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Sculpting Chromatin Beyond the Double Helix: Epigenetic Control of Skeletal Myogenesis

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Abstract

Satellite cells (SCs) are the main source of adult skeletal muscle stem cells responsible for muscle growth and regeneration. By interpreting extracellular cues, developmental regulators control quiescence, proliferation, and differentiation of SCs by influencing coordinate gene expression. The scope of this review is limited to the description and discussion of protein complexes that introduce and decode heritable histone and chromatin modifications and how these modifications are relevant for SC biology.

1. Introduction

Epigenetics can be defined as the ensemble of heritable changes in gene function that occur without modifications of primary DNA sequence (Bird, 2007; Russo *et al.*, 1996) to include DNA methylation and chromatin structural changes introduced by histone modifications and nucleosome positioning. During specification, proliferation, and differentiation of skeletal muscle cells (myogenesis), the epigenetic marks deposited by chromatin-modifying enzymes at specific loci determine whether different subsets of genes will be repressed or activated, effectively controlling the fate of muscle progenitors and the transition between each developmental phase. Therefore, the balance between cell self-renewal and differentiation is ultimately regulated by coordination of stage-specific transcriptional machineries through epigenetic mechanisms. Many excellent and comprehensive reviews on satellite cells (SCs) have been published (Buckingham, 2007; Charge and Rudnicki, 2004; Dhawan and Rando, 2005; Kang and Krauss, 2010) and the reader is referred to them.

2. Satellite Cells

SCs represent the primary source of multipotent stem cells responsible for postnatal skeletal muscle growth and regeneration (Charge and Rudnicki, 2004; Partridge, 2004). They originate from Pax3/7-expressing muscle progenitors in the embryonic dermomyotome (Gros *et al.*, 2005; Relaix *et al.*, 2005). In the mouse, SCs expressing Pax7 appear at approximately embryonic day 16.5 (E16.5) in the developing limb muscle (Kassar-Duchossoy *et al.*, 2005) and acquire their characteristic position under the basal lamina of mature muscle fibers (Mauro, 1961). SCs comprise about 30% of total muscle nuclei in neonatal mice and 2–7% of muscle nuclei in the adult mice. They express a distinct profile of surface markers and transcription factors (TFs; Charge and Rudnicki, 2004). Recent studies have revealed that SCs are a heterogeneous population (Beauchamp *et al.*, 2000; Collins *et al.*, 2005; Kuang *et al.*, 2007; Sherwood *et al.*, 2004) composed of two groups of cells: noncommitted stem cells which maintain self-renewal ability and committed myogenic progenitors which undergo lineage-specific differentiation (Kuang *et al.*, 2007). Because of these two distinguished characteristics, SCs qualify as a *bona fide* tissue-specific adult stem cell. Under normal circumstances, adult SCs are in a quiescent state. In response

to environmental cues, such as mechanical stress, muscle injury, or degenerative muscle diseases, SCs exit quiescence, enter cell cycle, and actively proliferate (activated state). Following activation, a subset of SC returns to its niche under the basal lamina to replenish the stem cell reservoir. Majority of SCs activate expression of the myogenic factor MyoD and give rise to committed myoblasts, which undergo rapid proliferation and subsequently exit from the cell cycle to terminally differentiate and fuse to form new muscle fibers or repair damaged muscle (Dhawan and Rando, 2005). The identification of mesangioblasts and other non-SC muscle resident and circulating progenitors expand the repertoire of cells potentially participating to muscle growth and regeneration (Benchaouir *et al.*, 2007; Corbel *et al.*, 2003; Cossu and Bianco, 2003; Dellavalle *et al.*, 2007; Joe *et al.*, 2010; Mitchell *et al.*, 2010; Sampaolesi *et al.*, 2003, 2006; reviewed in Tedesco *et al.*, 2010).

3. Repressing Muscle Gene Expression: Skeletal Muscle Developmental Regulators and Polycomb Proteins in Embryonic Stem (ES) and Nonmuscle Cells

