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Review

Temporal regulation of chromatin during myoblast differentiation

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ABSTRACT

The commitment to and execution of differentiation programmes involves a significant change in gene expression in the precursor cell to facilitate development of the mature cell type. In addition to being regulated by lineage-determining and auxiliary transcription factors that drive these changes, the structural status of the chromatin has a considerable impact on the transcriptional competence of differentiation-specific genes, which is clearly demonstrated by the large number of cofactors and the extraordinary complex mechanisms by which these genes become activated. The terminal differentiation of myoblasts to myotubes and mature skeletal muscle is an excellent system to illustrate these points. The MyoD family of closely related, lineage-determining transcription factors directs, largely through targeting to chromatin, a cascade of cooperating transcription factors and enzymes that incorporate or remove variant histones, post-translationally modify histones, and alter nucleosome structure and positioning via energy released by ATP hydrolysis. The coordinated action of these transcription factors and enzymes prevents expression of differentiation-specific genes in myoblasts and facilitates the transition of these genes from transcriptionally repressed to activated during the differentiation process. Regulation is achieved in both a temporal as well as spatial manner, as at least some of these factors and enzymes affect local chromatin structure at myogenic gene regulatory sequences as well as higher-order genome organization. Here we discuss the transition of genes that promote myoblast differentiation from the silenced to the activated state with an emphasis on the changes that occur to individual histones and the chromatin structure present at these loci.

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1. Introduction

The discovery of MyoD as a factor that could reprogram cells of other lineages into skeletal muscle-like cells [1] established the concept of lineage-determining transcription factors and made skeletal muscle differentiation a model system for understanding basic tenets about cellular differentiation (see also the article by Lassar in this issue). Subsequent work determined that lineage determination for skeletal muscle is mediated by the family of related basic helix-loop-helix transcription factors that includes MyoD, Myf5, Mrf4, and myogenin [2]. Each recognizes a DNA sequence called an E box (consensus: CANNTG) common to regulatory sequences of genes expressed during skeletal muscle differentiation [3], but, interestingly, these factors are dependent on cooperating transcription factors. Specifically, the members of the MyoD family interact with members of the ubiquitous E-protein family to form functional heterodimers [4] and with members of the Mef2 family of transcription factors to synergistically activate myogenic genes ([5]; see also the article by Hughes and Taylor in this issue). Additional transcription factors promote expression of myogenic genes [6], leading to numerous combinations of factors that cooperate with MyoD family member proteins to drive skeletal muscle formation.

The most remarkable feature of MyoD and its paralogues is the ability to drive new gene expression programmes that are required to develop the skeletal muscle cell phenotype. Such activity necessarily involves activating silent genes, which of course are incorporated into cellular chromatin. Thus differentiation-specific gene expression requires mechanisms to alleviate the effects of repressive chromatin and additional mechanisms to promote the activity of transcription factors and RNA polymerase II in a chromatin environment conducive to active gene expression.

