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REVIEW

New insights into the epigenetic control of satellite cells

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Abstract

Epigenetics finely tunes gene expression at a functional level without modifying the DNA sequence, thereby contributing to the complexity of genomic regulation. Satellite cells (SCs) are adult muscle stem cells that are important for skeletal post-natal muscle growth, homeostasis and repair. The understanding of the epigenome of SCs at different stages and of the multiple layers of the post-transcriptional regulation of gene expression is constantly expanding. Dynamic interactions between different epigenetic mechanisms regulate the appropriate timing of muscle-specific gene expression and influence the lineage fate of SCs. In this review, we report and discuss the recent literature about the epigenetic control of SCs during the myogenic process from activation to proliferation and from their commitment to a muscle cell fate to their differentiation and fusion to myotubes. We describe how the co-ordinated activities of the histone methyltransferase families Polycomb group (PcG), which represses the expression of developmentally regulated genes, and Trithorax group, which antagonizes the repressive activity of the PcG, regulate myogenesis by restricting gene expression in a time-dependent manner during each step of the process. We discuss how histone acetylation and deacetylation occurs in specific loci throughout SC differentiation to enable the time-dependent transcription of specific genes. Moreover, we describe the multiple roles of microRNA, an additional epigenetic mechanism, in regulating gene expression in SCs, by repressing or enhancing gene transcription or translation during each step of myogenesis. The importance of these epigenetic pathways in modulating SC activation and differentiation renders them as promising targets for disease interventions. Understanding the most recent findings regarding the epigenetic mechanisms that regulate SC behavior is useful from the perspective of pharmacological manipulation for improving muscle regeneration and for promoting muscle homeostasis under pathological conditions.

Key words: Histone methylation; Histone acetylation; Muscle stem cells; Adult stem cells; Noncoding RNAs; Satellite cell activation; Satellite cell differentiation; Satellite cell quiescence

Core tip: Skeletal muscle needs to efficiently respond to internal and external stimuli, and satellite cells (SCs), the stem cells of muscle, play key roles in the preservation of muscle mass under both physiological and pathological conditions. Epigenetic pathways participate in co-ordinating the precise time-dependent expression of different subsets of myogenic genes in SCs. Thus, these pathways represent promising targets for therapeutic interventions. In this review, we focus on the epigenetic changes mediated by histone modifications - methylation or acetylation - and by noncoding mRNAs throughout SC differentiation.

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SATELLITE CELLS

The first report and ultrastructural description of satellite cells (SCs) was in 1961 when Mauro reported the presence of cells containing a scant cytoplasm that were "intimately associated with the muscle fiber wedged between the plasma membrane of the muscle fiber and the basement membrane"; Mauro termed them SCs[1]. In the same report, despite the absence of direct functional evidence, Mauro proposed that SCs "might be pertinent to the vexing problem of skeletal muscle regeneration".

In subsequent decades, Mauro's hypothesis proved true, and a number of studies demonstrated that SCs are the key mediators of post-natal skeletal muscle growth, homeostasis and repair[2-4]. The core functions of SCs are the repair of damaged muscle fibers and the maintenance of an adequate pool of stem cells. In fact, dividing SCs were shown by autoradiographic studies to supply both new nuclei within growing or regenerating muscle fibers and new SCs adjacent to the muscle fibers[5,6].

Quiescent SCs express the transcription factor Pax7[7]. However, quiescent SCs constitute a heterogeneous population: most SCs are committed to the myogenic lineage ($Pax7^+$, $Myf5^+$), whereas a small subpopulation of SCs ($Pax7^+$, $Myf5^-$) are interpreted as representing satellite stem cells, whose asymmetric division produces both $Pax7^+$, $Myf5^-$ stem cells and $Pax7^+$, $Myf5^+$ committed SCs. SCs are also capable of maintaining or expanding their number *via* symmetric division[8,9]. The observation that SC proliferation contributes to both the growth or repair of the muscle fiber and the maintenance of the SC pool provided the basis for considering SCs as muscle stem cells[10]. The equilibrium between asymmetric and symmetric division is therefore relevant to the maintenance of a homeostatic population of stem cells. In SCs, this equilibrium is influenced by signaling that includes WNT7A and its receptor Frizzled 7 (Fzd7) *via* the -catenin-independent, non-canonical planar cell polarity pathway[11]. Such signals dictate the polarity (parallel or perpendicular) of the orientation of mitotic division with respect to the fiber sarcolemma (and the basal lamina). WNT7A activity induces stem cells to divide in a planar orientation, parallel to the fiber sarcolemma, thereby favoring symmetric division, which produces two $Pax7^+$, $Myf5^-$ stem cells. Conversely, in the absence of WNT7A activity, the mitotic spindle is oriented perpendicular to the fiber sarcolemma, thereby favoring asymmetric division into two daughter cells; the daughter cell that contacts the basal lamina retains stem cell characteristics ($Pax7^+$, $Myf5^-$), whereas the other daughter cells, which contacts the fiber sarcolemma, becomes a $Pax7^+$, $Myf5^+$ committed SC.

