated. For example, the initiator of the myogenic program, MyoD, remains in a transcriptionally silent status until myoblasts are induced to differentiate. In undifferentiated myoblasts, MyoD activity is repressed by HDAC1 [54], a member of class I HDACs. Upon differentiation, HDAC1 is down-regulated, while phospho-retinoblastoma (pRb) is hypo-phosphorylated, which allows the formation of the pRb–HDAC1 complex in differentiating myotubes. The pRb–HDAC1 association induces the disruption of the MyoD–HDAC1 complex, the transcriptional activation of muscle-specific genes, such as muscle creatine kinase or myogenin, and myoblast differentiation [55]. In addition, both PCAF and p300 acetylate MyoD, thereby enhancing its transcriptional activity and allowing the recruitment and association of HATs with muscle-specific genes, which in turn result in the activation of MyoD-dependent genes [56–58]. Similar mechanisms control MEF2, a transcriptional co-activator of myogenesis. Members of class II HDACs, such as HDAC4, -5, and -7, which are expressed and localize within the nucleus in proliferating myoblasts, associate with and inhibit MEF2-dependent transcription, thereby blocking MyoD-dependent conversion of fibroblasts into myotubes [59]. Upon differentiation, class II HDACs translocate into the cytoplasm, thereby releasing the inhibition on MEF2, which promotes myoblast differentiation (Fig. 2).

Mutant mice lacking individual HDACs are a powerful tool for defining HDAC functions in vivo. Studies of HDAC knockout mice have revealed highly specific and crucial functions of individual HDACs in tissue development and disease. Global deletion of a single HDAC in mice is often lethal in the embryonic or perinatal phase owing to severe developmental defects [60–63], thus confirming the essential role of these enzymes in cell function and survival. Studies on tissue-specific HDAC null mice have clarified the precise role of these proteins in each body compartment. One study has shown that HDAC1 and 2 play a redundant role in skeletal muscle development and homeostasis [64], as they do in the heart. Indeed, mice lacking up to three alleles of HDAC1 and HDAC2 in skeletal muscle are viable and display normal muscular architecture in histological analyses. When both HDAC1 and HDAC2 are absent in skeletal muscle, about 40% of mice die perinatally, probably owing to respiratory defects. The remaining 60% of mutant mice that survive the first day of life develop a progressive myopathy characterized by degeneration of skeletal muscle and centro-nucleated myofibers, a shift toward an oxidative metabolism and a block in autophagy flux. The same study revealed a role of HDAC1 and HDAC2 in regulating autophagy flux in skeletal muscle and confirmed a link between autophagy, metabolism and tissue homeostasis. Unlike HDAC1 and HDAC2, mice lacking both HDAC4 and HDAC5 in skeletal muscle are viable and display no apparent defects in muscle architecture by histological analysis [65]. Following denervation, HDAC4 and HDAC5 double mutant mice preserve muscle mass owing to their failure to up-regulate the expression of myogenin and its downstream target genes MuRF1 and atrogin1, which are responsible for muscle proteolysis [66], and because they cannot activate the mitogen-activated protein kinase pathway [67]. HDAC4 has been shown to play a role in regulating the fibroblast growth factor-mediated compensatory reinnervation of skeletal muscle following denervation or in ALS progression [68]. Notably, HDAC4 expression in skeletal muscle of ALS patients is up-regulated and inversely correlates with disease severity, the extent of muscle reinnervation and functional outcome [69], thereby pointing to the potential usefulness of class II HDAC inhibitors as a means of improving ALS patient conditions. Accordingly, treatment with HDAC inhibitors has also been shown to exert beneficial effects on survival and maintenance of muscle mass in mice affected by ALS or spinal muscular atrophy [70,71].

