Insights into chromatin remodelers in mesenchymal stem cells and differentiation

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1. ABSTRACT

Acquisition of lineage specific fate depends on the well orchestrated performance of transcription factors and on dynamic changes in chromatin structure that account for epigenetic regulation. Epigenetic mechanisms regulate transcription at the promoter level and involve the recruitment of numerous chromatin modifiers in order to permit tissue-selective gene transcription. The dynamic structural changes of chromatin are achieved by the actions of two classes of enzymes: ATP-dependent chromatin remodelers, and histone modifying enzymes. The enzymes are members of multi-protein complexes that operate to activate or repress transcription depending on the composition of proteins in the operating complexes. It is fully appreciated now that mechanisms triggering changes of chromatin structure are an integral part of the developmental program of the stem cells. Elucidating the nature of cross talk between chromatin remodelers and master genes is important for identifying pathways that govern stem cell fate and lineage decision.

2. INTRODUCTION

Adult stem cells (ASCs) are able to self-renew and to give rise to specialized progeny. ASCs maintain the pool of stem cells through life and also provide specialized cells required for tissue regeneration. Stem and mature cells are under strict control of their niche which maintains a balance between cells' quiescence, proliferation, differentiation and death. One of the most studied and characterized ASCs are the mesenchymal stem cells (MSCs) that were shown to give rise to a variety of cell phenotypes such as bone, cartilage, fat and muscle (1-6) and are therefore considered a promising source for regenerative medicine. The progression from a stem and precursor cell to a mature functional cell is governed by activation of lineage-specific and repression of genes that maintain the non-specific stem state. Identifying mechanisms that regulate lineage commitment is fundamental for understanding developmental processes as well as for establishing protocols to govern cell fate for the use of the emerging field of regenerative medicine.
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<p>| Table 1. ATP-dependent chromatin remodeling proteins |
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<th>Family</th>
<th>Conserved Domains</th>
<th>Reported Binding to</th>
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<tr>
<td>SWI/SNF</td>
<td>Bromodomains</td>
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<td>ISWI</td>
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Stem cell fate is determined by a cascade of events that is coordinated by the read out of the nuclear compacted DNA. DNA is compacted as chromatin, which is a complex of DNA and proteins, mostly histones. To allow transcription and replication, the DNA-protein complex needs to be remodeled and opened. Specifically, euchromatin is the "open" (uncompacted) chromatin and is permissive for transcription, whereas heterochromatin is compacted and repressive for gene expression. Chromatin remodeling factors regulate gene expression by allowing the transition between euchromatin and heterochromatin (7, 8). Stem cells self-renewal, proliferation and differentiation properties are controlled by transcription factors, some of which function in a tissue-specific pattern. The latter, often referred to as master regulators, induce a cascade of transcription and translation events that culminate in an orchestrated expression and activation of structural and functional tissue-specific genes. Chromatin remodeling operates at a level beyond the genetic code (9, 10). Thus, it is suggested that the ability to modulate local chromatin states maintains stem cells’ pluripotency. Studies on chromatin remodelers and transcription factors are important in dissecting molecular pathways that govern stem cell biology and lineage fate.

2.1. Mesenchymal Stem Cells

Bone marrow contains at least two types of stem cells: hematopoietic stem cells (11), which give rise to all types of blood cells (12) and mesenchymal stem cells (MSCs). The latter are part of the stroma that forms the reticular network which supports blood cell differentiation. Based on many features that discern MSCs from HSCs, these two cell types can be separated in vitro. When bone marrow is dissociated and cultured at low density, stromal cells adhere to the culture dish and give rise to fibroblast-like cells, while the HSCs are non-adherent and remain in the supernatant. MSCs proliferate in vitro and form colony-forming unit Fibroblasts (CFU-Fs) which are composed of quiescent stem cells, proliferating, differentiating, and specialized cells. Following activation, MSCs undergo commitment and depending on the signals conveyed by their niche they differentiate into various lineages, giving rise to osteogenic, chondrogenic, adipogenic and fibrous connective cells (2, 3) (5, 6) (13-20). Additionally, interchangeable phenotypes and cell plasticity of MSCs was reported (2, 14) (17-20). Mesodermal tissues, such as skeletal myocytes, osteocytes, chondrocytes and adipocytes arise from mesenchymal progenitors (16). For example, during embryonic development, mesenchymal derived muscle progenitors and satellite cells commit to the myogenic lineage. This is accompanied by restricting the expression of genes that are associated with other lineages. Similar mediators and molecular mechanisms were shown to control skeletal muscle differentiation in adult skeletal muscles (21).