SCs in muscle regeneration

Many stimuli, such as those present in injured or diseased muscle, induce SCs to activate, expand and contribute to new fiber formation. Importantly, SC activation is not restricted to the damaged area; rather, SC proliferation and migration to the regeneration site have been observed along entire fibers of injured muscles[12]. Muscle regeneration is absolutely dependent upon muscle-resident $Pax7^+$ cells[13], which predominantly, although not exclusively, consist of SCs[14]. The absolute requirement of $Pax7^+$ SCs for muscle regeneration was demonstrated in different studies[13,15,16]. In the absence of $Pax7^+$ SCs, regeneration does not take place; instead, fibro-adipogenic cells invade the tissue. In keeping with the notion that SC-dependent muscle regeneration processes are similar to those of embryonic myogenesis, SC activation involves the upregulation of myogenic basic helix-loop-helix transcription factors and SC differentiation[17]. In particular, at the molecular level, the activation of SCs is characterized by the rapid expression of *MyoD* and *Myf5*, which is triggered by Pax7 (and its paralog Pax3)[18] and is modulated by epigenetic mechanisms[19].

After the proliferation phase, the expression of the myogenesis regulatory factor (MRF) members myogenin and MRF4 is upregulated, leading to terminal SC differentiation[20]. This event is concomitant with the activation of the cell cycle arrest protein p21 and permanent exit from the cell cycle. The completion of the SC differentiation program includes the activation of muscle-specific proteins, such as myosin heavy chains, and the fusion of SCs to each other or the repair of damaged muscle. SC fusion, which is a complex and tightly controlled process[21], is regulated by numerous proteins involved in cell-cell adhesion and actin dynamics[22-25], as well as muscle-specific membrane proteins[26].

The depletion of SCs is a common occurrence in

chronic muscle degenerative diseases, and these cells cannot be replaced. Thus, the regulation of SC renewal is central to the promotion of muscle regeneration in muscle diseases, such as muscular dystrophies.

EPIGENETIC MECHANISMS OF GENE REGULATION

Epigenetics is responsible for the identity of distinct cell types despite the same genetic information by modulating gene expression without altering the genetic code. In other words, the ensemble of epigenetic characteristics, referred to as the epigenome, determines the gene expression pattern that defines the distinct characteristics and functions of each cell type[27]. In fact, although their genomes are essentially identical, the cell types in a multicellular organism perform strikingly different behaviors over extended periods. Lineage commitment during development is the most extreme example of epigenetics. During embryogenesis, cells progress from totipotency to terminal differentiation, and each step of this progression involves the establishment of a stable state in which specific developmental commitments that can be transmitted to daughter cells are encoded. The understanding of the epigenome of different cell types and the complexity of the post-transcriptional control of gene expression is constantly expanding due to the development of new technologies and the continuous discovery of noncoding RNAs that participate in epigenetic regulation.