Systemic HDAC inhibition with pan-HDAC inhibitors improves conditions in patients and mice in a wide range of disorders, ranging from cancer and immunological diseases to muscular dystrophy, cardiac hypertrophy and neurodegenerative diseases [49,71–73]. The exact

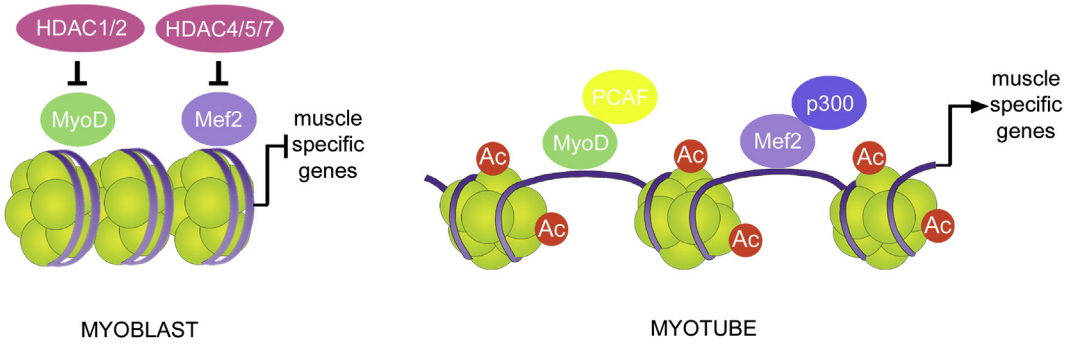

Fig. 2. Histone acetylation and deacetylation regulate myogenesis. Histone acetylation and deacetylation are the processes by which the lysine residues in the histone core of the nucleosome are acetylated and deacetylated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively. By removing the positive charges on the histones, acetylation allows chromatin relaxation and higher levels of gene transcription. This relaxation can be reversed by HDAC activity.

mechanisms underlying the effects of HDAC inhibitors are only partially known and numerous theories have been proposed, including changes in gene transcription, induction of apoptosis or autophagy, and cell-cycle arrest [74–77]. With regard to skeletal muscle, treatment with HDAC inhibitors ameliorates Duchenne muscular dystrophy in mice. In particular, HDAC inhibitors increase myofiber size, decrease inflammatory infiltrate and prevent the formation of fibrotic scars in *mdx* mice [78], thereby helping to counter muscle loss and functional decline. At the cellular level, HDAC inhibitors act on fibroadipogenic progenitor (FAP) cells by inhibiting their adipogenic potential and enhancing their ability to promote differentiation of adjacent satellite cells [79]. An interesting insight into the specific role of individual HDACs in muscular dystrophy is provided by the comparable efficacy of a class I HDAC inhibitor and pan-HDAC inhibitors [80]. This suggests that inhibition of class I HDACs is sufficient to exert most of the beneficial effects observed in HDAC inhibitor-treated *mdx* mice, which in turn highlights the important contribution of class I HDACs to Duchenne muscular dystrophy and muscle regeneration. Moreover, a recent paper revealed the importance of HDAC4 in muscle regeneration [81]. Satellite cells lacking HDAC4, once isolated from mice, display reduced proliferation and impaired differentiation in vitro, leading to compromised muscle regeneration in vivo. Interestingly, the lack of HDAC4 in satellite cells is not sufficient to block their differentiation, which implies that muscle regeneration in vivo is regulated by HDAC4 in a paracrine/autocrine fashion. The same study provided in vivo evidence of the positive correlation between HDAC4 levels and the expression of Pax7 and Lix1, two genes required for correct satellite cell proliferation, as well as of miR-133, which is required for skeletal muscle commitment, though the molecular explanation for the correlation between HDAC4 and these genes is still elusive [81].