Totipotent ES cells retain the ability of self-renewing and generating all adult cell types. These two properties are mutually exclusive: an individual ES cell either renews or differentiates into a given cell lineage. Understanding the molecular mechanisms that regulate this dichotomic decision is not only of scientific interest to developmental biologists but also holds great promise for regenerative medicine. Under defined culture conditions, ES cells can be indefinitely propagated in an undifferentiated state. ES cell differentiation into specialized cell lineages occurs in culture or during development when appropriate signals are provided and correctly interpreted. For these processes to be properly executed, transcription and translation of developmental regulators (DRs) need to be tightly controlled. DRs are TFs or related molecules that coordinate temporal and spatial expression of battery of genes involved in the specification and maintenance of a given cell state. DRs favoring ES self-renewal (such as Oct4, Nanog, and Sox2) are expressed in undifferentiated ES cells but extinguished upon lineage commitment and differentiation (Chambers *et al.*, 2003, 2007; Masui *et al.*, 2007; Nichols *et al.*, 1998). Conversely, cell type-specific DRs, such as MyoD (Davis *et al.*, 1987), are repressed in undifferentiated ES cells and their expression is activated once a given cell fate is specified. Polycomb group (PcG) proteins are pivotal regulators of DRs expression in ES cells (Bernstein *et al.*, 2006; Boyer *et al.*, 2006; Lee *et al.*, 2006). PcG proteins are assembled in multiple Polycomb Repressive Complexes (PRCs) that exert their regulatory functions by introducing epigenetic modifications to chromatin structure conducive to transcriptional repression (Simon and Kingston, 2009). PRC2—and related PRC3 and PRC4—contains the core components Ezh2, Suz12, and Eed. Ezh2 is the PRC2 catalytic component with methyltransferase activity directed at lysine 27 of histone H3 (H3K27; Cao *et al.*, 2002; Czermin *et al.*, 2002; Kirmizis *et al.*, 2004; Kuzmichev *et al.*, 2002; Muller *et al.*, 2002), with Suz12 being required for the enzymatic activity (Cao and Zhang, 2004; Pasini *et al.*, 2004). Eed specifically recognizes and binds to trimethylated repressive marks, including H3K27me3. This event leads to the allosteric activation of the methyltransferase activity of PRC2, resulting in further propagation of the H3K27me3 mark to extended chromatin blocks and possibly transmission and retention of this histone modification through DNA replication (Margueron *et al.*, 2009). H3K27me3 serves, in most cases, as a docking site for PRC1 recruitment, which promotes further chromatin condensation to ensure gene silencing (Francis *et al.*, 2004).

The paired domain- and homeobox-containing TFs Pax3 and Pax7 and the myogenic determinant factor MyoD are nodal DRs expressed in quiescent and activated SCs (Kassar-Duchossoy *et al.*, 2005; Megeney *et al.*, 1996; Relaix *et al.*, 2005; Rudnicki *et al.*, 1993; Seale *et al.*, 2000). Myf6 (also referred as to MRF4) is transcribed during SC differentiation.

In ES cells, Pax3, Pax7, MyoD, and MRF4 are not expressed and their respective loci are occupied by Suz12 and nucleosomes with H3K27me3 repressive mark (Lee *et al.*, 2006). However, in addition to the repressive H3K27me3 mark, the regulatory regions of Pax3, Pax7, MyoD, and MRF4 also contain the H3K4me3 mark (Zhao *et al.*, 2007), a histone modification associated with transcriptional activation (Barski *et al.*, 2007). The coexistence of negative and positive histone marks (bivalent domains; Bernstein *et al.*, 2006) would serve the purpose of silencing DRs in ES cells while keeping them poised for immediate activation once signals are received and decoded to initiate cell lineage specific gene expression. Consistent with this proposed function, bivalent domains are resolved in monovalent regions retaining only H3K4me3 when they experience gene activation or H3K27me3 when remaining repressed. The Pax3, Pax7, MyoD, and myogenin—another pivotal regulator of SC differentiation—loci engage Suz12, are H3K27me3 marked, and repressed also in human embryonic fibroblasts (Bracken *et al.*, 2006) and numerous nonepidermal "master" DRs, including MyoD, are marked by H3K27me3 and transcriptionally repressed in committed embryonic basal epidermal progenitors (Ezhkova *et al.*, 2009). Pax3 and Pax7 are also occupied by Suz12 and marked with H3K27me3 in F9 embryonic carcinoma cells (Squazzo *et al.*, 2006). Thus, DRs may need to be continuously repressed not only in ES cells but also in cells that have entered a cell lineage-specific fate, which is incompatible with expression of the repressed DRs. Alternatively, H3K27me3 may be a remnant mark introduced by PcG in ES cells and self-propagated (Hansen *et al.*, 2008) in specified cells. The presence of PRC2 at some DRs is indicative of an active and continuously repressive role exerted by PcG in specified cell lineages. ES cells in which either Suz12 or Eed has been genetically ablated (Boyer *et al.*, 2006; Lee *et al.*, 2006) or Ezh2 has been reduced by miR-214 overexpression (Juan *et al.*, 2009) display an aberrant expression of certain cell lineage-specific DRs, including Pax7, Gata1-6, and Sox17. Neither MyoD nor MRF4 appear to be expressed in Suz12- or Eed-null ES cells nor in ES cells with miR-214-mediated reduced Ezh2, indicating that derepres-sion does not necessarily coincides with transcriptional activation, at least for certain loci. Conditional Ezh2 inactivation in committed embryonic basal epidermal progenitors is not sufficient to activate expression of nonepider-mal PcG targets (Ezhkova *et al.*, 2009). Interestingly, mouse embryonic fibroblasts (MEFs) derived from mice carrying an hypomorphic allele and expressing ~25% of the normal complement for the TF YY1—a protein known to participate in PcG-mediated repression (Atchison *et al.*, 2003; Satijn *et al.*, 2001; Srinivasan and Atchison, 2004; Woo *et al.*, 2010; Yue *et al.*, 2009)—display increased expression of several muscle-specific transcripts (actins, myosins, troponins), which are physiologically absent in MEFs (Affar el *et al.*, 2006).