Histone methylation

The eukaryotic genome is packaged into chromatin, a chain of nucleosomes composed of four core histones - H2A, H2B, H3, and H4 - whose amino-terminal tails are exposed on the surface of nucleosomes and are subjected to a wide range of post-translational modifications[28,29]. Gene activation and repression, as well as transcriptional initiation and elongation, are regulated by many such histone modifications. In the last decade, studies of human and mouse embryonic stem cells have delineated the role of the histone methyltransferase (HMT) families Polycomb group (PcG) and Trithorax group (TrxG) in modulating the pluripotency and lineage restriction of several cell types[30]. For instance, numerous trimethylations of histone 3 lysine 4 (H3K4me3) mediated by the TrxG family surrounding the transcription start sites indicate transcriptional gene activation, and trimethylations of histone 3 lysine 36 (H3K36me3) in the gene body are generally associated with active gene transcription; alternatively, the trimethylation of histone 3 lysine 27 (H3K27me3) mediated by the PcG complex is associated with transcriptional repression[28]. Although the repressive H3K27me3 mark is transmitted to daughter cells[31] and is dominant over the permissive H3K4me3 mark[32], transcriptional gene activation requires the demethylation of H3K27me3, which is mediated by the demethylase families lysine-specific demethylase 6A (Kdm6a) and KDM1 lysine-specific demethylase 6B (Kdm6b)[33-35]. Thus, whereas polycomb repressive complex 2 (PRC2) establishes gene silencing at developmentally regulated loci, the TrxG and Kdm6a/Kdm6b families work together to antagonize the repressive activity of PRC2 and to promote gene expression in specific cell types.

Histone acetylation

Histone acetylation modulates transcription *via* multiple mechanisms. The acetylation of lysine residues within histone tails neutralizes their positive charge, thereby facilitating chromatin relaxation and increasing the accessibility of transcription factors to their target genes[36]. Acetylated histones are also recognized as binding sites for transcriptional activators. Conversely, histone deacetylation induces transcriptional repression by compacting the chromatin structure[37]. The combined activities of two enzyme families, histone acetyltransferases (HATs) and deacetylases (HDACs), determine the overall levels of histone acetylation in the genome. Both HATs and HDACs act on chromatin by associating with a variety of DNA-binding transactivator proteins. In some cases, DNA targeting involves other chromatin-modifying activities, such as histone methylation. Thus, the effects of HATs and HDACs on gene regulation depend on the cell type and the spectrum of available partners[38].

Noncoding RNAs

Advances in the field of gene regulation mediated by single-stranded noncoding RNA molecules have demonstrated their importance in gene regulatory networks. Until recently, small noncoding RNAs (miRNAs) were believed to solely negatively regulate target mRNAs[39]. However, published studies are increasingly indicating that miRNAs can also stimulate gene expression in response to specific cellular conditions or cofactors[40]. miRNAs are able to reduce gene expression *via* multiple mechanisms. At the transcriptional level, miRNAs repress gene expression by pairing nucleotides 2 to 8, termed the seed region, to the seed match site in the target mRNA, typically positioned at the 3' UTR or, less frequently, at the 5' UTR or the coding region[41]. In addition to transcriptional effects, miRNAs can repress translation initiation *via* multiple mechanisms, such as promoting mRNA degradation or interfering with the formation of closed-loop mRNA or other translation initiation factors[41]. Moreover, increasing evidence indicates that some miRNAs can upregulate gene expression in specific cell types and under certain conditions *via* the direct action of miRNAs or *via* the indirect inhibition of repressive miRNA activity[42]. Another class of noncoding RNAs, long noncoding RNAs, has been shown to take part in many transcription regulatory processes[43] and post-transcriptional events, such as mRNA stability and translational control[44-46], and to function as competing endogenous RNA[47-49] by acting as an miRNA sponge to participate with coding RNA in a regulatory circuit that controls the binding of RNA to

miRNA.

Reciprocal and dynamic interactions between different epigenetic mechanisms and transcription factors modulate gene expression. For instance, changes in histone modifications are caused by the recruitment of chromatin-modifying enzymes, such as HATs or HMTs, by transcription factors and the RNA polymerase Ⅱ complex[28]; at the same time, combinations of histone modifications in the proximity of consensus sequences may anticipate and direct the binding of the transcription factor, facilitating the transcriptional activation of a given gene[50].

Numerous epigenetic mechanisms regulate the different phases of myogenesis, including chromatin remodeling and post-transcriptional gene regulation mediated by noncoding RNAs[51-53]. Such orchestrated regulation permits the correct timing of muscle-specific gene expression and influences the fate of muscle progenitors into muscle or non-muscle cell lineages[54,55]. In this review, we report and discuss the recent literature about the epigenetic regulation of the myogenic process from activation to proliferation and SC commitment. We focus on the epigenetic changes, specifically those mediated by chromatin methylation or acetylation and noncoding RNA function to regulate gene expression, that occur during the different steps of SC differentiation.