Given the dramatic phenotypes that result from HDAC gene deletions, why are HDAC inhibitors so well tolerated in vivo? We propose some explanations that are not mutually exclusive. While the genetic deletion of a protein results in the complete absence of the specific enzyme, HDAC inhibitors are neither specific to a single HDAC nor result in the complete inhibition of HDAC activity, with treatment often starting upon diagnosis of the disease. Moreover, a genetic deletion of an HDAC eliminates the gene product permanently, whereas the action of inhibitors is transient. Notably, HDACs participate in multiprotein transcriptional complexes. While HDAC inhibitors are believed to block enzymatic activity without necessarily disrupting protein complexes, the genetic deletion of an HDAC probably perturbs the complexes with which it is normally associated.

4. MicroRNAs as additional tool of epigenetic control

MicroRNAs (miRNAs) are a class of small non-coding RNAs that negatively regulate gene expression by pairing their nucleotides 2–8 at the 5′ end, known as the "seed region", with sequences located predominantly in the 3′ UTRs of target mRNAs [82] (Fig. 3). The crucial role of miRNAs in mouse development is proved by the genetic mutation in the miRNA processing enzyme Dicer in all the tissues, which results in embryonic death [83]. Moreover, numerous types of disorders are associated with changes in the amount of miRNA in tissues and/or in levels of serum circulating miRNAs, which suggests that it may be possible to use miRNAs as new and valuable biomarkers for the diagnosis of a range of diseases [84–88].

MiRNAs play a crucial role in skeletal muscle development, as demonstrated by the perinatal death due to skeletal muscle hypoplasia of the skeletal muscle-specific null mice for Dicer [89]. Skeletal muscle-specific null mice for single miRNAs have been developed and analyzed

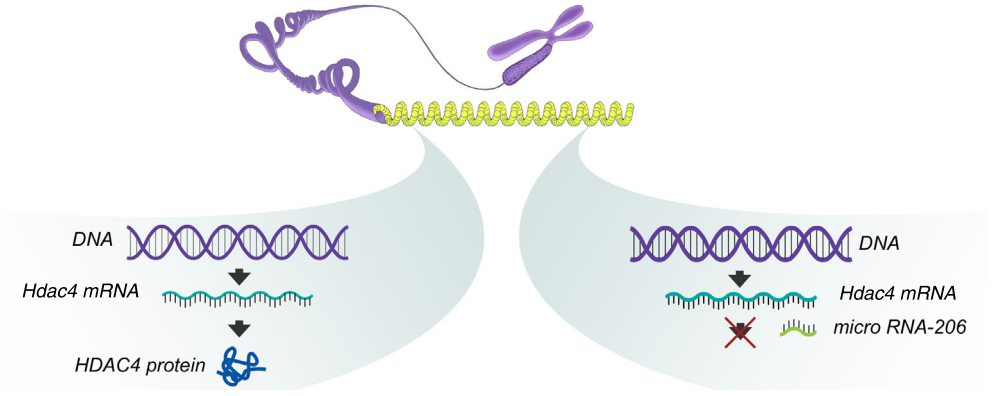

Fig. 3. MicroRNA-mediated regulation of gene expression. MicroRNAs are small non-coding RNA molecules that function via base-pairing with complementary sequences within mRNA targets. As a result, mRNA targets (e.g. Hdac4 mRNA for microRNA-206) are silenced because they can no longer be translated into proteins.

