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## The epigenetic regulation of embryonic myogenesis and adult muscle regeneration by histone methylation modification

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## ABSTRACT

Skeletal muscle formation in vertebrates is derived from the paraxial mesoderm, which develops into myogenic precursor cells and finally differentiates into mature myofibers. This myogenic program involves temporal-spatial molecular events performed by transcription regulators (such as members of the Pax, MRFs and Six families) and signaling pathways (such as Wnts, BMP and Shh signaling). Epigenetic regulation, including histone post-translational modifications is crucial for controlling gene expression through recruitment of various chromatin-modifying enzymes that alter chromatin dynamics during myogenesis. The chromatin modifying enzymes are also recruited at regions of muscle gene regulation, coordinating transcription regulators to influence gene expression. In particular, the reversible methylation status of histone N-terminal tails provides the important regulatory mechanisms in either activation or repression of muscle genes. In this report, we review the recent literatures to deduce mechanisms underlying the epigenetic regulation of gene expression with a focus on histone methylation modification during embryo myogenesis and adult muscle regeneration. Recent results from different histone methylation/demethylation modifications have increased our understanding about the highly intricate layers of epigenetic regulations involved in myogenesis and cross-talk of histone enzymes with the muscle-specific transcriptional machinery.

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**Abbreviations:** SCs, satellite cells; MRFs, myogenic regulatory factors; bHLH, basic helix-loop-helix; MEF2, myocyte enhancer factor 2; Shh, sonic hedgehog; BMP4, bone morphogenic protein 4; p38 MAPK, p38 mitogen-activated protein kinase; H3K4, methylation of histone H3 lysine 4; H3K9, methylation of histone H3 lysine 9; H3K27, methylation of histone H3 lysine 27; PRC2, polycomb repressive complex 2; LSD1, lysine specific demethyltransferase 1; KDMs, lysine demethyltransferases; UTX, ubiquitously transcribed tetratricopeptide repeat, X chromosome; ChIP, chromatin immunoprecipitation; TSS, transcription start sites

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## 1. Introduction

Embryo myogenesis or adult muscle regeneration is the programming of a population of muscle progenitors, embryonic or fetal myoblasts and satellite cells (SCs) into committing to the myogenic lineages and of myoblasts into differentiating into mature myofibers. The formation of skeletal muscles involves both genetic and epigenetic changes that culminate in alterations in gene expression [1]. Chromatin-modifying enzymes and remodeling complexes orchestrate the pattern of gene expression and reprogram the myogenic lineage toward terminal differentiation [1,2]. The transcriptional regulation of muscle specification has been well characterized, and the role of histone acetylation modification in control of muscle-specific gene expression has been studied extensively, however, less is known about the role of histone methylation modification in this process [3]. Here, we review the potential roles of histone modifications during myogenesis with a focus on H3 lysine 27 tri-methylation (H3K27me<sup>3</sup>), H3 lysine 4 tri-methylation (H3K4me<sup>3</sup>) and H3 lysine 9 di/tri-methylation (H3K9me<sup>2/3</sup>) markers at myogenic gene regulatory regions in myoblasts and satellite cells.

## 2. Myogenesis: gene regulatory networks and transcriptional mechanisms

### 2.1. Development of embryo myogenesis

Skeletal muscle is initiated in the somite (epithelial spheres along the anterior–posterior axis of the embryo) which derives from paraxial mesoderm adjacent to the neural tube and notochord [2,4,5].

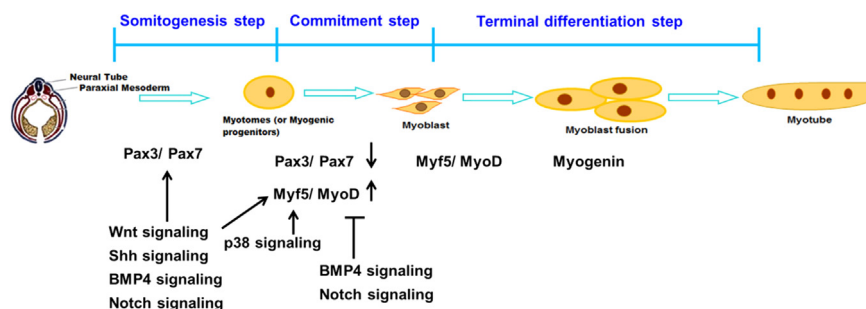
The newly formed dorsal somites rapidly differentiate into dermomyotomes, which are the source of muscle precursor cells. Cells from the dorsomedial part of the somites adjacent to the neural tubes migrate under the dermomyotomes to form the myotomes [6]. The myotomes are committed and differentiate into myoblasts, and final maturation of myotubes fuse into myofibers (Fig. 1). The epaxial (dorso-medial) part of the dermomyotomes and myotomes generate the back muscles while the hypaxial (ventro-lateral) somites generate the rest of the trunk and limb muscles [7–9].

### 2.2. Genetic regulatory networks in myogenesis

#### 2.2.1. Regulation of transcription regulators in myogenesis

The paired-homeobox family of transcription factors Pax3 and Pax7 are important upstream regulators of the myogenic process in the embryo myogenesis. In *Splotch* mice, because of mutation of *Pax3*, cells fail to develop the hypaxial domain of the somite and thus lack limb musculature and other muscle masses in the body. However, epaxial-derived muscles are less affected [6,10–12]. In the chick embryo, *Pax3:Pax7*-positive cells are maintained as proliferating cells and do not express myogenic regulatory factors or muscle proteins. However, they can give rise to skeletal muscle cells leading to subsequent skeletal muscle differentiation and producing muscle satellite cells [13]. *Pax3:Pax7* double mutants die at early fetal stages. In the absence of both Pax3 and Pax7 proteins, muscle progenitor cells do not activate the myogenic determination genes to enter the myogenic program [14].