EPIGENETICS IN SCs

Epigenetics mediates most of the signaling integrating the regeneration cues released by interstitial cells and by the external environment within the SC niche. Our understanding of the highly coordinated layers of epigenetic regulation of SC maintenance, activation and differentiation and cross-talk of epigenetic regulatory mechanisms with muscle-specific transcriptional machinery has tremendously increased due to the recent results obtained *via* next-generation genome-wide sequencing[56]. Using ChIP-Seq experiments, chipped chromatin can currently be entirely mapped across the genome to identify the regions that are over-represented among these sequences, revealing the interactions between chromatin-remodeling enzymes, transcription factors and DNA, thereby facilitating the production of chromatin-state maps.

Epigenetic control of SC quiescence

In quiescent SCs, while the *Pax7* gene must be expressed, modulators of cell cycle progression and transcription factors of the myogenic lineage need to remain silenced. Increasing studies have suggested that quiescent SCs are not in a dormant state but rather are primed for activation and differentiation in response to external stimuli[57,58]. At the chromatin level, this primed state is maintained by the general lack of the repressive mark H3K27me3 across the genome and the concomitant presence of H3K4me3 at the transcription start sites of a large number of genes (nearly 50% of all annotated genes)[59], including myogenic regulatory factors such as MyoD, SRF and Myf5[60], whose encoded proteins are the primary activators of the myogenic program. Consistent with the notion that H3K4me3 alone does not predict the transcriptional state of a gene but rather marks the gene for transcriptional activation[61], neither the number nor the identity of genes marked by H3K4me3 is significantly different between activated and quiescent SCs. Indeed, SC activation is accompanied by the retention of H3K4me3 and the acquisition of H3K27me3 *via* PcG members[62], often in association with the transcriptional repressors YY1 and HDAC1. Interestingly, low levels of H3K27me3 are associated with the pluripotency of embryonic stem cells[56,63]. The current understanding is that the general lack of repressive H3K27me3 marks and the concomitant presence of H3K4me3 at the transcription start sites of a large number of genes may establish a permissive chromatin state that underlies and permits the pluripotency of stem cells. In addition, numerous transcription start sites across the genome of quiescent SCs contain bivalent chromatin domains[59], which are characterized by the concomitant presence of both H3K4me3 and H3K27me3 marks. Consistent with the presence of H3K27me3 marks, these genes are either not transcribed or transcribed at very low levels. Interestingly, bivalent domains correspond to genes that are associated with the development of other organs and tissues aside from muscle, suggesting that SCs retain the potential to adopt a non-myogenic fate because of the presence of bivalent domains that contribute to the determination of cell lineage[59].

miRNAs also contribute to the generation of an epigenetic state that enables the maintenance of the myogenic lineage in quiescent SCs and that facilitates the activation of muscle gene expression and the formation of differentiated myotubes in response to SC activation. An important role in the maintenance of muscle stem-cell quiescence has been demonstrated for microRNA-489, which is highly expressed in quiescent SCs, in which it suppresses the expression of the oncogene DEK, and which is rapidly downregulated upon SC differentiation[57]. Additionally, miR-31 has been demonstrated to play an important role in quiescent SCs[58]. In quiescent SCs, the *Myf5* gene has already been transcribed but cannot be expressed because miR-31 functionally inactivates Myf5 mRNA by retaining it inside cytoplasmic mRNP granules, thereby preventing its translation and blocking myogenic differentiation[58].

Epigenetic control of SC activation

In response to different stimuli, *e.g.,* muscle damage, SCs become activated, begin to express cell cycle markers, which are readily marked by the permissive H3K4me3[64], and re-enter the cell cycle. SCs that divide in a parallel orientation to the myofibers, undergo a symmetrical cell division and give rise to two SCs that can return to the quiescent state[8]. In contrast, cells that divide in the sagittal orientation undergo asymmetric cell division to produce one cell that returns to the

quiescent state and one proliferating myoblast[8]. The latter cell expresses the *Myf5* and *MyoD* genes, as well as genes that regulate cell cycle progression, all of which are characterized by the enrichment of the transcriptionally permissive H3K4me3 mark within their associated chromatin[19]; Pax7 is progressively silenced while transitioning from a transcriptionally permissive state of H3K4me3 to a repressive state of H3K27me3 throughout cell differentiation[65]. Additional mechanisms that regulate SC proliferation include p38-gamma MAPK, which phosphorylates the MyoD protein to reinforce the interaction between MyoD and the HMT KMT1A, and the consequent inhibition of the premature expression of the myogenin gene. Consistently, in p38-gamma MAPK-null SCs, KMT1A cannot associate with the myogenin promoter; therefore, myogenin is expressed earlier, resulting in decreased SC proliferation and defective differentiation[66].