in the last decade to assess whether this essential function of Dicer in skeletal muscle development reflects requisite roles of specific miRNAs or multiple miRNAs. MyomiRs are miRNAs expressed in striated muscle; they include miR-1, miR-133a, miR-206, miR-208a, which is cardiac-specific, and miR-208b, miR-499 and miR-486 [90–94]. The expression of over one hundred miRNAs is modulated in different ways in murine myoblasts and in myotubes in vitro [95], thus suggesting that miRNAs are critical regulators of skeletal muscle differentiation. Indeed, several miRNAs have been implicated in the regulation of myoblast activation, proliferation and differentiation, as well as in the maintenance of the myogenic lineage in vitro. MiR-489, which suppresses the expression of the oncogene DEK [96], and miR-31, which inactivates the transcription of the myogenic factor Myf5 [97], ensure the maintenance of muscle stem-cell quiescence, thereby preventing precocious myogenic differentiation. Myoblast proliferation is promoted and maintained by the combined actions of miR-27a/b, which inhibit myostatin and Pax3 protein levels [98,99], miR-133a, which targets serum response factor [100], and miR-682 [101]. Whereas myoblast differentiation and fusion into myotubes are promoted by miR-206, which inhibits the expression of a number of negative regulators of myogenesis, such as notch3, igfbp5, Meox2, RARB, Fzd7, MAP4K3, CLCN3, NFAT5 and the tissue inhibitor of metalloproteinase 3 [102–105]. Moreover, in differentiating myoblasts, the repression of TGF-beta signaling, a repressor of myoblast differentiation, is ensured by the combined action of miR-206 and miR-29, which inhibit Smad3 expression [106], and miR-26a, which represses Smad1 and Smad4 expression [107], ultimately leading to myoblast differentiation. Besides promoting myoblast differentiation, together with miR-128a and miR-1, miR-206 helps to block cell proliferation by inhibiting the expression of several genes involved in the insulin signaling pathway, as well as Pax7 expression [107–109]. Indeed, inhibition of miR-1 and miR-206 leads to increased Pax7 protein levels and myoblast proliferation; conversely, loss of miR-1 and miR-206 reduces Pax7 expression and myoblast differentiation [105,108]. Inhibition of cell proliferation and promotion of myoblast differentiation are also mediated by miR-26a and miR-1, which repress Ccnd1 expression [110], and miR-133a/b, which negatively regulates FGFR1 and PP2AC proteins [111]. As myoblasts differentiate, the downregulation of the enzymatic subunit of the PRC2, Ezh2, and its partner YY1 is mediated by the combined action of miR-214 [112], miR-26a [113] and miR-29 [114], thereby relieving PRC2-mediated repression of muscle genes. An important role in promoting myoblast differentiation has also been described for miR-133a, which modulates the IGF-1 receptor [115] and sarcomeric actin organization [116]. Moreover, by targeting PRDM16, a master gene for brown fat determination, miR-133 modulates the choice between myogenic and brown adipose lineage [117]. Besides myomiRs, whose expression is upregulated during muscle differentiation, there are other miRNAs that participate in myogenesis by relieving the expression of muscle specific genes, such as miR-23a, which directly regulates the expression of myosin heavy chain genes [118].

Despite the importance miRNAs play in regulating myogenesis in vitro, surprisingly little impact has been observed on skeletal muscle phenotype following the deletion of the majority of miRNAs in mice [94]. This is in keeping with the role of miRNAs as stress mediators that restore cell homeostasis by finely regulating gene expression [119]. For instance, although miR-206 null mice develop healthy and functional skeletal muscle, upon stress miR-206 is required for efficient regeneration of neuromuscular synapses following denervation and for correct satellite cell differentiation and muscle regeneration [68,105]. Moreover, the absence of miR-206 accelerates ALS progression and exacerbates the dystrophic phenotype in mice [68,105]. Mice lacking either miR-133a-1 or miR-133a-2 are normal; conversely, double mutant mice develop centronuclear myopathy in fast-twitch myofibers, accompanied by impaired mitochondrial function and fast-to-slow myofiber conversion [120], thereby revealing the essential role of miR-133a in multiple facets of skeletal muscle function and homeostasis in mice. It is not clear why knockout mice do not display a more dramatic phenotype, as would be expected from in vitro studies. One possible explanation is that myomiRs are redundant in regulating the same target genes, including miR-1 and miR-206. Therefore, the lack of a single miRNA might be compensated for by the presence of another family member, thus preventing any deleterious phenotype resulting from the miRNA knockout. This hypothesis is supported by the fact that only the double knockout of the two family members, miR-133a-1 and miR-133a-2, reveals an evident phenotype in striated muscle. In skeletal muscle, miR-208b and miR-499 are encoded in introns of two myosin heavy chain genes, respectively Myh7 and Myh7b, which in turn control muscle myosin content and myofiber identity. Similarly to miR-133a-1 and miR-133a-2, in vivo studies have shown that miR-208b and miR-499 play redundant roles in the specification of muscle fiber identity by activating slow and by repressing fast myofiber gene programs, thereby ultimately affecting muscle performance [93]. Despite the efforts of numerous studies, the role of miRNA in skeletal muscle development and diseases has still been partially elucidated, given the numerous possible interactions between transcription factors, miRNAs and their target mRNAs. Further studies are needed to characterize the in vivo functions of miRNAs and to identify their downstream target genes.