4. Sculpting Chromatin for Transcription in Skeletal Muscle Cells

Chromatin accessibility to enzymes and TFs characterizes different cell types (Weintraub and Groudine, 1976) and different developmental stages within the same cell lineage (Groudine and Weintraub, 1981), including skeletal muscle cells (Carmon *et al.*, 1982). This is a reflection of different conformations that nucleosomes adopt as a consequence of histone and DNA modifications and positioning introduced by specific enzymatic complexes. These enzymatic protein complexes are recruited at discrete DNA regions via interaction with proteins (TFs) that recognize sequence-specific DNA modules. Chromatin-modifying complexes are transferred to stalled RNA polymerases or travel in association with elongating RNA polymerases. Noncoding RNAs can also recruit enzymatic complexes at defined chromatin regions (Mohammad *et al.*, 2008; Rinn *et al.*, 2007; Zhao *et al.*, 2008).

4.1. Pax3/Pax7 and alternative SC fates

As already mentioned, Pax3 and Pax7 are important regulators of SC biology (Oustanina *et al.*, 2004; Relaix *et al.*, 2005; Seale *et al.*, 2000). They both regulate expression of numerous

genes including the myogenic determinant factor Myf5 (Maroto *et al.*, 1997; Tajbakhsh *et al.*, 1997). In C2C12 cell and satellite-derived primary myoblasts, Pax7 interacts with and engages the Wdr5-Ash2-MLL2 histone methyltransferase at the Myf5 locus, promoting H3K4me3 and gene activation (McKinnell *et al.*, 2008). Pax3 activates Myf5 through the intermediate induction of Dmrt2, a TF that interacts with one of the Myf5 enhancers (Sato *et al.*, 2010). Differences were noted in transcriptional potency, with Pax3 being a poor activator compared to Pax7 (McKinnell *et al.*, 2008; Relaix *et al.*, 2003), perhaps reflective of recruitment of distinct regulatory protein complexes. An important question relates to the inability of Pax7 to activate Myf5 in SCs returning to their niche. In these cells ($Pax7^+$/$Myf5^-$; Kuang *et al.*, 2007), the Myf5 locus may retain H3K27me3 introduced by PcG in ES cells (epigenetic memory; Lee *et al.*, 2006) or be occupied by histones, such as histone linker H1, or histone variants that may preclude Pax7 chromatin access. Alternatively, the Pax7 protein may be modified to avoid association with regulatory protein complexes required to activate Myf5 or such regulatory complexes may be absent in the self-renewing daughter cell. The hypothesized H3K27me3-marked Myf5 alleles may segregate with $Pax7^+$/$Myf5^-$ cells and bear methylated DNA. Indeed, Ezh2 directly controls DNA methylation by recruiting DNA methyltransferase proteins (Vire *et al.*, 2006). Preferential asymmetric segregation of histone- and/or DNA-methylated Myf5 alleles in the self-renewing cell maybe achieved by DNA cosegregation with the immortal DNA strand (Conboy *et al.*, 2007; Shinin *et al.*, 2006).

4.2. Myogenic bHLH protein binding modalities

MyoD, Myf5, myogenin, and MRF4 heterodimerize with ubiquitously expressed bHLH E-proteins and recognize the DNA core consensus sequence CANNTG (the E-box; reviewed in Tapscott, 2005). Chromatin immunoprecipitation (ChIP) combined with either microarray hybridization or high-throughput sequencing and gene expression profiling (Bergstrom *et al.*, 2002; Blais *et al.*, 2005; Cao *et al.*, 2006, 2010) has allowed identification of myogenic bHLH targets on a genome-wide scale. As anticipated, MyoD and myogenin bind to regulatory regions of genes whose transcription is regulated during skeletal muscle differentiation (Blais *et al.*, 2005; Cao *et al.*, 2006). Unexpectedly, MyoD binding is evident at several sites before differentiation (Blais *et al.*, 2005) and majority of MyoD binding occurs at either introns or intergenic regions, coinciding with local histone acetylation (Cao *et al.*, 2010). One interpretation of these findings is that, in addition to regulating gene expression, MyoD may have a role in the epigenetic reprogramming of skeletal muscle cells (Cao *et al.*, 2010). Importantly, genome-wide MyoD binding distribution in the C2C12 cell line, primary muscle cells, and fibroblasts expressing MyoD are extremely similar (Cao *et al.*, 2010), a reassuring finding further confirming coincidence of regulatory transcriptional modalities in different cellular model of skeletal muscle differentiation.