During myoblast proliferation, distinct classes of HDACs are also involved in the repression of muscle gene transcription by countering the activities of HATs. Whereas local hyper-acetylation at consensus MyoD-binding sites in myoblasts likely predetermines the regions of chromatin accessibility, class Ⅰ and Ⅱ HDACs contribute to the hypo-acetylation of the *MyoD* gene and the inhibition of *MEF2* transcription and activation, respectively. In undifferentiated SCs, *MyoD* interacts with HDAC1, and this interaction is responsible for silencing the MyoD-dependent transcription of p21 and muscle-specific genes[67,68]. Moreover, class Ⅱ HDACs are localized to the nucleus during SC proliferation and are responsible for blocking the activity of the myogenic co-factor MEF2[69]. A recent study of HDAC4 function and SC proliferation reported that the HDAC4 levels positively correlate with the expression of *Pax7* and *Lix1*, both of which are important for appropriate SC proliferation[70]; however, the molecular mechanism underlying this phenomenon remains unclear.

SC proliferation is also promoted and maintained by miR-27a/b, which targets and downregulates myostatin mRNA[71]. Consistently, SCs treated with antagomirs specific to miR-27a/b displayed increased myostatin expression and reduced proliferation. In activated SCs, miR-27b plays an important role in determining the appropriate timing of myogenic gene expression and regulates the Pax3 protein levels to control the entry of these cells into the myogenic differentiation program[72]. SC proliferation is also promoted by miR-133a, which represses the expression of serum response factor[73], and by miR-682, which is highly upregulated during myoblast proliferation both *in vitro* and *in vivo*; the inhibition of miR-682 results in reduced myoblast proliferation[74]. Moreover, in activated SCs, tissue inhibitor of metalloproteinase 3 (TIMP3), an inhibitor of tumor necrosis factor (TNF)-alpha-converting enzyme, regulates TNF-alpha release and acts as a switch for myogenic differentiation. miR-206 promotes TIMP3 downregulation[75] and suppresses Pax3 expression[74], thereby promoting SC differentiation. Paradoxically, quiescent SCs express high levels of both Pax3 and miR-206. An additional layer of gene regulation explains these contradictory data. In fact, it has been shown that in quiescent SCs, Pax3 transcripts are alternatively polyadenylated and are expressed as shorter 3' UTR transcripts, thereby resulting in the resistance of *Pax3* expression to miR-206-mediated regulation[76].

Epigenetic control of SC differentiation

As a general rule, genes no longer required for lineage progression are targeted for stable repression[59,62]. Accordingly, during differentiation, SC chromatin converts to a more repressed state by accumulating H3K27me3 across the genome at both transcription start sites and intergenic regions. In fact, in contrast to the level of H3K4me3, the level of the repressive mark H3K27me3 is low in quiescent SCs and is dramatically increased in differentiating SCs. In particular, when SCs differentiate, PRC2 is released from muscle differentiation genes (*MyoD* and *SRF*) to translocate to loci that are typically repressed in differentiated myotubes, *e.g.,* Pax7. By inducing a transition from the transcriptionally permissive mark H3K4me3 to the repressive mark H3K27me3 on the *Pax7* gene, PRC2 contributes to the switching off of SC proliferation[65]. Similarly, a switch from the permissive mark H3K4me3 to the repressive mark H3K27me3 on genes involved in the cell cycle is mediated by the E2F family of transcription factors and by the retinoblastoma protein as the SC exits the cell cycle to terminally differentiate[64,77,78]. Moreover, Pax7 associates with the Wdr5-Ash2L-MLL2 HMT complex, which mediates H3K4me3[19]. The binding of the Pax7-HMT complex to Myf5 results in the formation of H3K4me3 on the surrounding chromatin. Thus, Pax7 also participates in the induction of chromatin modifications that stimulate transcriptional activation of target genes to regulate the entry into the myogenic developmental program. Concomitantly, lysine-specific demethylase 4A, together with heterochromatin protein 1 alpha, promotes the demethylation of H3K9me3 at myogenic promoters, facilitating myoblast commitment[79].