The myogenic regulatory factors (MRFs) of *MyoD*, *Myf5*, *myogenin* and *Mrf4* genes have highly conserved basic helix-loop-helix domain (bHLH) structure and are expressed in the skeletal muscle



**Fig. 1.** A schematic representation of developmental myogenesis. It shows that the somites give rise to muscle progenitor cells, progenitor cells determinate and proliferate as myoblasts, and myoblasts differentiate into myotubes. During this process, the action of both positive and negative signals control the spatio-temporal expression of muscle genes. And gene regulatory networks are performed by myogenic transcriptional factors.

lineage [15,16]. When myogenesis continues, *Pax3* expression decreases gradually while MRF family gene expression increases significantly [17]. The high expression of *Myf5* gene forms the primitive muscle structure containing committed muscle cells [15,18]. Subsequently, *MyoD* gene is activated after the onset of *Myf5* expression in the dermomyotome [4,19]. Two of these factors are muscle determination genes. They are the major factors that activate the myogenic program in muscle and non-muscle cells [20]. In contrast to *MyoD* and *Myf5*, *myogenin* is a key gene for activating the muscle differentiation program. The number of skeletal muscle fibers are reduced in mice carrying mutations in *myogenin* [21,22]. The role of *Mrf4* is more complicated in myogenesis. *Mrf4* closely linked with *Myf5* gene in mice is activated in myotomes following the *Myf5* expression, and its expression is reinitiated in differentiating muscle cells stage. Overexpression of *Mrf4* can compensate for the muscle fibers in *myogenin* double mutations embryo [23,24].

The myocyte enhancer factor 2 family alone has no myogenic activity but they assist the MRFs through transcriptional co-operation to mediate expression of muscle-specific genes [25,26]. *MyoD* family of MRFs have MEF2 binding sites, so MEF2 could provide a positive feedback loop and cooperative interactions between many MRF proteins [27]. The other families of transcription factors for myogenesis are the Six family of homeobox proteins *Six1* (the sine oculis-related homeobox 1) and *Six4* and their transcriptional cofactors eyes-absent homologs *Eya1* and *Eya2*. Six proteins associate with the *Eya1* and *Eya2*, generating a regulatory cascade that directs dermomyotomal progenitor cells toward the myogenic lineage. Hence, they are critical in the migration of hypaxial myogenic precursor cells from the somite to the limb and serve as upstream regulators of *Pax3*, *MyoD* and *myogenin* during somitogenesis [28–30].

### 2.2.2. Regulation of extracellular signals in myogenesis

During embryogenesis, the adjacent structures in embryo release both positive (Wnt, Sonic hedgehog (Shh) and noggin) and negative (BMP4 and Notch) signals that control the spatial and temporal expression pattern (Fig. 1). All of these signals regulate the amount of myogenic regulatory factors for balancing between proliferation and differentiation status during muscle development [2,15].

Wnt signaling is involved in forming the dermomyotome and myotome [15,31]. *Wnt1* and *Wnt3* are produced by the dorsal neural tube, and *Wnt4*, *Wnt6* and *Wnt7a* are produced by the surface ectoderm [32]. The expression of the *Pax3* and *Myf5* is increased by *Wnt1* and *Wnt3* [33], while the expression of *MyoD* is reduced by *Wnt6* and *Wnt7a* [34]. Moreover, Wnt signaling activates the program of myogenesis through the TCF/ $\beta$ -catenin pathway [8].  $\beta$ -catenin acts as a Wnts receptor and is present in the myotome depending on *Wnt1* or *Wnt3a*.  $\beta$ -catenin interacts with Shh and is up-regulated in the dorsal somite prior to *MyoD* activation.

Shh signaling regulates myogenesis mechanism through the down-regulation of *Pax3/7* and up-regulation of *Myf5/MyoD* expression, leading to myogenic cells to withdraw from proliferation and start differentiation [38–40]. Whereas Shh signaling is controlled by Wnt signaling through the regulation of *Gli2* and *Gli3* [35].

BMP4 (bone morphogenic protein 4) can up-regulate *Pax3* expression in the embryonic trunk [36]. Overexpression of *BMP4* in the somite can inhibit *MyoD* expression, resulting in the inhibition of myotome formation [37]. Overexpression of *BMP2b* increases expression of *Pax3* and the number of *Pax7*-positive myogenic precursor cells and delays muscle differentiation via decreasing *MyoD* expression in the zebrafish embryo [38]. As BMP4's antagonist, noggin lies downstream of the Shh and Wnt signaling

pathways and physically interacts with it and counteracts the effects of BMP4 on myotome formation [39,40].

The activity of Notch signaling influences cell differentiation, proliferation, and apoptotic programs [41]. Stimulation of Notch signaling in *Pax3*-positive myogenic progenitor cells inhibits muscle differentiation and causes a reduction in myogenic cells that migrate into the limbs [42]. *MyoD* cooperated with the DNA binding protein RBP-J and the transcriptional repressor *Hes1* (hairy and Enhancer of split) can suppress Notch signaling activity [43]. *Hes1* also effectively inhibits *MyoD*, inducing myogenic conversion of C3H10T1/2 cells into muscle cells [44]. Two-hybrid assays indicate that constitutively active Notch is able to block MEF2C DNA binding ability [45].