The signaling environment of the stem cell niche is important for maintaining its pluripotency and relies on cell-cell and cell-matrix interactions which create a local microenvironment that determines the cells' fate decisions. MSCs express low levels of genes that are characteristics of other lineages (22-25). Lineage promiscuity may explain pluripotency if cells that express various gene products at a low level do not start transcription de novo of a particular protein, but rather instantaneously up-regulate its transcription. Thus, it is suggested that expression pattern of genes that characterize the stem cell state or others that control differentiation are regulated at the epigenetic level. A balance is maintained between cells' renewal capacity and differentiation allowing cell proliferation or differentiation.

2.2. Epigenetic regulation

Dynamic chromatin remodeling includes two levels of regulation which allow or prevent the access of the transcription machinery to nucleosomes: (a) DNA methylation and covalent histone modifications and (b) local disruption or alteration of histones’ association with DNA by chromatin remodeling proteins that acts via ATP hydrolysis. Patterns of post-translational histone modifications were suggested to form a combinatorial ‘histone code’ which regulates mitosis, cell growth, DNA repair and apoptosis. Some modifications, such as histone acetylation, are implicated to have a structural role making the nucleosome structure ‘looser’ and more accessible to transcription factors (10). Histone acetyltransferase (HAT) and histone deacetylase (HDAC) complexes regulate the transcriptional activity of genes by determining the level of acetylation in amino-terminal domains of nucleosomal histones. Unlike histone acetylation, which occurs on lysine residues and is generally related with active transcription, methylation is detected on both lysine and arginine residues and is linked to both transcriptional activation and repression (26). Cellular fate is tightly associated with the degree of methylation (mono, di, or trimethyl histones) and with the type of modified residues (27). The role of different classes of chromatin remodeling proteins is fundamental in altering chromatin structure, composition and positioning of nucleosomes which allows or prevents the access to nucleosomal DNA (28-30). Different classes of chromatin remodeling factors establish the 'epigenetic landscape' and contribute to distinct regulatory mechanism of cell differentiation and function.

2.3. ATP-dependent chromatin remodeling proteins

ATP-dependent chromatin remodeling enzymes trigger conformational changes of nucleosomes. These complexes contain an ATPase subunit with helicase-like motifs that belong to the SNF2 super family of proteins (31-33). Other conserved domains in this subunit serve for further classification into the SWI/SNF (mating type switching/sucrose non-fermenting), ISWI (imitation switch) or CHD (chromodomain helicase DNA-binding) families (34). Generally, SWI/SNF ATPases contain bromodomains (35), ISWI ATPases have a SANT domain (36), and CHD ATPases are characterized by two adjacent chromodomains (37-39). The functional motifs of proteins...
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are regulated by the chromatin binding domains, which display specific binding to characteristic DNA regions. Chromodomains bind methylated histone tails that are located in either active or repressed chromatin (40, 41). Bromodomains bind acetylated histone tails and are most likely associated with actively transcribed genes (42). SANT domains mediate protein-protein interactions through binding unmodified histone tails (43, 44). ATP-dependent remodelers are present in many regulatory complexes and mediate a variety of cellular processes including differentiation (8, 45).