4.3. Marking chromatin for repression

The composition of the transcripitonal machinery (protein complexes) and the chromatin asset (histone and DNA) at muscle-specific genes reflects the different states of the cell. In the vicinity of transcriptional start sites (TSS) of genes not expressed in undifferentiated myoblasts, core histones H3 and H4 are mainly deacetylated and methylated at specific lysines (H3K9,14,18 deAc, H4K5,8,16 deAc, H3K9me2, and H3K27me3) by histone deaceylases (HDACs; Fulco *et al.*, 2003; Lu *et al.*, 2000b; Mal *et al.*, 2001; Ohkawa *et al.*, 2006; Puri *et al.*, 2001) and methyltransferases (HMTs; Suv39h1/KMT1A and PcG; Caretti *et al.*, 2004; Mal, 2006). These enzymes have developed the ability to function as cooperative modules (Margueron and Reinberg, 2010). This is a property deriving by mutually exclusive histone modifications. Acetylation and methylation cannot occur on the same lysine residue and deacetylation is often a prerequisite for subsequent methylation. Thus, HDACs are often found in protein complexes containing HMTs. Class I, II, and III

HDACs, SUv39h1/KMT1A, the chromodomain-containing methyl-binding protein HP1, and PcG Ezh2 associate in different protein complexes (Caretti *et al.*, 2004; Kuzmichev *et al.*, 2005; van der Vlag and Otte, 1999; Vaquero *et al.*, 2007; Vaute *et al.*, 2002) and are recruited, along with the PcG-related TF YY1, at chromatin regulatory regions of inactive muscle genes (Fig. 3.1A; Caretti *et al.*, 2004; Fulco *et al.*, 2003; Mal, 2006; Ohkawa *et al.*, 2006; Wang *et al.*, 2007; Zhang *et al.*, 2002). Initially identified as histone deacetylases and methyltransferases, HDACs, and HMTs were subsequently found to act also on nonhistone proteins, including TFs such as MyoD, MEF2, and p53 (Chuikov *et al.*, 2004; Fulco *et al.*, 2003; Huang *et al.*, 2006, 2010; Mal *et al.*, 2001; Puri *et al.*, 2001; Zhao *et al.*, 2005).

Specific histone isoforms participate in shaping repressive chromatin structure. Through specific interaction with the homeoprotein Msx1, histone H1b is deposited at the core enhancer region of the MyoD locus within a repressive chromatin region characterized by H3K9 methylation, decreased H3K9 and 14 acetylation, and reduced H3Ser10 phosphorylation (Lee *et al.*, 2004). H1b depletion abrogated the ability of Msx1 to inhibit muscle cell differentiation, directly linking the repressive function of Msx1 to histone H1b.

4.4. SIRT1: A multifaceted regulator

SIRT1 is an NAD^+-dependent protein deacetylase (Imai *et al.*, 2000) expressed in quiescent and activated SCs (J. G. Ryall, A. Pasut, M. A. Rudnicki, and V. S., unpublished results). Reducing SIRT1 in the C2C12 cell line or in primary myoblasts results in their premature differentiation (Fulco *et al.*, 2003) and, analogously, primary myoblasts derived from heterozygous $SIRT1^{+/-}$ exhibit early differentiation and are resistant to antidifferentiative cues, such as glucose restriction (Fulco *et al.*, 2008). Overexpression experiments have revealed that SIRT1 increases SC proliferation (Rathbone *et al.*, 2008). It is likely that the effects of SIRT1 on muscle cell differentiation results from its deacetylase activity on different substrates, including histones, acetyltransferases, and transcriptional regulators (Brunet *et al.*, 2004; Fulco *et al.*, 2003; Motta *et al.*, 2004). Indeed, SIRT1 deacetylates MyoD and P/CAF (Fulco *et al.*, 2003), an acetyltrans-ferase that activates MyoD (Dilworth *et al.*, 2004; Kuninger *et al.*, 2006; Sartorelli *et al.*, 1999). MEF2D, an important TF that collaborates with MyoD to activate genes critical for muscle differentiation, is also deacetylated by SIRT1 (Zhao *et al.*, 2005). In addition to controlling cell differentiation, SIRT1, and related sirtuins, may have other functions in SCs that remain to be explored. For instance, SIRT1 interacts with and mediates transcriptional repression induced by hairy/Hes1 and HEY2 (Bianchi-Frias *et al.*, 2004; Rosenberg and Parkhurst, 2002; Takata and Ishikawa, 2003), two transcriptional repressors whose activation is promoted by the Notch pathway. Given the central role played by the Notch pathway in regulating SC activation and cell fate determination in postnatal myogenesis (Brack *et al.*, 2008; Conboy and Rando, 2002), asymmetric cell division (Conboy *et al.*, 2007; Kuang *et al.*, 2007; Shinin *et al.*, 2006), restoring the regenerative potential of aged muscle (Conboy *et al.*, 2003; Luo *et al.*, 2005), and the ability of SIRT1 to control SC proliferation and differentiation (Fulco *et al.*, 2003; Rathbone *et al.*, 2008), to retard degenerative processes and increase lifespan across species (reviewed in Imai and Guarente, 2010), it will be of great interest to determine whether the Notch and SIRT1 pathways crosstalk. Another process that may be potentially influenced by SIRT1 or other sirtuins is the cell response to oxidative stress. It is intriguing that quiescent SCs have developed strategies that protect them from xenobiotics, geno-toxics, and oxidative stress (Pallafacchina *et al.*, 2010), likely to maintain genome integrity. Since SIRT1 is activated by and protects from the deleterious effects induced by oxidative stress, DNA damage, and hypoxia (Brunet *et al.*, 2004; Dioum *et al.*, 2009; Motta *et al.*, 2004; Oberdoerffer *et al.*, 2008), it may contribute to SC resistance to environmetal insults. In principle, SIRT1 transcription needs not to be regulated in quiescent versus activated SCs, as its enzymatic activity can be modulated by the redox state (Fulco *et al.*, 2003).