The p38 MAPK (p38 mitogen-activated protein kinase) signaling is an intracellular signaling pathway that activates myogenic cell lines to affect the muscle transcription program. In mice, (1) p38 is rapidly activated during myocyte differentiation. Conversely, inhibition of p38 activity prevents the differentiation in myogenic cell lines and human primary myocytes, (2) overexpression of p38 stimulates the transcriptional activity of *MyoD* and in embryonic fibroblasts of p38 double mutant mice, the efficiency of *MyoD*-dependent myogenic conversion is reduced, and (3) p38 signaling activates MEF2C transcription factor through selective phosphorylation of MEF2C on Thr293 residue in differentiating myocytes [46–48].

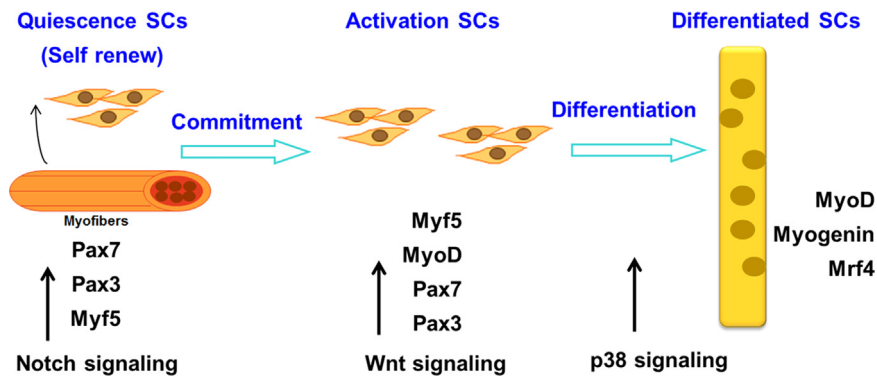
### 2.3. Adult muscle regeneration: common mechanisms and mediators

Adult muscle regeneration or *de novo* myogenesis in vertebrates depends on the injured tissue recruiting an undifferentiated myogenic progenitor cells or muscle stem cells to the site of injury. In adult skeletal muscle, this function is provided by the satellite cells [4,15,49,50]. Responding to injury, quiescent satellite cells are activated and then proliferate as myoblast cells and differentiate to form new muscle fibers or returned to quiescence to maintain the stem cell pool (self-renewal).

#### 2.3.1. Regulation of transcription regulators in adult muscle regeneration

Similarly, in embryo myogenesis, *Pax7* as a satellite cell marker is expressed in quiescent satellite cells in muscles from throughout the body [4,14,19,49,51–53] and *Pax7* is co-expressed with *MyoD* in their proliferating myoblast progeny [54]. *Pax3* is expressed in satellite cell in muscles from approximately 50% of forelimb muscles and most ventral trunk muscles [49]. Constitutive expression of *Pax3* or *Pax7* in satellite cells results in an increased proliferative rate and prevents differentiation [54]. Interestingly, in *Pax7* mutant cells, the cell number progressively decreases in both *Pax3*-expressing and *Pax3*-non-expressing muscles. It has been shown that *Pax7* cannot be compensated by *Pax3* during the postnatal development of skeletal muscles [49]. In addition, recent studies analyzing the role of *Pax7* in adult satellite cells have demonstrated that temporary deletion of *Pax7* in adult satellite cells results in normal muscle regeneration after injury, indicating that *Pax7* is not required for *de novo* myogenesis in the adult [55], but long-term *Pax7* abrogation leads to loss of adult satellite cells, resulting in impaired muscle regeneration after injury [56,57].

*Myf5* gene is already expressed in quiescent satellite cells. *MyoD* gene is expressed in the activated satellite cells and, along with down-regulation of *Pax7* expression, subsequently differentiates with the expression of *myogenin* gene [49,50,58–60]. However, overexpressing *Pax7* in myoblasts represses *MyoD* expression and inhibits myogenesis. Ectopic expression of *Pax7* can efficiently block the *MyoD*-dependent conversion of mesenchymal stem cells (10T1/2 cells) to the muscle lineage [61]. These studies suggest that satellite cells are heterogeneous population cells.



**Fig. 2.** A schematic representation of adult muscle regeneration. Upon muscle injury, quiescent satellite cells are activated and divided asymmetrically, generating a self-renewing cell and a committed progenitor which begins to express *Myf5*. Next, activated satellite cells express *MyoD* and down-regulate *Pax7*. Then activated satellite cells will differentiate and fuse to form new myofibers during adult muscle regeneration.

They have maintained stem cells self-renewal ability and given rise to committed myogenic progenitors which later undergoes differentiation. The molecular mechanisms may involve in a reciprocal inhibition between *Pax7* and the muscle regulatory factors (Fig. 2).

### 2.3.2. Regulation of extracellular signaling in adult muscle regeneration

Studies with adult muscle regeneration indicate that Wnt signaling induces  $CD45^+$  stem cells purified from regenerating muscle to form determined myoblasts but fails to induce  $CD45^+$  stem cells purified from uninjured muscle to form myogenic cells. Regenerating muscles with rejection of Wnt antagonists sFRP2/3 inhibits  $CD45^+$  stem cells proliferation and myogenic specification.  $\beta$ -catenin, as a key downstream transcriptional co-activator of Wnt signaling, is strongly up-regulated in satellite cells and during muscle regeneration. Other studies indicate that activation of the Wnt/ $\beta$ -catenin signaling pathway causes changes in the structure of chromatin at the *MyoD* and *Myf5* promoters, leading to increases in the expression of *Myf5* and *MyoD* in satellite cells and in the number of proliferative  $Pax7^+/Myf5^+$  and  $Pax7^+/MyoD^+$  cells in skeletal muscle. All of these findings suggest that Wnt signaling plays a critical role in the regulation of satellite cells in adult muscle regeneration [62–65].