5. Conclusions

Although we do not yet know the precise mechanisms underlying epigenetic gene regulation in the pathogenesis of several diseases, the finding that the progression of such diseases can be altered by modulating epigenetic programs, via HDAC inhibitors, antimiRs or miRNA mimics, is highly promising for medical purposes. Epigenetics provides another level of regulation that, combined with genetic differences, might mediate the relationship between genotype and environmental factors (Tables 1 and 2). Thus, the epigenetic component might help to explain the marked age-related increase in the incidence of common diseases, as well as the frequent discordance of diseases between monozygotic twins. Since epigenetics is one of the main causes of phenotypic

Table 1
Summarizing table with examples of the relevant skeletal muscle genes regulated through DNA methylation and acetylation that are reviewed in the text.

Gene symbol	Epigenetic regulation	Functional output	References
Peg3	Hypermethylation	Skeletal muscle atrophy	[16]
Sgce	Loss of methylation	Myoclonus-dystonia	[20]
H19, IGF2	Loss of methylation	Rhabdomyosarcoma	[21,22]
Ryr1	Hypermethylation	Core myopathies	[23]
Six1; Pax3; Tbx1	Hypermethylation	Skeletal muscle development	[23–25]
Obscn; Myh7b	Hypomethylation	Skeletal muscle development	[25]
NOTCH1; NOTCH2; JAG2; DLL1	Hypomethylation	Specification of muscle stem cells	[27]
PGC-1alpha	Hypermethylation	Metabolic dysfunctions	[28,29]
DUX4	Hypomethylation	Facioscapulohumeral muscular dystrophy	[33]
Ckm; Myog	Deacetylation	Block of myoblast differentiation	[59]
Dach2	Deacetylation	Neurogenic muscle atrophy	[66]

Table 2
Summarizing table with examples of relevant miRNAs regulating skeletal muscle genes that are reviewed in the text.

miRNA nomenclature	Target gene symbol	Functional output	References
miR-489	DEK	Muscle stem cell quiescence	[96]
miR-31	Myf5	Muscle stem cell quiescence	[97]
miR-27 a/b	Mstn Pax3	Myoblast proliferation	[98,99]
miR-133a	SRF, IGF-1	Myoblast proliferation	[114,115]
miR-133 a/b	FGFR1, PP2AC, PRDM16	Myoblast differentiation	[110,116]
miR-206	Notch3, igfbp, Meox2, RARB, Fzd7, MAP4K3, CLCN3, NFAT5, Mstn, Smad3, Pax7	Myoblast differentiation	[102–105,108]
miR-29	Smad3, YY1	Myoblast differentiation	[106,114]
miR-26a	Smad1, Smad4, Ccnd1, Ezh2	Myoblast differentiation	[107,109,112]
miR-128a	Pax7	Myoblast differentiation	[109]
miR-1	Pax7, Ccnd1	Myoblast differentiation	[108]
miR-214	Ezh2, YY1	Myoblast differentiation	[112]
miR-23a	Myh 1,2,4	Myoblast differentiation	[118]

variation in physiological and pathological conditions, our understanding of and ability to manipulate the epigenome holds enormous promise for preventing and treating illness.

Competing interests

No competing interests are declared.

Authors' contributions

VM: conceived and drafted the manuscript. All other authors contributed to the writing of the final version of the manuscript.

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