2.4. SWI/SNF

SWI/SNF proteins contain ATPase subunits and bromodomains. These proteins participate in various chromatin binding complexes that include also histone-acetyltransferases. The bromodomains were shown to specifically recognize acetylated lysines in histone tails. Additionally, SWI/SNF remodeling complexes contain distinct DNA-binding motifs that presumably target SWI/SNF remodeling factors to chromatin. The DNA-binding domains act in concert with histone-binding modules to allow efficient chromatin remodeling rather than directing the complex to specific DNA sequence motifs. In mammals, there are tissue-specific subunits of SWI/SNF remodelers (46) some of such examples are detailed in this review. Different subunits bring unique properties to SWI/SNF complexes play a function in distinct "biological programming" involving chromatin in cells. The role of factors such as RCA1 (47) or components of the histone deacetylating Sin3 complex (48) are associated with SWI/SNF remodelers.

2.5. ISWI

ISWI family is the most diverse family of ATP-dependent remodelers. Members of this family contain a SANT domain (domain is present in Swi3, Ada2, N-CoR, and TFIIB) at their C-terminus in addition to the ATPase domain (34). ISWI-containing complexes were identified in yeast, Drosophila, Xenopus, Arabidopsis and mammals. They play a key role in cell viability and during embryonic development of reproductive organs and neural tissues. Studies of the in vivo roles of particular ISWIs are complicated as they are partners in a variety of protein complexes. Dominant-negative ISWI mutants are used to study the effect of ISWI loss in different tissues during development. Expression of dominant-negative ISWI in any tissue in Drosophila leads to subsequent loss of corresponding adult structures, which indicates a global requirement of ISWI for both cell viability and division (34).

2.6. CHDs

CHDs family includes several proteins that are highly conserved from yeast to humans. The function of most these proteins is yet unknown or is poorly characterized. The CHD protein family is composed of ATP-dependent remodelers named after three domains present in all of its members: Chromodomain, Helicase, and DNA-binding domain (49). The CHD family is characterized by two tandem chromodomains located in the N-terminal region and SNF2-like ATPase domain (50).

Protein members of this family, CHD1 through CHD9 are divided into three subfamilies, based on additional domains (11, 51-53). The first subfamily contains CHD1 and CHD2 proteins (50) (54). The second subfamily contains CHD3-5 proteins that have additional amino-terminus PHD zinc finger DNA binding domains (55). The third subfamily members are CHD6-9 that contains SANT and BRK domains. The function of the BRK domain is unknown, but it is a common motif in CHD6-9, BRG1 and BRM proteins (SWI/SNF ATPases) (52, 56-58). Two of the best known proteins of the third subfamily are CHD7, mainly studied at the genetic level (59) and CREMM/CHD9 that its gene and protein structure, expression profile and potential function were recently characterized (52, 60-63).

2.7. Chromatin remodeling is essential for proper development

Dynamics of chromatin structure regulate gene expression during embryonic development. The function of chromatin remodeling complexes SWI/SNF, ISWI and CHD were studied using mutated genes or in knockout mice. Studies with mice lacking the SNF5 protein, a member of SWI/SNF complex, revealed its importance to early development and viability of embryonic cells. Embryos of these mice stopped developing at the peri-implantation stage (64). Srg3 is a core component of the SWI/SNF complex which is expressed in many tissues during mouse embryogenesis in a spatiotemporal pattern that typically overlaps with Brg1. Deficiency in Srg3 expression results in early embryonic lethality soon after decidualization due to defects in the inner cell mass and the primitive endoderm (65). Analysis of ISWI mutant animals indicated the role of these proteins in homeoetic gene activation and chromatin condensation (66, 67). Snf2h, the core ATPase of ISWI complexes, is essential for early embryonic mammalian development. Snf2h−/− embryos die during the peri-implantation stage. Blastocyst outgrowth experiments showed that a loss of Snf2h results in growth arrest and in cell death of both the trophectoderm and the inner cell mass.