Notch-1 is expressed in satellite cells, and its activity is essential for maintaining the expression of *Pax7*. Attenuation of Notch signaling by increasing expression of inhibitor Numb leads to the commitment of satellite cells to the myoblasts fate [66,67].

## 3. The epigenetic modifications in myogenesis and adult muscle regeneration

### 3.1. Epigenetic code

The concept of “Epigenetics” was first introduced by Conrad Waddington in 1942. After decades of research, epigenetics has been found to involve DNA methylation, histone modification, chromatin remodeling, and non-coding RNAs (ncRNAs) in mammalian animals [68]. For nucleosomes, the basic unit of chromatin, the amino residues on histone tails (histone amino termini or histone N-termini) are subject to diverse arrays of covalent post translational modifications, including acetylation, methylation, phosphorylation, and ubiquitination. Distinct histone modifications generate synergistic or antagonistic interaction for chromatin-associated proteins, which in turn determine dynamic transitions between transcriptionally active or silent states of chromatin [69,70]. Histone modifications influence chromatin packaging and are read by adaptor molecules, chromatin modifying enzymes,

transcription factors and transcriptional repressors, and thus contribute to the regulation of transcription. Epigenetic histone modifications have been best characterized for histones H3 and H4 [71]. Histone methylation occurs on arginine and lysine amino acids residues. Mono-, di- or tri-methylation has been discovered on histone H3 and H4 [68].  $H3K4me^3$  has been associated with euchromatin and facilitates active transcription by recruiting the RNA polymerase II complex at gene promoter/enhancer regions [72]. In contrast,  $H3K27me^3$  is mutually exclusive with  $H3K4me^3$ , which is generally considered a repression marker for transcription [73].  $H3K9me^2$  or  $H3K9me^3$  is linked to silencing of gene expression at euchromatin and heterochromatin [74].

### 3.2. Epigenetic modifications in embryo development

#### 3.2.1. Epigenetic modifications in embryonic stem (ES) cells

Embryo development proceeds from a cascade of gene activation and repression. Differentially expressed embryonic genes are regulated by various patterns of histone modifications on unmethylated DNA, which create a developmentally permissive chromatin state and confer a specific chromatin configuration on gene regulatory and coding regions [71,75]. The analysis of histone modifications in ES cells has generated genome-wide maps of  $H3K27me^3$  and  $H3K4me^3$  [76]. ChIP assays for zebrafish embryos show that all embryonic gene promoters have severe deacetylation on H3K9 and H4 relative to  $H3K4me^3$ . Deacetylation is accompanied by enrichment in  $H3K9me^3$  and  $H3K27me^3$ , suggesting that embryonic genes are associated with repressing histone modifications in fibroblasts [75]. ChIP-chip experiments from developmental transition from late fetus to lamb during late ovine skeletal muscle development reveal that  $H3K27me^3$  modification is associated with genes, transcription start sites (TSS) and CpG islands and with transcriptional silencing. Most modified genes have no changes during the muscle transition, indicating that  $H3K27me^3$  does not have a large role in late muscle maturation [77]. These findings suggest that  $H3K27me^3$  represses developmental genes at initial embryonic stages.

Recent data from studies in ES cells show that the function of  $H3K4me^3$  in ES cells is poised the expression of embryonic genes that allows for the proper activation of lineage regulators upon differentiation, but its mechanism remains unclear. How  $H3K4me^3$  and  $H3K27me^3$  markers are established in ES cells is still unclear. The existing evidence shows that some developmental regulatory genes are already marked by  $H3K4me^3$  and  $H3K27me^3$  in sperm [76,78].

A prevalent model in stem cell biology suggests that the loss of pluripotency entails global increase in heterochromatin and coincident shutdown of lineage-unrelated genes [79].  $H3K9me^2$



appears to be the most abundant heterochromatic modification and occupies large parts (> 50%) of the genome in ES cells. Analysis of the H3K9me<sup>2</sup> in ES cells shows that active regions are mutually exclusive with H3K9me<sup>2</sup>, and the majority of H3K4me<sup>2</sup> regions are mutually exclusive with H3K9me<sup>2</sup> [79,80]. Moreover, G9a has been implicated in embryonic development, based on the embryonic lethality of G9a knockout mice [81].

### 3.2.2. Bivalency of H3K4 and H3K27 methylation

Bivalent domains were first identified at the TSS of key regulators of lineage determination in cultured ES cells [65]. ChIP-chip studies in human and mouse ES cells show that developmental genes are maintained in a bivalent status. These bivalent promoters are maintained in a repressive chromatin state through H3K27me<sup>3</sup>, however, the presence of an active chromatin modification H3K4me<sup>3</sup> suggests that these genes are poised for rapid induction [82,83].

In ES cells, Polycomb group (PcG) proteins predominantly suppress H3K4-methylated CpG island promoters. Polycomb repressive complex 2 (PRC2) and polycomb repressive complex 1 (PRC1) seem to cooperate to counteract H3K4 methylation. PRC2 contributes to silencing by recruiting H3K4 histone demethyltransferases, thereby regulating the homeostasis of the bivalent state. Furthermore, PRC2 facilitates PRC1 targeting by providing the H3K27me<sup>3</sup> binding site [83]. Similarly, the studies of Orford and colleagues show that H3K4me<sup>2+/me3-</sup> or H3K4me<sup>2+/me3+</sup> CpG island promoters are repressed at the progenitor stage by the presence of H3K27me<sup>3</sup>, but non-CpG island tissue-specific genes are amenable to marking by H3K4me<sup>2</sup> “only” [83,84]. During myoblasts differentiation, modifications of H3-K4 by Set7 and H3-K9 by Suv39h1 are mutually exclusive at the promoters/enhancers of myogenic differentiation genes [85].