4.5. Turning on transcription: Erasing and writing

Reception and decodification of prodifferentiative signals induce modification of the chromatin structure conducive to gene activation. Repressive marks need to be erased and substituted with histone modifications and nucleosome restructuring compatible with RNA polymerase II (PolII) engagement and elongation. A pivotal step in this process is the recruitment of histone acetyltransferases (HATs), ATP-dependent chromatin remodeling complexes, methyltransferases, demethylases, and specific subunits of the basal transcriptional machinery.

H3K27me3 is reduced at specific muscle regulatory regions upon gene activation (Caretti *et al.*, 2004). Several independent, but functionally coherent, mechanisms contribute to this phenomenon (Fig. 3.1B). H3K27me3 deposition is curtailed as Ezh2 transcription is reduced (Caretti *et al.*, 2004) and the residual Ezh2 transcripts are targeted for translational inhibition by the microRNA miR-26 and miR-214 (Juan *et al.*, 2009; Wong and Tellam, 2008). Active H3K27 demethylation is concomitantly brought about by Six4-mediated recruitment of the UTX demethylase (Seenundun *et al.*, 2010). The presence of the H3K4 methyl-transferases mixed lineage leukemia (MLL) proteins within the UTX complex provides a parsimonious and elegant mechanism whereby a repressive mark is erased and one with activation property is introduced by the same protein complex (Fig. 3.1B; Rampalli *et al.*, 2007). Jmjd1, a specific H3K9me2 demethylase (Yamane *et al.*, 2006) may be involved in erasing H3K9me2 from muscle regulatory regions. During the differentiation process, class I HDACs are disengaged from MyoD and possibly other transcriptional regulators and redistributed to alternative protein complexes via cell cycle-regulated events involving pRb hypophosphorylation (Puri *et al.*, 2001) and calcium-mediated activation of the calmodulin-dependent protein kinase (CaMK) stimulates MEF2 activity by dissociating it from class II HDACs (Lu *et al.*, 2000a). Pharmacological HDACs inhibition promotes, in a temporal-specific manner, muscle gene expression (Iezzi *et al.*, 2002, 2004), favoring a functional and morphological amelioration in two different animal models of muscle dystrophies (Minetti *et al.*, 2006; reviewed in (Mozzetta *et al.*, 2009). Removal of HDACs from transcribed regions has been classically seen as a prerequisite for gene activation and HATs and HDACs cooccupancy mutually exclusive. However, in genome-wide mapping studies, HDACs have been detected with HATs at active genes with acetylated histones and their recruitment imputed to phosphorylated PolII, providing the basis for dynamic cycles of acetylation/deacetylation required to reset chromatin after PolII elongation (Wang *et al.*, 2009). These findings are consistent with the observation that SIRT1 and PCAF cooc-cupy transcribed chromatin regions (Fulco *et al.*, 2003). However, it cannot be excluded that, at activated genes, SIRT1 deacetylase activity may be tempered by unfavorable $[NAD^+]/[NADH]$ ratio (Sartorelli and Caretti, 2005). The HATs p300, PCAF, and related GNC5 are engaged at muscle-activated genes by different TFs—including myogenic bHLH, MEF2 factors, SRF, six proteins, and ubiquitous transcriptional regulators (reviewed in Guasconi and Puri, 2009; Perdiguero *et al.*, 2009). Association of MyoD with the HATs p300 and PCAF (Puri *et al.*, 1997b) is promoted by AKT1 and 2 kinases via direct phosphorylation of p300 (Serra *et al.*, 2007). Several TFs regulating muscle gene expression are acetylated by the same HATs they recruit on the chromatin (Avantaggiati *et al.*, 1997; Duquet *et al.*, 2006; Gu *et al.*, 1997; Lill *et al.*, 1997; Polesskaya *et al.*, 2000; Sartorelli *et al.*, 1999; Simone *et al.*, 2004). In some instances, that is, p53 and MyoD, acetylation increases DNA binding affinity (Gu *et al.*, 1997; Sartorelli *et al.*, 1999), providing a positive feedback mechanism to increase HATs recruitment and consequent histone acetylation.

4.6. Moving obstacles

Nucleosomes containing epigenetic marks compatible with transcriptional activation need to be accordingly redistributed as to avoid occluding access of regulatory DNA regions to TFs.