The basic unit of chromatin is the nucleosome, which is composed of 147 bp of DNA wound ~1.8 turns around a globular octamer of histone proteins containing two copies of each of the four core histones: H2A, H2B, H3 and H4 [7]. Nucleosomes are arranged linearly on the DNA as arrays, and fold into higher order structures in conjunction with the linker histone H1, which is present stoichiometrically with nucleosomes. Detailed structural and biophysical understanding of nucleosome array structures consisting of a dozen or more nucleosomes is still somewhat limited [8]. Ultimately, however, these arrays form interphase chromatin containing loops and other higher-order structures that define the physical state of the genome. When genes are activated, chromatin structure at the locus is altered and generally becomes less compacted, originally documented by relative increases in accessibility to nuclease digestion [9,10]. Consistent with such findings, genes associated with skeletal muscle differentiation were shown to acquire nuclease sensitivity upon differentiation [11]. Subsequent genome-wide probing documented skeletal muscle differentiation-dependent changes in nuclease sensitivity that led to defined changes in nucleosome positioning [12,13]. How the chromatin structural changes represented by these increases in nuclease sensitivity are achieved at differentiation-specific genes is the focus of this review. We will address the changes in chromatin composition and structure caused by enzymes that incorporate variant histones, that modify histones post-translationally, that alter chromatin structure via ATP hydrolysis, and that contribute to higher order chromatin structure. We will cover these topics in a manner following temporal events at these loci, first describing the repressed state, then moving toward changes immediately preceding or concurrent with differentiation signaling, and then progressing to activated chromatin at transcriptionally active myogenic genes. Some chromatin modifications and structural changes are functionally understood; others are not but can be consistently correlated with transcriptionally activated, poised, or inactive chromatin and/or with other regions of the genome. The review will concentrate on terminal differentiation of myoblasts; activation of gene expression in quiescent satellite cells, the adult stem cells responsible for post-natal growth and recovery from injury, is a topic of great interest that has been reviewed extensively in recent years [14–18] and will not be covered in depth here.

2. The chromatin state of repressed myogenic loci

2.1. Histone modifiers and modifications prior to myoblast differentiation

Silencing of myogenic genes associated with terminal differentiation in proliferating precursor cells is mediated through a combination of chromatin modifying enzymes that generate well-known histone marks associated with gene repression. Among these are preclusion of histone acetylation and deposition of lysine methylation at H3K9 and H3K27.

Type I and type II histone deacetylases (HDACs), which are distinguished from each other based on relative sequence homology [19], maintain hypoacetylated chromatin at the promoters of myogenic genes and also prevent acetylation of MyoD and other non-histone components of the transcriptional machinery. The type I HDACs, HDAC1 and HDAC2, associate with MyoD [20,21] and are recruited to myogenic promoters by MyoD and as well as by the ubiquitous transcription factor YY1 [22,23]. More recent work implicates the repressor Snail as an additional factor that recruits type I HDACs as a mechanism to prevent MyoD binding [24]. Type II HDACs typically associate with Mef2 proteins and repress Mef2-based transcriptional activity [25], at least in part through association with a corepressor complex called NCOR/SMART [26]. Members of a third type of HDAC class are related to the NAD+ dependent Sir2 deacetylase protein of yeast. These HDACs associate with MyoD and the acetyltransferase PCAF to prevent PCAF activity and MyoD acetylation and may act as a redox sensor to regulate chromatin structure in response to changing physiological conditions [27].

The Polycomb group (PcG) proteins were defined genetically in Drosophila as repressors of developmentally regulated transcription [28,29]. Subsequent characterization revealed that PcG proteins form two distinct complexes, PRC1 and PRC2 [30,31], the latter of which contains the lysine methylase Ezh2, which catalyzes trimethylation on H3K27 [32–35] Targeting of PRC2 to myogenic genes occurs through YY1 [22], thereby giving YY1 a central role in two gene silencing mechanisms. A distinct repression mechanism, catalyzed by the Suv39H1 methyltransferase, results in methylation of H3K9 [36], providing a binding site for heterochromatin protein 1 [37,38] which interacts with MyoD and represses its transcriptional activity [23,39]. Another methyltransferase, G9a, dimethylates H3K9 and MyoD [40] repressing the transcriptional activity of the transcription factor as well as promoting a repressive chromatin environment. However, knockout of G9a in mouse skeletal muscle has no phenotype despite a global reduction in dimethylated H3K9 [41], possibly suggesting redundant function of another methyltransferase or a contributory but not essential role. A schematic compilation of the enzymes implicated in these post-translational modifications is presented in Fig. 1 (top).

2.2. Chromatin remodeling and histone variants prior to myoblast differentiation

Variants of three of the four core histones (H2A, H2B, H3) exist and play specialized roles in different biological processes. To date, there is no evidence for a role for H2B variants in myogenesis [42]. Replacement of canonical histones with histone variants of H2A

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