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Osteoblast-Adipocyte Lineage Plasticity in Tissue Development, Maintenance and Pathology

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Abstract

Osteoblasts and adipocytes share a common precursor in adult bone marrow and there is a degree of plasticity between the two cell lineages. This has important implications for the aetiology of not only osteoporosis but also several other diseases involving an imbalance between osteoblasts and adipocytes. Understanding the process of differentiation of osteoblasts and adipocytes and their trans-differentiation is crucial in order to identify genes and other factors that may contribute to the pathophysiology of such diseases. Several transcriptional regulators have been shown to control osteoblast and adipocyte differentiation and function. Regulation of cell commitment occurs at the level of the progenitor cell through cross talk between complex signaling pathways and epigenetic mechanisms such as DNA methylation, chromatin remodeling and microRNAs. Here we review the complex precursor cell microenvironment controlling osteoblastogenesis and adipogenesis during tissue development, maintenance and pathology.

Keywords

osteoblastogenesis; adipogenesis; progenitor; transcription; microenvironment

Introduction

Bone marrow stroma contains pluripotent mesenchymal progenitor cells that can give rise to many mesenchymal lineages, including chondroblasts, adipocytes or osteoblasts. At birth, hematopoietic red marrow occupies the bone marrow space while adipocytes are barely present but their number and size increases with aging. (1–3). In the elderly and in osteoporosis the increased volume of marrow adipose tissue correlates with a decrease in bone mass (4) and many conditions that can induce bone loss, such as estrogen insufficiency, disuse, hindlimb unloading, and microgravity exposure show increased bone marrow adiposity (5–7). The differentiation of mesenchymal stem cells (MSCs) into adipocytes or osteoblasts is tightly regulated by mechanisms promoting cell fate into one lineage while repressing the other. Interestingly, osteoblastic cells derived from trabecular bone fragments have the potential to differentiate into multiple mesenchymal lineages including adipocytes *in vitro* (8). Furthermore, adipocytic cells cultured from marrow show the ability to revert to a more proliferative phase and then differentiate in an osteogenic direction (9, 10). This suggests that adipocytic and osteogenic cells share a common precursor in adult marrow and that there is a high degree of plasticity between the two cell lineages even at the most advanced stages of maturation. Regulation of adipogenesis and osteogenesis occurs at the level of the precursor cell in adult marrow, which has important

implications for the aetiology of not only osteoporosis but also several other diseases involving an imbalance between osteoblasts and adipocytes. Understanding the process of differentiation of osteoblasts and adipocytes and their trans-differentiation is crucial in order to identify genes and other factors that may contribute to the pathophysiology of such diseases.

Pathological conditions associated with osteoblast-adipocyte lineage plasticity

Several related genetic disorders have the common feature of superficial/dermal ossification with the formation of islands of heterotopic bone in skin and subcutaneous fat (11). These diseases are associated with heterozygous inactivating mutations of guanine nucleotide-binding protein (α) stimulating activity polypeptide 1 (GNAS) and include progressive osseous heteroplasia (POH), Albright hereditary osteodystrophy/pseudopseudohypoparathyroidism (AHO/PPHP), pseudohypoparathyroidism (PHP), and osteoma cutis (OC). The tissue distribution of heterotopic ossification lesions in GNAS inactivation disorders such as POH suggests that the pathogenesis involves abnormal differentiation of MSCs and/or more committed precursor cells that are present in skin, subcutaneous fat, muscle, tendon and ligament tissue. Considerable evidence supports the notion that tissues contain multipotential progenitor cells that can give rise to osteoblasts and adipocytes (12–18). In addition, vascular endothelial cells were reported to transform into multipotent stem-like cells (19).

Another example of a disease involving fat and bone tissue interaction is multiple myeloma (MM). Within the bone marrow microenvironment MM cells interact with bone marrow stromal cells, endothelial cells, osteoclasts, osteoblasts, adipocytes, immune cells and the extracellular matrix (20). MM cells suppress osteoblast differentiation and thereby inhibit bone formation. Several mechanisms appear to be involved such as direct blocking of the activity of the osteoblast transcription factor Runt-related transcription factor 2 (Runx2) in mesenchymal and osteoprogenitor cells through direct cell-to-cell contact with the involvement of very late antigen 4 (VLA-4)/vascular cell adhesion molecule 1 (VCAM-1).