*Pax3* is the only myogenic transcription factor with bivalent domains in quiescent satellite cells, which correlates well with the low expression levels of *Pax3* in satellite cells of adult mice. In contrast, *Pax7* is only marked by H3K4me<sup>3</sup> at its TSS. On the other hand, *myogenin* is not marked by either H3K4me<sup>3</sup> or H3K27me<sup>3</sup> in quiescent satellite cells, but shows significant enrichment of the H3K4me<sup>3</sup> mark at its TSS upon activation [86].

### 3.3. Histone methylation modifications in myogenesis

The transition from proliferation into differentiation of muscle cells is accompanied by a number of chromatin-associated

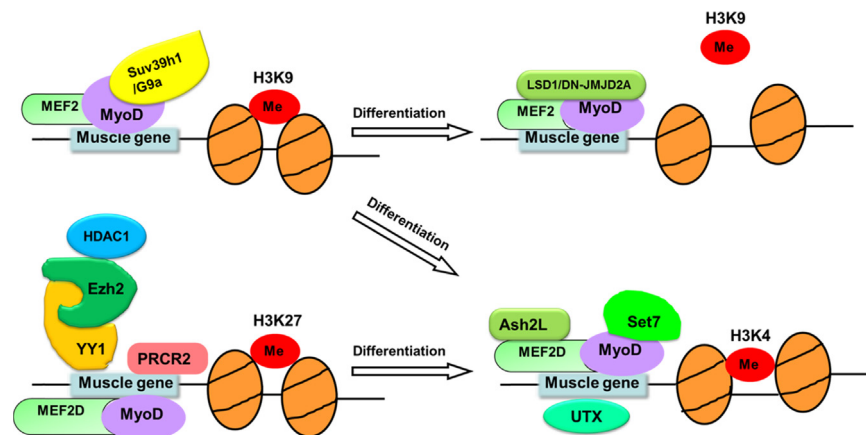
complexes with histone modifications through dynamic changes in chromatin to balance activation or repression at regulation of muscle genes transcription. Histone methylation modifications as “on/off” switches play an important role in lineage commitment and differentiation (Fig. 3). Generally, transient and long-term gene silencing are performed by tri-methyl histone H3 on lysine 9 and 27, and gene activation is regulated by tri-methylation of H3K4.

#### 3.3.1. H3K27 methylation modification

Tri-methyl lysine modifications on histones are the most stable epigenetic marks and control chromatin-mediated regulation of gene expression [87,88]. H3K27me<sup>3</sup> is known to regulate muscle differentiation through silencing muscle-specific genes and is widely distributed throughout the genome in both myoblasts and myotubes, including promoters, gene bodies, and intergenic regions [89]. While PcG proteins have histone lysine methyltransferase activity, PRC2 catalyzes tri-methylation of histone H3 lysine 27 that is associated with transcriptional silencing [90–92]. The global mapping analysis reveals that the PcG proteins bind a large number of tissue-specific differentiation genes such as *myogenin* and *CKM*, which are specifically induced in muscle differentiation [92]. The *Ezh2* protein is one component of PRC2 [93]. *Ezh2* is expressed in the myotome compartment of mouse somite and in proliferating satellite cells and is down-regulated in terminally differentiated muscle cells. This coincides with activation of muscle gene expression in differentiation of myoblasts. In undifferentiated myoblasts, endogenous *Ezh2* is associated with the transcriptional regulator YY1 and histone deacetylase HDAC1. And the complex will occupy genomic regions of silent muscle-specific genes [91].

#### 3.3.2. H3K4 methylation modification

Trithorax (TrxG) group proteins are known for antagonizing polycomb group proteins repressing. These two group of proteins establish the transcription patterns that maintain the repressed or active transcription states of developmentally important genes [94]. TrxG proteins with a SET domain catalyze tri-methylation of H3 lysine 4 [94]. H3K4me<sup>3</sup>, as an active marker, is almost exclusively found in promoter regions of actively transcribed genes [87,88]. Chromatin immunoprecipitation experiments find that the promoter region of *myogenin* gene becomes enriched in H3K4me<sup>3</sup> during C2C12 cell differentiation. As Ash2L protein is a component of H3K4 methyltransferase complexes and is



**Fig. 3.** Regulation of histone methyltransferases in muscle differentiation. In proliferation of myoblasts and quiescent satellite cells, the cooperation of myogenic genes and histone methyltransferases represses expression of muscle differentiation genes and maintains H3K27 or H3K9 methylation on muscle-specific gene promoters. Once myoblasts and quiescent satellite cells are activated, the cooperation of myogenic genes and histone methyltransferases are released by histone demethyltransferases or pro-myogenic triggering signaling cascades (e.g. p38 signaling). The H3K4 tri-methylation status exists at the chromatin region of muscle-specific gene promoters in differentiated muscle cells.

expressed in C2C12 cells, protein-protein interaction analysis indicates that MEF2 (MEF2D and MEF2C) is associated with Ash2L and MLL complexes (including MLL2, Set1 and MLL3) which is recruited to the *myogenin* promoter in differentiated C2C12 cells and the nucleosomes containing H3K4me<sub>3</sub> during C2C12 cell differentiation. And this process needs phosphorylation of MEF2D by p38- $\alpha$  via p38 signaling pathway [95–97].