The role of CHDs in cell fate decisions during development was shown in Drosophila, where the loss of kismet expression (a CHD9 homologue) caused abnormal segmentation and homeotic transformations (55). Kismet was identified, along with brm, in a screen for dominant suppressors of Polycomb (68), a protein associated with maintaining the repression of homeoetic genes during development. CHD2 role was demonstrated in cell cycle progression, development and differentiation regulation CHD2 deletion in mice, causes perinatal lethality and embryonic growth retardation (69) and heterozygously decreased neonatal viability and a shorter life span. In some cases, these mice developed primary organ abnormalities such as glomerulopathies and cardiomyopathies. CHD3 and CHD4 are members of NuRD/Mi-2 protein complex and take part in transcriptional repression that is governed by Polycomb and Hunchback in Drosophila and mouse development (70). Hunchback induces repression of homeotic genes and Polycomb maintains this repression. Multiple dominant autosomal mutations in CHD7 in humans were identified in patients with CHARGE.
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syndrome (71-74); various congenital abnormalities were identified in the CNS, retina, heart, inner ear and nasal regions (75). CREMM/CHD9 is differentially expressed in skeletal tissues, was identified primarily in mesenchymal cells and in osteoprogenitors of mice embryos at 16.5 p.c. (52, 60-62).

2.8. Tissue specific regulation by chromatin remodelers

Tissue-specific transcription factors act in concert with chromatin remodeling complexes to coordinate proper differentiation. For example, the role of Brg1 that contains the SWI/SNF complex in T cell development was investigated in knockout mice. Brg1 and SWI/SNF complexes were shown to participate in the regulation of thymocyte response to developmental cues and of mature T cell response to activation-induced signaling pathways (76, 77). Brg1 is an essential regulator during the nervous system formation in vertebrates (78). Brg1 (and by extension the SWI/SNF complex) mediates the transcriptional activities of proneural bHLH Ngn and NeuroD proteins participating in neurogenesis.

Two ISWI orthologs, SNF2H and SNF2L are mammalian genes which are suggested to participate in neuronal development. In the mouse, SNF2H is expressed ubiquitously, whereas SNF2L expression is restricted to the gonadal tissue and to the central nervous system where it is expressed at high levels in differentiatated postmitotic neurons (79). CHD8 (80) are components of NuRD complex, which also includes histone deacetylases (81). The NuRD complex is expressed in T-cell differentiation and was proposed to be recruited to heterochromatin by Ikaros, a transcription factor associated with T-cell maturation (82, 83). This interaction may be involved in maintenance and/or induction of the repressive chromatin state (7). Ikaros-NuRD is expressed also in adult erythroid cells, suggesting it participates in additional regulatory mechanisms (84). NuRD plays a role in B-cell differentiation by interacting with the master regulator BCL-6 (85). CHD4/Mi-2beta is present in thymocytes and promotes CD4 expression which is required for T-cell differentiation; this complex also functions as a repressor when associated with NuRD complex (86). CHD5 expression was detected in neurogenic tissues, but not in neuroblastoma. It is likely that CHD5 possesses a tumor-suppressor function, as its location maps to a commonly deleted region in various tumors that develop during childhood (87). An abnormal regulation of CHD5 may be related to the promotion of neuronal lineage tumors (80). CHD6 was proposed to be engaged in hematopoietic stem cell disorders (53) and its presence in lymphoblasts may be linked to proliferation and radio-sensitivity (88). CHD9/CREMM protein is transiently expressed in mesenchymal cells differentiation in vivo and in vitro in osteoprogenitors and that this expression is down-regulated in mature osteoblasts (52, 60-62).

2.9. Adipogenesis

Adipogenic lineage commitment involves activation of specific transcription factors and tissue specific genes including some examples such as adiponectin, PPARγ2, C/EBPα and leptin. Chromatin remodeling and histone-modifying enzymes interact with lineage-specific transcription factors to govern terminal adipogenic differentiation (89, 90). The promoters of PPARγ and leptin are hypomethylated in preadipocytes, while promoters of genes associated with late stages of adipogenesis are still methylated and become hypomethylated as adipogenesis proceeds (91, 92). C/EBPα has an inductive role in adipogenesis which has been correlated to its ability to up-regulate the expression of PPARγ (93). C/EBPα was also shown to directly activate adipocyte-specific promoters (94, 95). The basis for the lineage specific differentiation of C/EBPα is based on its interaction with the SWI/SNF chromatin remodeling complex. The latter is recruited by C/EBPα and mediates adipogenic lineage commitment and differentiation (96).