In addition to energy storage, adipose tissue plays an important physiological role as an endocrine organ by secreting adipokines, such as leptin and adiponectin. Therefore, dysregulation of osteoblastogenesis and adipogenesis may contribute to the pathophysiology of diseases such as obesity, atherogenesis, diabetes and inflammation (21).

Transcriptional regulators of osteoblast-adipocyte differentiation

Genetic approaches in which genes are silenced or overexpressed reveal factors controlling the plasticity between the osteoblast-adipocyte cell lineages. This provides insight into the critical pathways that determine the fate of the bone marrow MSCs. Several transcriptional regulators have been shown to control the osteoblast and adipocyte lineages. Runx2 is expressed in osteoblasts at all stages of development and its targeted disruption abolishes the osteoblast lineage (22–24). Also, inactivation of Osterix (Osx) by gene targeting results in a block in osteoblast development downstream of Runx2 (25). Activating transcription factor 4 (ATF4) (26) and activator protein 1 (AP-1) (17) further promote the transition to functional osteoblasts. Conversely, peroxisome proliferator-activated receptor gamma (PPAR γ) is crucial for adipocyte differentiation and function (27), and members of the CCAAT/enhancer binding proteins (C/EBP) family of transcription factors have been implicated in controlling aspects of adipocyte biology (28). The balance between osteogenic and adipogenic transcription factors in multipotent mesenchymal precursor cells regulates their quiescence and determines lineage commitment. Furthermore, osteogenic and adipogenic transcription factors can affect each other; PPAR γ is a suppressor of Runx2 expression and transcriptional activity thus inhibiting osteoblast differentiation (29, 30).

Regulation of the commitment between the two cell lineages occurs through cross talk between complex signaling pathways including those derived from parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP), bone morphogenetic proteins (BMPs) and retinoic acid (RA), transforming growth factor β (TGF β), wntless-type MMTV integration site (Wnt) proteins, hedgehogs (Hhs), delta/jagged proteins, fibroblastic growth factors (FGFs), insulin, and insulin-like growth factors (IGFs), and leptin (reviewed in (31, 32)). Additional factors that were identified to play an important role in osteoblast and adipocyte differentiation include Δ FBJ murine osteosarcoma viral oncogene homolog B (Δ FosB), a naturally occurring truncated form of FosB (17), Msh homeobox 2 (Msx2) (33), transcriptional coactivator with PDZ-binding motif (TAZ) (34), inhibitor of DNA binding 4 (Id4) (35), Sirtuin 1 (Sirt1) (36), and early B cell factor 1 (Ebf1) (37). However, their specificity as determinants of age-related changes in bone homeostasis is unclear. In contrast, in the case of the retinoblastoma protein (pRB; (38)), V-maf musculoaponeurotic fibrosarcoma oncogene homolog (Maf) (39) and vascular endothelial growth factor A (VEGF; (40)), also reported to control the balance between osteoblast-adipocyte cell fates *in vivo*, expression levels are reduced in mesenchymal cells during aging. Loss of the tumor suppressor gene retinoblastoma protein (Rb) favors adipogenesis over osteogenesis resulting in reduced levels of calcified bone and increased levels of brown fat, and Rb-deficient preosteoblasts show multipotency at the expense of commitment to the osteogenic state. The basic leucine-zipper transcription factor Maf was demonstrated to be central to osteoblast lineage commitment through binding to Runx2 and directly regulating the osteocalcin-coding gene bone gamma-carboxyglutamic acid-containing protein 1 (Bglap1). Furthermore, Maf disturbs adipocyte differentiation by suppressing the interaction of Cebp δ and the cAMP response element-binding protein (CREB)-binding protein gene (Crebbp). VEGF stimulates osteoblastogenesis at the expense of adipogenesis by regulating the expression levels of Runx2 and PPAR γ by mechanisms that appear to be affected by a functional interaction with the nuclear envelope protein lamin A. Defective processing of lamin A by the enzyme Zmpste24 has also been linked to changes in osteoblastogenesis and adipogenesis in the bone marrow (41). Furthermore, cell shape and cytoskeletal tension were reported to regulate stem cell lineage commitment to either osteoblastogenesis or adipogenesis by modulating endogenous Ras homolog gene family, member A (RhoA) activity (42) or stress response pathways (43).