Mixed lineage leukemia 5 (MLL5) is an H3K4 methyltransferase encoding a SET and PHD domain protein homologous to *Drosophila* Trithorax and yeast SET3, but appears to lack intrinsic HMT activity. In quiescent myoblasts, MLL5 regulates both the cell cycle and differentiation via a hierarchy of chromatin and transcriptional regulators. Knocking down *MLL5* delays entry of quiescent myoblasts into S phase, but hastens S-phase completion by inducing the expression of *cyclin E* and *cyclin A* (*CycA*). Meanwhile, *CycA* mRNA is induced throughout G<sub>0</sub>/G<sub>1</sub>, with activation of the cell cycle regulated element (CCRE) in the *CycA* promoter. Comparing with normal cells, defective differentiation in *MLL5* knockdown myoblasts correlates with reduced expression of *Pax7* throughout the cell cycle, suppressed expression of *Myf5* in G<sub>0</sub>, with delayed G<sub>1</sub> induction, altered function of *MyoD*, and inefficient activation of *myogenin* [98].

Set7, the H3K4 specific methyltransferase, catalyzes H3K4 methylation *in vitro* and *in vivo* and potentiates transcription activation. Set7 contains a SET domain, but lacks the pre- and post-SET domains [99]. Studies show that the expression of *Set7* is dynamically increased during normal skeletal muscle differentiation. Knockdown of *Set7* by siRNA represses the expression of *MyoD*, *myogenin* and *MyHC* and reduces the number of myotubes. Moreover, Set7 physically interacts with MyoD and Set7 association and the H3K4 monomethylation status on the regulatory regions of myogenic differentiation genes substantially increased during C2C12 cells differentiation. All of these findings suggest that Set7 has a role in skeletal muscle development and is required for the terminal differentiation of skeletal muscle myoblasts [85].

### 3.3.3. H3K9 methylation modification

Suv39h1/KMT1A is a H3K9 specific methyltransferase catalyzing di- or tri-methylation of histone H3 lysine 9 [100,101], that is associated with Heterochromatin protein 1 (HP1) in gene silencing [102,103]. Studies reveal that Suv39h1 has multi-roles in regulating muscle genes transcription during muscle cell differentiation. Mal et al. demonstrate that Suv39h1 interacts with MyoD and represses MyoD-dependent muscle gene expression. This repression requires Suv39h1 association with MyoD and sustains methylation of H3K9 on *myogenin* promoter [104]. Ait-Si-Ali et al. demonstrate that Suv39h1 depleted myoblasts have a poor capacity to fuse into myotubes and are unable to express early and late muscle differentiation markers, such as *myogenin*, *MCK* and *MyHC* [105].

G9a is a member of SET domain containing Suv39 family [106] and it mainly catalyzes mono- or di-methylation of histone H3 lysine 9 in euchromatin [81,107]. G9a is also involved in catalyzing histone H3 lysine 9 tri-methylation [108] and histone H3 lysine 27 methylation [106]. Recently, G9a is reported to have a dynamical expression mode during skeletal muscle cells differentiation. G9a can inhibit skeletal muscle cells differentiation in a methyltransferase activity-dependent manner by mediating H3K9me<sup>2</sup> around MyoD target gene promoters. In addition, G9a catalyzes MyoD methylation at K104 site in a methyltransferase activity-dependent manner to constrain its transcriptional activity [107].

Sharp-1, a DNA-binding transcription and basic helix-loop-helix transcription factor, is a potent repressor of skeletal muscle differentiation via negatively affecting MyoD function by competition for binding to E-box sites, formation of inactive heterodimers, and inhibition of its transcriptional activity. Sharp-1 is

expressed widely in a number of cell types, including developing skeletal muscles. Current evidence demonstrates that G9a associates with and enhances Sharp-1-mediated transcriptional repression and meanwhile overexpression of Sharp-1 correlates with increased H3K9me<sup>2</sup> on the myogenin promoter and enhanced MyoD-G9a association and MyoD methylation in C2C12 cells [109].

## 3.4. Histone demethylation modifications in myogenesis

### 3.4.1. H3K9 demethylation modification

Histone demethyltransferases regulates gene expression by removing histone methyl group marks [110]. LSD1 (Lysine Specific Demethylase 1), a nuclear homolog of amine oxidases, is a lysine specific demethyltransferase which is responsible for removing methyl group from mono-, di-methylation of H3K4 and H3K9 [111–113]. Therefore, LSD1 can repress H3K4 transcription activation and activate H3K9 transcription repression [114]. Current studies have proven that expression of *LSD1* is increasing during myogenic cells differentiation. LSD1 is directly associated with MyoD and MEF2 on their target promoters to activate myogenic genes *in vivo*. Abrogation of *LSD1* can cause myoblasts without differentiation ability. In short, it suggests that catalytic activity of LSD1 is vital for skeletal muscle cells differentiation [115].

Another histone lysine demethyltransferase (KDM) JHDM2A, a jumonji (or JmjC) domain containing protein that specifically removes methyl group from H3K9 [116,117]. JHDM2A mediates the demethylation of mono- and di-methyl H3K9 *in vitro* and *in vivo* [117]. A new isoform of JMJD2A, named DN-JMJD2A, lacks the N-terminal demethyltransferase domain whose expression is up-regulated during muscle cells differentiation [3]. DNA microarray analysis indicates that the expression of muscle-specific genes as *myogenin* and *CKM* are strongly decreased by knockdown DN-JMJD2A. ChIP analysis indicates that DN-JMJD2A is recruited to *myogenin* promoter and DN-JMJD2A can promote the demethylation of H3K9me<sup>2</sup> at *myogenin* promoter [3]. Moreover, DN-JMJD2A promotes MyoD induced-myogenic conversion of NIH3T3 cells into muscle cells [3].