Nucleosome positioning can be achieved by ATP-dependent chromatin remodeling complexes or by TFs in the absence of additional factors (reviewed in Radman-Livaja and Rando, 2010). Binding of a TF near the entry/exit point of a nucleosome modifies the chromatin structure making accessible other sites located toward the center of the nucleosome (Polach and Widom, 1996). With a related mechanism, an NFkB-p65 subunit mutant without activation domains continues to regulate transcription of a subset of target genes by permitting access to secondary TFs (van Essen *et al.*, 2009). Pbx1/Meis1 is a "pioneer" TF capable of penetrating repressive chromatin. While the detailed mechanisms endowing Pbx1/Meis with such ability are not known, it may be that its binding sites are preferentially situated in nucleo-some free-regions, as in the case of the IFN-b promoter, or that Pbx1/Meis1 may directly interact with and displace histones, as it occurs for HNF3 (Sagerstrom, 2004). Pbx1/Meis1 is constitutively bound to muscle regulatory regions before transcriptional activation and in the absence of MyoD. Pbx1/Meis interacts with MyoD (Knoepfler *et al.*, 1999) and can position it and tether it even at imperfect MyoD binding sites (Berkes *et al.*, 2004). Interaction of Pbx1/Meis1 with MyoD occurs via two domains required for initiation of chromatin remodeling (Bergstrom and Tapscott, 2001; Gerber *et al.*, 1997). These studies provide a mechanistic explanation of how MyoD can penetrate repressive chromatin to initiate remodeling. Pbx1/Meis1 may need to be somehow modified or interact with transcriptional repressors to repel MyoD and avoid premature gene activation. Alternatively, regulated interaction of Pbx1/Meis1 with SWI/SNF may permit productive MyoD recruitment (de la Serna *et al.*, 2005). Recruitment of the ATP-dependent SWI/SNF BRM and brahma-like 1 (BRG-1) chromatin remodeling complex through interaction with MyoD (de la Serna *et al.*, 2001; reviewed in de la Serna *et al.*, 2006) is regulated via direct phosphorylation of the SWI/SNF BAF60c subunit mediated by the MAPK p38 (mitogen-activated kinases; Simone *et al.*, 2004; reviewed in Albini and Puri, 2010) and required for binding of MyoD, myogenin, and MEF2 (de la Serna *et al.*, 2005) and sustained gene expression (Ohkawa *et al.*, 2007). At the myogenin promoter, MyoD induces histone hyperacetylation before and independently of BRG-1 activity (de la Serna *et al.*, 2005), suggesting the formation of a temporally regulated transcriptional protein complex where MyoD-mediated HATs recruitment (Eckner *et al.*, 1996; Puri *et al.*, 1997a, b; Sartorelli *et al.*, 1997; Yuan *et al.*, 1996) precedes BRG-1-dependent chromatin remodeling. BRG-1-meditaed remodeling at different muscle loci is temporally regulated by sequential activities of the arginine methyltransferases PRMT5 and CARM1/PRMT4 (Dacwag *et al.*, 2009; Mallappa *et al.*, 2010). An interesting relation between SWI/SNF and PcG proteins was uncovered when brahma was identified as a suppressor of PcG mutants in homeotic gene expression, suggesting that SWI/SNF may regulate gene expression by antagonizing repressive chromatin structure organized by PcG proteins (Tamkun *et al.*, 1992). A dedicated role of BAF60c to myogenesis is suggested by its preferential expression in developing heart and somites and has been confirmed by its genetic ablation, which results in cardiac and skeletal muscle defects (Lickert *et al.*, 2004). Intriguingly, and consistent with its chromatin remodeling ability, BRG-1 has been found to facilitate iPS formation (Singhal *et al.*, 2010).

4.7. RNA helicases: Connecting histone acetylation, chromatin remodeling, and microRNA maturation

The highly related RNA helicases p68 and p72 (p68/p72) and the long noncoding RNA (lncRNA) steroid receptor activator (SRA) associate with MyoD and coregulate its transcriptional activity (Caretti *et al.*, 2006). They also serve as coregulators of other TFs, including p53, estrogen, and androgen receptors. Their mechanistic role is not fully understood as the RNA helicase activity seems dispensable to regulate transcription (Bates *et al.*, 2005; Caretti *et al.*, 2006). However, several other features endow p68/p72 with regulatory properties. P68 interacts with HDAC1, repressing transcription in a promoter-