2.10. Chondrogenic and osteogenic lineages

Chondrocytes and osteoblasts are derived from a common mesenchymal precursor and participate in cartilage and bone formation. The transformation of these progenitors into highly organized and patterned skeletal structures requires orchestration of cell-cell interactions and signaling events that regulate gene transcription and function (1). Developmental and regenerative skeletogenesis provide a paradigm for skeletal tissue engineering. Molecular and cellular signals that regulate skeletogenesis have been intensively investigated and several key factors including FGFs, BMPs, Wnts, Hedgehog proteins and parathyroid hormone were studied. Determination of progenitor cells’ fate is under the control of hormonal and local factors that affect transcription. At the cellular level, the developmental stages of skeletogenesis are characterized by epigenetic templates that are affected by structural chromatin proteins and chromatin remodeling complexes (97). For example, transcription factors of the Sox family are required for chondrogenic differentiation commitment, while Runx plays a pivotal role in chondro-osteoblast differentiation decision and Osterix is a key factor for directing osteogenic lineage fate (98, 99). Chromatin remodeling during chondrocyte differentiation is affected by a group of high mobility proteins (HMG) that play a role in regulating Sox and Sox-dependent genes expression (100). Master regulator genes that control osteo-chondrogenesis commitment belong to the Runx family. Runx1 mediates early events of endochondral and intramembranous bone formation, and Runx2 is a potent inducer of late stages of chondrocyte and osteoblast differentiation (101-104). Runx2 is an early key regulator of osteogenic commitment and is also involved in cell cycle regulation and in proper extracellular matrix deposition that occurs during late differentiation stages that are exclusive to osteoblasts (105). Runx2 is capable of inducing these processes only when assisted with structural changes in chromatin that promote the availability of target functional elements (106). Chromatin remodeling in osteogenesis was extensively studied in the context of Runx2 transcriptional regulation. Initiation of Runx2-dependent osteogenic lineage determination is induced by regulatory factors such as BMP2 or HOXA10 and requires chromatin remodeling. Initiation of BMP2-induced Runx2-dependent activation of skeletal gene expression requires SWI/SNF chromatin
remodeling complexes (107). HOXA10 contributes to osteogenic lineage determination both through activation of Runx2 and direct regulation of osteoblast phenotypic genes including those encoding for alkaline phosphatase, bone sialoprotein and osteocalcin through chromatin remodeling. HOXA10 mediates chromatin hyperacetylation and histone K4 (H3K4) tri-methylation, which correlates with active transcription of osteoblast phenotypic genes (108).

Transforming growth factor- (TGF-) is a negative regulator of osteoblast differentiation through inhibition of Runx2 by Smad3. Recently, it was shown that this inhibition occurs via the action of class IIa histone deacetylase 4 and 5, which are recruited through interaction with Smad3 to the Smad3/Runx2 complex at the Runx2-binding promoter. TGF- induces histone deacetylation at the osteocalcin promoter, which is repressed by TGF-.

Histone deacetylation is required for repression of Runx2 by TGF- (109). Runx2 influences modifications in chromatin organization and transcription of the osteocalcin gene (110). The role of SWI/SNF complex in chromatin remodeling of tissue-specific transcription in osteoblasts was analyzed at the Osteocalcin gene promoter (111) (112). CREMM/CHD9 is a remodeler that is expressed in skeletal tissues in vivo (61) and in vitro and is highly expressed in osteoprogenitors (60,62). CREMM levels were analyzed in clonal osteogenic cell derived from CFU-F and was compared with non-osteogenic clones or cells cultured from trabecular bone (60). Chip assay of was compared with non-osteogenic clones or cells cultured analyzed in clonal osteogenic cell derived from CFU-F and expressed in osteoprogenitors (60,62). CREMM levels were analyzed in clonal osteogenic cell derived from CFU-F and was compared with non-osteogenic clones or cells cultured from trabecular bone (60). Chip assay of was compared with non-osteogenic clones or cells cultured analyzed in clonal osteogenic cell derived from CFU-F and expressed in osteoprogenitors (60,62). Myogenic commitment and differentiation in embryogenesis involves the homeobox protein Msx1 that during embryogenesis negatively regulates the differentiation of several mesenchymal lineages, including that of skeletal muscles (126, 127). Msx1 forms a complex with histone H1b and targets it to the regulatory region of MyoD (128). The complex Msx1-H1b represses MyoD and inhibits myogenesis. H1b histone is indeed expressed in undifferentiated myoblasts and muscle precursors, and its expression decreases with differentiation (129).