Another JmjC domain containing demethyltransferases (Jmjd), Jmjd2C, one of Jmjd2 family members, demethylates histone H3K9me<sup>2</sup> and H3K9me<sup>3</sup>. It has been reported that Jmjd2C increases MyoD transcriptional activity to facilitate skeletal muscle differentiation by increasing MyoD stability through inhibiting G9a-dependent MyoD degradation [118].

### 3.4.2. H3K27 demethylation modification

The UTX (ubiquitously transcribed tetratricopeptide repeat, X chromosome) protein, belongs to a subfamily of JmjC domain-containing proteins. As mammalian H3K27 specific demethyltransferases, the UTX removes di- and tri-methyl group from H3K27me<sup>2/3</sup> [119–121]. UTX is enriched around the transcription starting sites of many *HOX* genes in primary human fibroblasts, and UTX is present in the MLL2/3/4 containing histone H3K4 methyltransferase complexes altering histone methylation dynamics. These findings suggest that UTX is essential for H3K27 methylation regulation and is also important for the stringent regulation of transcription during cellular differentiation [119–121]. In differentiating myoblasts, UTX is recruited to the transcriptional regulatory region of both the *myogenin* and *CKM* genes with removal of the repressive H3K27me<sup>3</sup> mark at both genes. Knockdown of UTX in C2C12 cells prevents the formation of multinucleated, MyHC-positive myotubes [122]. The recent findings demonstrate that UTX with an important role in mediating demethylation of H3K27me<sup>3</sup> at muscle-specific genes during myogenesis. In addition, histone chaperone Spt6 is reported to promote UTX chromatin enrichment and reduce H3K27me<sup>3</sup> level at *myogenin* regulation regions [123].

### 3.5. Histone methylation modifications in satellite cell regeneration

In proliferating satellite cells, histones associated with the promoters of genes specifically involved in muscle differentiation are hypo-acetylated and contain H3K9me<sup>2</sup>, H3K9me<sup>3</sup> and H3K27me<sup>3</sup> residues [65]. *Pax7* is a key mark in satellite cells and has predominant function during the postnatal development of skeletal muscles. Studies on protein–protein interactions provide a post-translational modification mechanism for regulating *Pax7* and *Pax7* target genes *Myf5* and *MyoD* function in satellite cells.

#### 3.5.1. H3K27 methylation modification

H3K27 methyltransferases play important roles in the epigenetic regulation of stem cell quiescence. *Ezh2* is expressed in quiescent satellite cells and required for homeostasis of the adult satellite cell pool [124]. When proliferating myoblasts receive differentiation signals, phosphorylation of the enhancer of *Ezh2* recruits the Trithorax group/Ash2L complex through p38-phosphorylated MEF2D and induces transition from a transcriptionally permissive H3K4me<sup>3</sup> mark to a repressive H3K27me<sup>3</sup> mark on the *Pax7* promoter to down-regulate its expression. Myogenic genes that are highly expressed in proliferating or differentiated cells, such as *MyoD* and *myogenin*, are also marked by the repressive H3K27me<sup>3</sup> mark [97,125,126]. While in activated satellite cells, the level of H3K27me<sup>3</sup> increases significantly across the genome, whereas the H3K4me<sup>3</sup> mark is retained [65,127].

Mice with satellite cell-specific inactivation of *Ezh2* have reduced muscle mass, a decreased number of satellite cells and exhibit defective regeneration after injury. These differences have been attributed to a failure of the proliferative progenitor population to expand (*Ezh2* maintains a key phase of muscle satellite cell expansion but does not regulate terminal differentiation.) and to impair maintenance and/or return to quiescence (self-renewal) after injury [124].

#### 3.5.2. H3K4 methylation modification

Yeast two-hybrid screening, tandem affinity purification (TAP) and mass spectrometry experiments indicate that *Pax7* is associated with the Wdr5–Ash2L–MLL2 histone methyltransferases complex which directs methylation of H3K4 at the *Myf5* promoter, resulting in H3K4 tri-methylation of surrounding chromatin [96,128,129]. The comparative microarray analysis, siRNA, fluorescence-activated cell sorting (FACS) and ChIP confirm that *Myf5* is directly regulated by *Pax7* in C2C12 cells which are derived from satellite cells [128]. Currently protein–protein interaction experiments indicate that *Pax7* is a substrate of CARM1, and CARM1 could specifically methylate multiple arginine in the N-terminus of *Pax7*. Methylated *Pax7* directly binds to C-terminal cleavage forms of MLL1/2 and recruits Ash2L:MLL1/2:Wdr5:Rbbp5 histone H3K4 methyltransferase complex to regulatory enhancers and the proximal promoter of *Myf5* [95,130]. Together, these experiments provide important epigenetic mechanisms that *Pax7* stimulates transcriptional activation of *MyoD* family of target genes to regulate entry into the myogenic developmental program by inducing chromatin methylation modification.

#### 3.5.3. H3K9 methylation modification

The p38 signaling is a trigger in satellite cells during muscle regeneration. p38- $\gamma$  is highly expressed in skeletal muscles. During adult myogenesis, p38- $\gamma$  phosphorylates *MyoD* on Ser199 and Ser200, which results in enhanced occupancy of *MyoD* on the promoter of *myogenin* together with markedly decreased transcriptional activity. This repression is associated with extensive methylation of histone H3K9 together with recruitment of the Suv39h1/KMT1A methyltransferase to the *myogenin* promoter. Notably, a *MyoD* S199A/S200A mutant exhibits markedly reduced

binding to Suv39h1/KMT1A. Therefore, p38- $\gamma$  signaling directly induces the assembly of a repressive *MyoD* transcriptional complex [131].