The Ezh2 subunit of PCR2 complex has been demonstrated to play a critical role in mediating SC differentiation into the skeletal muscle lineage by suppressing a subset of regulators of non-muscle cell fate. Indeed, Ezh2-mediated H3K27me3 marks are specifically present on genes associated with alternative lineage selection, although Ezh2 dos not suppress terminal differentiation into skeletal muscle[80]. In contrast to PRC2-Ezh2, PRC2-Ezh1 is required for the myogenic differentiation of SCs; specifically, PRC2-Ezh1 replaces PRC2-Ezh2 on the myogenin promoter to regulate the appropriate timing of the transcriptional activation of myogenin[81].

When SCs differentiate, HDAC1 downregulation and pRb hypo-phosphorylation occurs, enabling the formation of the pRb-HDAC1 complex in differentiated myotubes. The pRb-HDAC1 interaction coincides with the disruption of the MyoD-HDAC1 complex, the

transcriptional activation of muscle-specific genes, and the differentiation of myoblasts[68]. Muscle differentiation also induces the nuclear-to-cytoplasmic translocation of class Ⅱ HDACs, thereby releasing the inhibitory constraints on MEF2 and consequently activating the expression of muscle-specific genes[69].

Over the course of differentiation, p38 alpha/beta MAPK activity increases and is required for complete myoblast differentiation and fusion, which is partially due to its regulation of the epigenetic mechanisms controlling gene expression[82]. In particular, p38alpha/beta MAPK, by selectively enabling the recruitment of SWI-SNF to the gene promoters of myogenin and creatine kinase, facilitates chromatin remodeling and the consequent expression of muscle genes. Indeed, p38-alpha-null SCs display increased Pax7 expression, persistent proliferation, and impaired differentiation and fusion[83], highlighting the distinct role of different members of the p38 MAPK family in SC proliferation and differentiation. It appears likely that the relative abundance of p38-alpha and p38-gamma MAPK activity in activated SCs serves as a balance between SC proliferation and differentiation.

As SCs differentiate, the downregulation of the enzymatic subunit of PRC2-Ezh2 and its partner YY1 is mediated by the combined action of miR-214[84], miR-26a[85] and miR-29[86], thereby relieving PRC2-mediated repression of muscle genes. Once SCs differentiate, miR-128a, miR-1 and miR-206 cooperate to block cell proliferation by inhibiting the expression of several targets in the insulin signaling pathway and Pax7 expression[87,88]. Indeed, the loss of miR-1 and miR-206 increases Pax7 expression, enhances SC proliferation and significantly inhibits myoblast differentiation[87,89]. The inhibition of cell proliferation is also achieved *via* the downregulation of the *Ccnd1* gene by both miR-26a and miR-1[90]. In addition, miR-133a and miR-133b inhibit cell proliferation and promote myoblast differentiation by negatively regulating the FGFR1 and PP2AC proteins, which participate in ERK1/2-mediated signal transduction[91]. In addition to inhibiting Pax7, miR-206 promotes SC differentiation and fusion to muscle fibers *via* the suppression of a collection of negative regulators of myogenesis, such as notch3, igfbp5, Meox2, RARB, Fzd7, MAP4K3, CLCN3, and NFAT5[89,92]. An important role in determining SC lineage commitment has been attributed to miR-133[93]. By targeting the mRNA of PRDM16, a master gene for brown fat determination, miR-133 modulates the choice between the myogenic and brown adipose lineages during SC differentiation. In SCs, HDAC4 expression correlates with that of miR-133, and HDAC4 inhibition induces SCs to partially differentiate into adipocytes[70]; however, the link between HDAC4 and miR-133 has not been yet characterized. Moreover, by modulating the insulin-like growth factor (IGF)-1 pathway *via* the downregulation of the IGF-1 receptor, miR-133a promotes SC differentiation[94] and sarcomeric actin organization[95]. In differentiating myoblasts, the repression of tumor growth factor-beta signaling, which is known to negatively affect SC differentiation, is ensured by the combined activity of miR-26a, which represses Smad1 and Smad4 expression[96], miR-206 and miR-29, which are capable of inhibiting Smad3 expression[97]. Together with myomiRs whose expression is upregulated during SC differentiation, the expression of other microRNAs needs to be down-regulated in order to achieve SC terminal differentiation. One such example is miR-23a, which directly regulates the expression of myosin heavy chain genes[98].