specific manner (Wilson *et al.*, 2004). In other biological circumstances, p68 can interact with and is acetylated by p300. Acetylation increases p68/p72 stability, thus stimulating its ability to coac-tivate estrogen receptor-mediated transcription (Mooney *et al.*, 2010). Sumoylation may constitute a regulatory switch as it enhances p68 transcriptional repression by favoring its association with HDAC1 (Fig. 3.2A; Jacobs *et al.*, 2007). In differentiated skeletal muscle cells, p68/p72 were detected on chromatin regulatory regions in association with the lncRNA SRA and MyoD (Fig. 3.2B). Reducing p68 level by RNAi in either C2C12 cell line or satellite-cell-derived primary muscle cells hampered differentiation, transcription of selected muscle genes, and chromatin engagement of BRG-1, TATA-binding protein (TBP), and PolII without affecting either MyoD or p300 recruitment (Caretti *et al.*, 2006). Genes whose expression was affected by p68 require BRG-1 (de la Serna *et al.*, 2005). More recently, the estrogen receptor ERα has been demonstrated to form a protein complex with p300, p68/p72, and MyoD to regulate BRCA2 transcription (Jin *et al.*, 2008). The HMG-related small chromatin protein p8 also associates and is recruited at muscle-specific genes with p300, p68, and MyoD (Fig. 3.2B). p8 knockdown compromises chromatin recruitment of p300, p68, and MyoD, thus impairing muscle transcription (Sambasivan *et al.*, 2009). In addition to a direct role on the formation and stabilization of chromatin-modifying protein complexes, p68/p72 influence also other processes related to gene expression. P68/p72 are part of the nuclear RNase III Drosha complex, which cleaves primary transcripts of miRNA genes (pri-miRNAs) into hairpin precursor intermediates (pre-miRNAs), further processed to mature miRNAs by the cytosolic RNase III Dicer. Association of p68/72 with the TFs p53 or SMAD regulates the processing of primary miRNAs into precurors miRNAs (Davis *et al.*, 2008; Suzuki *et al.*, 2009). Gene disruption of either p68 or p72 results in early lethality, with specific defects in maturation of selected miRNAs. P72 deletion negatively impacts maturation of miR-214 (Fukuda *et al.*, 2007), a micro-RNA regulating Ezh2 availability and involved in muscle cell differentiation (Juan *et al.*, 2009). Thus, p72 may regulate muscle gene expression by two independent mechanisms, by coactivating MyoD-dependent transcription and favoring miR-214 processing (Juan and Sartorelli, 2010).

4.8. Switching basal players: TRF3 and TAF3

It might have been naively predicted that a family of tissue-specific TFs (activators), such as the myogenic bHLH, would suffice to ensure cell-lineage restricted gene expression, with the constant core basal transcriptional machinery serving many masters. It turned out that activators and core machinery members display mutual preferences (D'Alessio *et al.*, 2009). Upon muscle cell differentiation, TBP and several TAFs—expressed in undifferentiated cells—are degraded and replaced by TRF3 and TAF3. Indeed, MyoD can directly target TAF3, and such interaction support *in vitro* transcription. Moreover, TRF3/TAF3 are recruited at the myo-genin promoter and interference with their accumulation prevents myotube formation (Deato and Tjian, 2007; Deato *et al.*, 2008). As MyoD is transcriptionally active in undifferentiated myoblasts, these findings imply that MyoD can communicate and direct transcription with two alternative core basal machineries. As reported for SWI/SNF (Tamkun *et al.*, 1992), also tissue-specific TAFs counteract PcG proteins to promote terminal differentiation (Chen *et al.*, 2005).

4.9. Conveying signals to the nucleus by the MAPK p38

In skeletal muscle cells, extracellular cues mediated by morphogen gradients, ligand–receptor, and soluble growth factor–receptor interactions are decoded and ultimately conveyed to the genome by chromatin-modifying complexes to regulate transcriptional output (reviewed in Guasconi and Puri, 2009). Protein modifications mediated by kinases and phosphates rapidly and effectively mediate cellular responses to environmental signals and internal processes by regulating protein interactions, enzymes activity, and protein localization (Pawson, 2007).

Within this context, signaling mediated by the MAPK p38 has received a great deal of experimental attention. The important role exerted by p38a in regulating the satellite quiescent state (Jones *et al.*, 2005) is evidenced by the analysis of p38a mutant mice, which shows delayed-cell-cycle exit and altered expression of cell cycle regulators in cultured myoblasts (Perdiguero *et al.*, 2007). Activation of p38, initiated by the transmembrane Ig-fibro-nectin—type III repeat CDO protein—promotes formation of MyoD-E47 dimers, which in turn activate CDO transcription (Cole *et al.*, 2004; Takaesu *et al.*, 2006). E47 is a direct target of p38-mediated phosphorylation promoting MyoD-E47 heterodimer formation (Lluis *et al.*, 2005). Different members of the MAPK p38 family exert opposing effects on muscle gene expression. While p38a/b favor muscle transcription by promoting MyoD-E47 heterodimer formation (Lluis *et al.*, 2005) and MEF2D binding (Penn *et al.*, 2004), engagement of the SWI/SNF chromatin remodeling complex via phosphorylation of the BAF60c subunit (Simone *et al.*, 2004), and recruitment of the Ash2L-containing MLL protein complex through MEF2D phosphorylation (Rampalli *et al.*, 2007), p38g antagonizes muscle gene expression by promoting recruitment of the H3K9 methyltransferase Suv39h1/KMT1 at the myogenin promoter through direct phosphoryla-tion of Ser199 and Ser200 of MyoD (Gillespie *et al.*, 2009).