### 3.6. Other methylation modifications and histone chaperones in myogenesis

CARM1, referred to as PRMT4 (protein arginine N methyltransferase 4), is defined as a type of the S-adenosyl-L-methionine-dependent methyltransferases, which catalyzes the methylation of arginine residues on specific proteins [132]. The expression of *CARM1* is detected in somites during embryogenesis and in the nuclei of muscle cells. Protein–protein interaction assay systems demonstrate that CARM1 directly interacts with the C-terminal region of MEF2C *in vivo* and CARM1 cooperates with the steroid receptor co-activator (SRC) cofactor GRIP-1 to stimulate MEF2C. Inhibition of CARM1 dramatically reduces the myogenin and MEF2 protein level and morphological differentiation of proliferating myoblasts into multinucleated myotubes. CARM1/PRMT4 is necessary for skeletal muscle differentiation [133].

Spt6 (Suppressor of Ty 6), as a transcription elongation factor and histone chaperone, interacts with RNA polymerase II (Pol II) to reassemble nucleosomes during Pol II elongation [134] and interacts with histones and primarily with histone H3 in controlling chromatin structure, respectively [135–137]. Spt6 is considered critical for somite formation in zebrafish embryogenesis. Genetic and biochemical experiments demonstrate that Spt6 is essential for the transcriptional response to activation of the Notch pathway: *her1* and *her7*, two of Notch pathway key target genes for somite formation, are suppressed by disruption of Spt6 function in *pan<sup>SBU2</sup>* (Zebrafish *Spt6* mutants) embryos [138]. Spt6 associated with Pol II is recruited at chromatin regions of muscle-specific genes and is required for appropriate muscle-specific genes expression in myoblasts (e.g., *MyoD* and *des*) and differentiated myotubes (e.g., *myogenin*, *MyH3*, *MyoD*, *des* and *MyIpf*) [123].

Histone chaperone HIRA (HIR histone cell cycle regulation defective homolog A) is a human homolog of the *S. cerevisiae* HIR1 and HIR2 (histone regulatory) [139–141]. HIR1 and HIR2 proteins act as co-repressors to assist a repressor that repress histone gene transcription in *S. cerevisiae* [142]. HIRA is classified as DNA replication-independent chaperone and specifically chaperones at H3.3 in mammalian variants [139]. It has been confirmed that HIRA interacts with MEF2 and stimulates MEF2 target genes transcription during muscle differentiation [143].

### 3.7. Methylation modification at myogenic regulators

As a myogenic regulator, *MyoD* can regulate transcription at gene promoters. Moreover, *MyoD* can also bind enhancers and mediates the recruitment of several chromatin-modifying enzymes, such as Set7, which catalyzes histone H3K4me<sup>1</sup> to active enhancers [65,144,145], or Suv39h1, which catalyzes histone H3K9me<sup>2/3</sup> to inhibit *MyoD* transcriptional activity [104]. In addition, *MyoD* can also be as a substrate that catalyzed by chromatin-modifying enzyme. Unlike Suv39h1, G9a not only mediates H3K9me<sup>2</sup> but also directly methylates *MyoD* at K104 to inhibit its transcriptional activity [107]. Similarly, MEF2 activity is also regulated by posttranslational modifications, such as methylation. Recently studies find that MEF2D is methylated and demethylated by G9a and LSD1 at its K267, respectively, which effects the dynamic regulation of MEF2D transcriptional activity and the expression of its target genes during skeletal muscle differentiation [146].



#### 4. Conclusions

Chromatin modifiers mediate dynamic modifications of histone tails that are vital to reprogramming cells toward terminal differentiation. Genetic and epigenetic mechanisms ensure that complex developmental programs are correctly executed [83].

In this report, we review the recent literature to deduce mechanisms underlying a complex interplay between myogenic regulatory factors and histone methylation modifications and reveal the reciprocal regulation between histone methyltransferases and demethyltransferases in the control of gene expression during skeletal muscle myogenesis and regeneration (Fig. 3). We also elucidate that histone chaperones play critical roles in controlling of muscle gene regulatory programs in this review. In addition, we find that histone methyltransferases not only mediate dynamic modifications of histone tails for influencing myogenic gene expression during skeletal myogenesis but also catalyze myogenic regulatory factors methylation at lysine site in controlling of gene transcription activity. To date, little is known about the role of histone methylation modifications in adult muscle regeneration. However, a similar regulatory mechanism from myogenesis might regulate the availability and composition of chromatin modifying-complexes that promote muscle gene transcription in adult muscle regeneration. Likewise, we predict that histone methylation-modifying enzymes mediate dynamic modifications of histone tails that are vital to programming myogenic precursors (satellite cells) toward terminal differentiation in adult muscle regeneration.

The networks established by myogenic regulatory factors and chromatin-associated enzymatic complexes will provide an important paradigm to understand the epigenetic regulation of skeletal muscle development and regeneration, and help to decipher the molecular pathways that control the transition from skeletal muscle progenitors to fibers—a current challenge in regenerative medicine [147].

Moreover, the current approach of ChIP assays is suitable for chromatin from small cell numbers, but limited by the number cell samples. Thus, establishing chromatin state maps across genome (genome-wide changes in the epigenetic landscape) is an open avenue for investigation. While most of the findings outlined here are based on cell culture studies, *in vivo* models or animal experiments need to be explored. Moreover, chromatin plasticity and epigenetic changes during muscle differentiation have yet to be revealed.

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#### Appendix A. Transparency document

Transparency document associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.bbrep.2016.04.009>.

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