Epigenetic mechanisms involved in osteogenic-adipogenic differentiation

Recently, Scheideler et al. (44) found that gene repression is most prevalent prior to commitment in both osteoblast and adipocyte cell lineages, and computational analysis suggested that gene repression before commitment of mesenchymal stem cells is mediated by microRNAs (miRNAs). Thus, miRNAs were proposed to be involved in regulating differentiation and cell fate decisions (45). So far, only a few key miRNAs controlling the balance between osteogenesis and adipogenesis have been identified, such as miR-22 (46), miR-31 (47), miR-106a (47), miR-148a (47), miR-424 (47), miR-637 (48), miR-705 (49), miR-3077-5p (49) and several members of the miR-17 family (50). Different families of miRNAs affect osteoblast-adipocyte differentiation by targeting distinct downstream targets, including histone deacetylase 6 (HDAC6), Osx and BMP2 for miR-22, miR-637, and the miR-17 family members miR-17-5p and miR-106a, respectively, as well as Runx2, core binding factor β (Cbfb) and BMPs for miR-31, miR-106a, miR-148a and miR-424.

Accumulating evidence suggests that epigenetic mechanisms involving post-translational and covalent modifications of histones in chromatin may be a central mechanism controlling gene transcription. Histone modifications can occur during specification into a cell lineage and in response to changes in the extracellular environment. For example, a change in cell fate from adipogenesis to osteoblastogenesis of bone marrow MSCs was shown to occur as a

result of transactivation of agonist-bound PPAR γ being repressed by a non-canonical cascade. Wnt5a was reported to activate Nemo-like kinase (NLK), which in turn phosphorylates a histone methyltransferase, SET domain bifurcated 1 (SETDB1), leading to the formation of a co-repressor complex that inactivates PPAR γ function through histone H3-K9 methylation (51). This indicated a novel molecular mechanism where a signal from a cell membrane receptor leads to altered histone modification and changes in gene regulation and cell-lineage decisions.

Co-factors promoting adipocyte differentiation while suppressing osteoblast differentiation were identified as zinc finger protein 467 (Zfp467), which may function by recruiting a HDAC associated co-repressor complex to suppress target gene transcription (52), and HDAC3, which mediates numerous developmental signaling pathways (53). Furthermore, histone demethylases KDM4B and KDM6B were shown to epigenetically regulate commitment of MSCs to the osteoblast-adipocyte lineage (54). Depletion of KDM4B or KDM6B significantly reduced osteogenic differentiation and increased adipogenic differentiation by controlling DLX (by removing H3K9me3) and homeobox (HOX) expression (by removing H3K27me3), respectively.

Controlling osteoblast-adipocyte lineage plasticity and consequent therapeutic implications

The data reviewed above suggest that the relationship between osteoblastogenesis and adipogenesis is complex (55) (56) (Fig. 1). Osteoblastogenesis is dominant over adipogenesis in the bone marrow of young animals and the cell-differentiation balance between the two cell fates is usually reversed in bone marrow of older or osteoporotic animals (57). The differentiation of mesenchymal stem cells towards a specific lineage is dependent on activation of specific transcription factors (see Fig. 1) by local, hormonal and mechanical factors (58), including VEGF, BMPs, TGF β , Wnts, FGFs, IGFs, 1,25-dihydroxyvitamin D3, PTH, glucocorticoids, insulin and leptin. Recently, elegant genetic pulse-chase experiments indicated that osteoblastic cells are short-lived and nonreplicative, requiring replenishment from bone marrow-derived precursor cells (59). Thus, it will be crucial to fully understand the precursor cell microenvironment during tissue development, maintenance and pathology in order to identify targets for pharmacological intervention in diseases related to osteoblast-adipocyte lineage plasticity.

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Figure 1.

Osteoblast-adipocyte lineage plasticity is a complex, multifactorial process that shapes tissue development, maintenance and pathology. Mesenchymal stem cells (MSCs) differentiate into mature osteoblasts and adipocytes via intermediate precursor cell stages that are subject to transdifferentiation. Local, hormonal and mechanical factors in MSCs result in the activation of transcription factors (TF) and epigenetic mechanisms, which jointly control the balance between osteoblastogenesis and adipogenesis.