Upon differentiation, HDACs and their associated co-repressors dissociate from MEF2 and from muscle specific transcription factors allowing the recruitment of chromatin remodelers, such as acetyl transferases (HATs) CBP/p300, PCAF, p/CIP, SRC1, GRIP, the arginine methyltransferase CARM-1 and SWI/SNFs, to muscle gene promoters (118, 130). p300/CBP and P/CAF directly acetylate MyoD and by that increase its affinity for DNA and for p300/CBP itself (131-133) (134). Myogenic terminal differentiation depends on MyoD that promotes the transcription of p21 and interacts with p300 and PCAF to activate the pRB promoter. The latter cooperates with histone deacetylases and lysine methyltransferases establishing and maintaining the post mitotic state of nuclei in myotubes (135-137). Realizing how chromatin remodelers affect muscle specific gene expression in altered physiological and pathological conditions will reveal novel targets for treatment of skeletal muscle-related maladies.

2.13. Genome-wide genetic approaches to reveal intrinsic properties of epigenetic mechanisms

Recently the high through put approaches used to study stem cell gene regulation employed 'CHIP-on-chip', genome-wide binding site analysis of transcription factors and of chromatin-remodeling proteins enhance. These tools allow to study at the three-dimensional organization of gene loci leading to understanding the complexity of epigenetic regulation and mapping the epigenetic regulatory signatures of protein-DNA interactions, chromatin composition and DNA methylation. Integrating the level of chromatin regulation into dynamic models of networks will contribute to better understanding molecular pathways that are involved in maintaining stem cells in their stemness stage and in changes that inflict lineage specific commitment and differentiation.
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Transcription factors occupying gene promoters participate in protein complexes that regulate gene transcription. ChIP-chip assay allow the screening at the genome-scale level of transcription factor binding sites in vivo. The chip-chip assay study the protein-DNA interactions identifying the epigenetic characteristics of these sites. ChIP-chip techniques includes: (A) DNase I digestion combined with microarrays which define the status of compact and loose chromatin in a genome-wide manner. DNA regions that are free of nucleosomes are more readily digested by DNase I; these regions point to places where chromatin is accessible to DNA binding proteins. Subsequently, DNase-chip locates functional elements in the DNA sequence such as promoters, enhancers, and silencers. (B) Genome-wide microarray detection of DNA methylation, an epigenetic marker of gene expression both inherited and generated de novo. Detection of DNA methylation is performed using 5-methyl-cytosine residue specific antibodies. These sequences are then hybridized to microarrays in mDIP assay (138) which enables to identify novel promoters that participate in tissue specific differentiation. Combining ChIP-chip with expression profiling techniques allow to elucidate the function of proteins present on gene promoters and enhances our understanding how transcription factors and chromatin modifications are coordinated to control gene expression. Mapping genomic locations of specifically modified histones, characterizing chromatin features and studying transcription factors that are related to differentiation are important and serve as powerful tools highlighting on the complexities of regulatory networks.

3. SUMMARY

Holistic comprehension of stemness and cell differentiation is possible only when considering the diverse regulatory functions mediated by chromatin and histone modifications. Instead of being structural scaffolds, histones are now recognized as regulators of gene expression at the epigenetic level. In this review we presented some components of chromatin remodeling that play an integral role in the developmental program of stem cells of mesenchymal lineages. Deciphering the epigenetic regulation that inflicts quiescence or commitment to a specific differentiation path of stem cells will allow elucidating the nature of cross talk between chromatin remodelers and master genes which govern these processes. The ability to impose a specific lineage fate on a MSC, for example, holds great promises for regenerative medicine purposes.

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