CONCLUSION

The maintenance of skeletal muscle homeostasis is a key survival factor, considering that skeletal muscle accounts for approximately 40% of body mass. Skeletal muscle needs to efficiently respond to internal and external stimuli - such as changes in levels of blood sugar, circulating hormones, or growth factors or mechanical insults - or to pathological conditions to maintain homeostasis, particularly in muscle. Unequivocally, SCs play central roles in adult regenerative myogenesis and in the preservation of muscle mass. Different epigenetic marks contribute to the coordination of the precise time-dependent expression of different subsets of myogenic genes in SCs (Table 1 and Figure 1). For instance, the PcG catalytic subunit Ezh2 is specifically distributed on the regulatory regions of late but not early muscle genes[60], whereas the methyltransferases PRMT5 and CARM1 are detected on promoters of early and late muscle genes, respectively[99].

Despite the observation that most muscular diseases do not have an epigenetic cause *per se*, the importance of epigenetic pathways in modulating muscle-specific gene expression renders them as excellent candidate targets for disease interventions. For instance, an elegant study demonstrated that epigenetic commitment mediated by SMARCD3, a member of the SWI/SNF family of proteins, and MyoD is required for the efficient generation of skeletal muscle cells from human embryonic stem cells[100]. Several drugs that target epigenetic mechanisms are currently undergoing clinical trials for many diseases. These drugs include HDAC inhibitors[101] and HMT inhibitors alone[102] or in combination[103]. In amyotrophic lateral sclerosis, HDAC inhibitors have been proposed as potential drugs to ameliorate patient symptoms[104,105]. In the case of muscular dystrophy, HDAC inhibitors have been extensively studied using the mdx mouse model[106]; currently, these drugs are under review in a clinical trial for muscular dystrophy[107]. Their effects are believed to be primarily due to the inhibition of class Ⅰ HDACs[108]. However, the prolonged treatment of patients with drugs that inhibit these ubiquitously required chromatin-modifying enzymes is a potential concern. An alternative approach ideally relies on the identification of small molecules that interfere with the epigenetic enzymes to specific loci within the genome. This approach may provide similar benefits

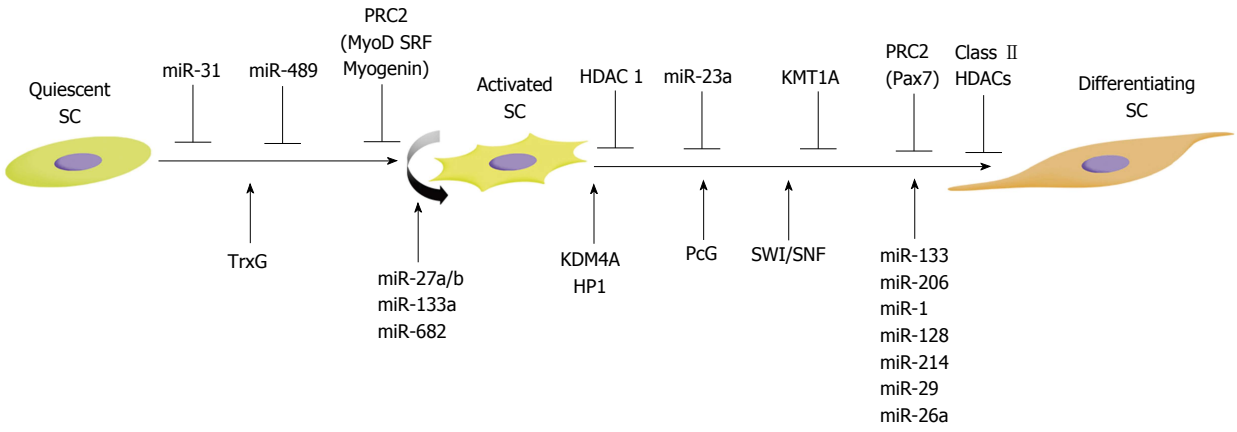

Figure 1 Schematic diagram of the epigenetic control of satellite cells during their activation and differentiation. SC: Satellite cells; PRC2: Polycomb repressive complex 2; TrxG: Trithorax group; PcG: Polycomb group; HDAC: Histone deacetylase.