An unexpected role of p38a in linking tumor necrosis factor (TNF) signaling to PcG proteins during muscle regeneration has been recently uncovered. Inflammatory cells populating sites of damaged muscles are an essential component of the regenerative phase, characterized by SC expansion and differentiation. Locally released cytokines, including interleukin 1,4,6, and TNFa promote muscle regeneration (Charge and Rudnicki, 2004; Dhawan and Rando, 2005; Horsley *et al.*, 2003; Serrano *et al.*, 2008). TNFa regulates muscle regeneration by activating MAPK p38 (Chen *et al.*, 2007). In proliferating, undifferentiated muscle cells, where p38a signaling is ineffective (Wu *et al.*, 2000), the PRC2 complex prevents unscheduled gene expression by repressing transcription of muscle-specific myosins and muscle creatine kinase genes (Caretti *et al.*, 2004). When proliferating SCs undergo differentiation, PRC2 is released from muscle structural genes—where is replaced by an activation complex (Caretti *et al.*, 2004)—and relocated to Pax7 regulatory regions to repress gene expression (Palacios *et al.*, 2010). Such PRC2 redistribution from muscle structural genes to Pax7 is regulated by p38a, which directly phosphorylates the human PRC2 catalytic subunit Ezh2 at Thr372 (corresponding to mouse Ezh2 Thr367), influencing recruitment of the Polycomb-related transcriptional repressor YY1 (Palacios *et al.*, 2010). Indeed, p38a, Ezh2, YY1, and H3K27me3 are codetected at the Pax7 regulatory regions of differentiating primary myoblasts. Genetically or pharmacologically interfering with p38 or PRC2, results in continued Pax7 expression and expansion of SCs, which retain their ability to differentiate once p38 or PRC2 blockade is removed (Palacios *et al.*, 2010). While chromatin engagement of MAPKs p38 has been previously documented (Chow and Davis, 2006; de Nadal and Posas, 2010; Pokholok *et al.*, 2006), the contribution of p38α to redistribute PcG proteins at specific genomic loci in response to inflammatory signals introduces an additional layer of regulatory refinement.

5. Conclusions

As a result of the concerted action of acetyltransferases and deacety-lases, methyltransferases and demethylases, kinases and phosphatases, epige-netic modifications are dynamic and reversible. This property of the epigenome, associated with the availability and development of new small molecules with the ability of regulating the activities of specific chromatin-modifying protein complexes, allows, in principle, a regulatable manipulation of cell fate decisions.

In the context of muscle stem cell biology, the combined investigation of molecules and mechanisms regulating the epigenome and small molecule screening may prove useful toward the development of effective therapies for degenerative diseases.

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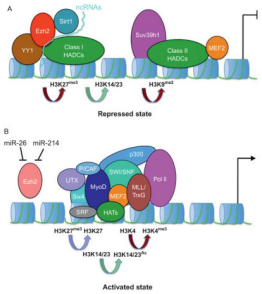

Figure 3.1.

(A) Repressive histone marks are introduced by protein complexes composed by class I, II, and III (SIRT1) deacetylases and histone methyltransferases (Suv39h1 and Polycomb Ezh2). Ezh2 may be recruited by the Pleiohomeotic (PHO)-related YY1 protein or noncoding RNAs (ncRNAs). Lysines 14–23 of histone H3 are deacetylated and lysine 27 (Ezh2) and lysine 9 (Suv39h1) are methylated. (B) Repressors are replaced by a new set of protein complexes at transcribed genes. Via interaction with the transcriptional activators MyoD, MEF2, SRF, and Six4, acetyltransferases (HATs, p300, P/CAF) and nucleosome remodeling machines (SWI/SNF) promote lysine acetylation (H3K14-23^{AC}) and nucleosome remodeling, respectively. Demethylation of lysine 27 is achieved by transcriptional downregulation and microRNA-mediated (miR-26 and miR-214) repression of Ezh2. In addition, the lysine 27-specific UTX actively removes methyl groups from lysine 27. The Trithorax-related mixed lineage leukemia (MLL) proteins promote methylation of histone H3 lysine 4, a mark associated with polymerase II (PolII) recruitment and gene activation.

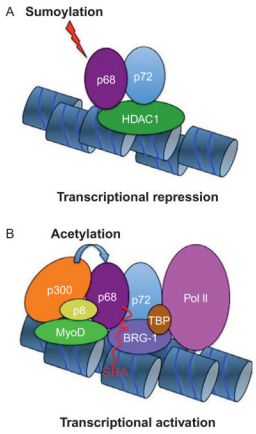

Figure 3.2.

(A) Sumoylation of the RNA helicase p68 (forming heterodimers with the RNA helicase p72) can favor repression by promoting p68 interaction with the histone deacetylase HDAC1. (B) At transcribed genes, the RNA helicases p68/p72, the noncoding RNA SRA, form a transcriptional complex with the HAT p300, the high-mobility group-related p8, MyoD, the nucleosome remodeling SWI/SNF complex, the TATA-binding protein (TBP), and PolII. In addition to histones, p300 also acetylates p68.