Table 1 Summary of the main epigenetic events regulating the satellite cells status during myogenesis

SC status	Epigenetic regulation	Ref.
Quiescent	↓ H3K27me3[1] and ↑ H3K4me3[2]	[59,60]
	Bivalent domains (H3K27me3 + H3K4me3)	[59]
	↑ miR-489 ⊣ DEK[3]	[57]
	↑ miR-31 ⊣ Myf5[4]	[58]
Activated	↑ H3K4me3 on cell cycle genes	[19]
	↑ H3K27me3 on the *Pax7*[5] gene	[65]
	↑ P38 γ-MAPK[6] → p-MyoD[7] + KMT1A[8] ⊣ myogenin	[66]
	MyoD + HDAC1[9] ⊣ p21[10] and muscle genes	[67,68]
	HDAC4/5[11] ⊣ MEF2[12]	[69]
	HDAC4 → Pax7, Lix1[13]	[70]
	↑ miR-27a/b ⊣ myostatin and Pax3[13]	[71,72]
	↑ miR-133a ⊣ serum response factor	[73]
	↑ miR-206 ⊣ TIMP3[14] and Pax3	[75,76]
Differentiating	↑ H3K27me3 on cell cycle and alternative fate genes	[59,64,65,76-78]
	↑ H3K43me on Myf5	[19]
	↓ HDAC1 → MyoD-dependent genes	[68]
	HDAC4/5 in the cytoplasm → MEF2	[69]
	↑ P38 α/β-MAPK[15] → SWI-SNF[16] → myogenin and creatine kinase genes	[82,83]
	↑ miR-214, miR-26a, and miR-29 ⊣ Ezh2[17] and YY1[18]	[84-86]
	↑ miR-128a, miR-26a, miR-1, miR-206, miR-133a, and miR-133b ⊣ cell cycle	[87,88,90,91]
	↑ miR-206 ⊣ notch3[19], igfbp5[20], Meox2[21], RARB[22], Fzd7[23],MAP4K3[24],CLCN3[25], and NFAT5[26]	[59,89]
	↑ miR-133a ⊣ PRDM16[27] and the IGF-1[28] receptor	[78,80]
	↑ miR-26a ⊣ Smad1[29] and Smad4[30]	[96]
	↑ miR-206 and miR-29 ⊣ Smad3[31]	[97]
	↓ miR-23a ⊣ myosin heavy chain	[98]

[1]Trimethylated histone H3 lysine 27 (H3K27me3); [2]Trimethylated histone H3 lysine 4 (H3K4me3); [3]DEK oncogene; [4]Myogenic factor 5; [5]Paired box 7; [6]p38 gamma mitogen-activated protein kinase (P38 MAPK); [7]Phospho-myogenic differentiation; [8]Also referred to as suppressor of variegation 3-9 homolog 1 (Suv39h1); [9]Histone deacetylase 1; [10]Cyclin-dependent kinase inhibitor 1A; [11]Histone deacetylase 4/5; [12]Limb expression 1 homolog (chicken); [13]Paired box 3; [14]TIMP metallopeptidase inhibitor 3; [15]p38 alpha/gamma mitogen-activated protein kinase; [16]SWI/SNF complex; [17]Enhancer of zeste homolog 2; [18]YY1 transcription factor; [19]Neurogenic locus notch homolog protein 3 gene; [20]Insulin-like growth factor binding protein 5; [21]Mesenchyme homeobox 2 (Meox2); [22]Retinoic acid receptor, beta (RARB); [23]Frizzled class receptor 7 (Fzd7); [24]Mitogen-activated protein kinase kinase kinase kinase 3 (MAP4K3); [25]Chloride channel, voltage-sensitive 3 (CLCN3); [26]Nuclear factor of activated T-cells 5, tonicity-responsive (NFAT5); [27]PR domain containing 16 (PRDM16); [28]Insulin-like growth factor 1 (IGF-1); [29]SMAD family member 1; [30]SMAD family member 4; [31]SMAD family member 3. HDAC: Histone deacetylase.

without exerting side effects caused by the modification of gene expression in other cell types. In the last few years, numerous studies involving RNA-seq or ChIP-seq have contributed to provide a picture of the epigenetic characteristics of muscle-specific gene promoters during the different stages of myogenesis. However, most of these studies were performed using muscle cell lines and remain to be validated using *in vivo* models, for instance by analyzing mice in which individual epigenetic regulators are inactivated in a muscle-specific manner. The elucidation of the epigenetic mechanisms regulating SC function might reveal new targets for pharmacological manipulation to improve muscle regeneration and to promote muscle homeostasis under pathological

conditions.

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