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# Skeletal (stromal) stem cells: An update on intracellular signaling pathways controlling osteoblast differentiation

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ABSTRACT

Skeletal (marrow stromal) stem cells (BMSCs) are a group of multipotent cells that reside in the bone marrow stroma and can differentiate into osteoblasts, chondrocytes and adipocytes. Studying signaling pathways that regulate BMSC differentiation into osteoblastic cells is a strategy for identifying druggable targets for enhancing bone formation. This review will discuss the functions and the molecular mechanisms of action on osteoblast differentiation and bone formation; of a number of recently identified regulatory molecules: the non-canonical Notch signaling molecule Delta-like 1/preadipocyte factor 1 (Dlk1/Pref-1), the Wnt co-receptor Lrp5 and intracellular kinases. **This article is part of a Special Issue entitled: Stem Cells and Bone.**

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## Introduction

Human skeletal stem cells (also known as human bone marrow stromal (hBMSCs)) are non-hematopoietic stromal cells that reside in a perivascular niche within the bone marrow stroma [1]. hBMSCs are defined in vitro as plastic-adherent cells expressing a constellation of surface markers e.g. CD146, CD44, CD63, and CD105 and has the capacity for multi-lineage differentiation into osteoblast, adipocyte, and chondrocyte [2]. The "stemness" characteristic phenotype of hBMSCs is based on their ability to form heterotopic bone and bone marrow organ during serial transplantation in vivo, a characteristic exhibited only by a fraction of hBMSCs [3,4].

Several approaches have been employed to identify factors and pathways regulating lineage-specific differentiation of hBMSCs. Using genetic approaches, several lineage-specific transcription factors have been identified. For examples, core-binding factor 1 (CBFA1/Runx2) [5], ostrix (OSX) [6], peroxisome proliferator-activated receptor gamma 2 (PPARγ2) [7] and Sox9 [8] induce osteoblastic, adipocytic and chondrocytic lineages respectively. Alternatively, analysis of the "micro-environment" that includes growth factors, hormones and extra-cellular matrix components and known to induce lineage specific differentiation, led to the identification of several factors that enhance the osteoblast differentiation e.g. bone morphogenetic proteins (BMPs) [9] or inhibit osteoblast differentiation e.g. Dlk1/Pref-1 [10] and Noggin [11].

A number of in vitro and in vivo studies suggest the presence of an inverse relationship between BMSC differentiation choices into osteoblastic versus adipocytic cells. In vitro, osteoblastic differentiation of BMSCs is associated with the downregulation of adipocytic differentiation, whereas induction of adipocytic differentiation is associated with reduced osteoblastic differentiation [12,13]. In vivo, reduced bone mass observed during aging and in osteoporotic patients is associated with increased marrow fat mass [14,15]. Throughout the studies presented here, the relationship between osteoblast and adipocyte differentiation of BMSCs will be commented upon. One of the hypotheses examined was whether the studied signaling pathways function as molecular "switches" to enhance osteoblast differentiation and block adipocytic differentiation of BMSCs. Such molecular switches (Table 1 shows several of these factors) are ideal "druggable" targets for pharmacological intervention aiming at enhancing bone formation.

### *Delta like-1/preadipocyte factor 1 (Dlk1/Pref-1)*

Dlk1/Pref-1 is a paternally imprinted gene encoding for a transmembrane protein with six epidermal growth factor (EGF)-like repeats and

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**Table 1**
Factors involved in the determination of BMSC commitment into osteoblasts versus adipocytes.

| Gene name | Gene symbol | Osteoblast differentiation | Adipocyte differentiation | References |
|---|---|---|---|---|
| Canonical Wnt signaling | Wnt3a/Wnt10b | ↑ | ↓ | [16–18] |
| Non-canonical Wnt signaling | Wnt5a | ↑ | ↓ | [19] |
| Bone morphogenetic protein | BMP2 | ↑ | ↑ | [20] |
| Sonic hedgehog | Shh | ↑ | ↓ | [21,22] |
| Transforming growth factor-β1 | TGF-β1 | ↑ | ↓ | [23] |
| Nel-like molecule, type 1 | Nell-1 | ↑ | ↓ | [24] |
| WW domain containing transcription regulator 1 | Wwtr1 | ↑ | ↓ | [25] |
| Sprouty homolog 1 (*Drosophila*) | Spry1 | ↑ | ↓ | [26] |
| Retinoblastoma 1 | Rb1 | ↑ | ↓ | [27–29] |
| Myocyte enhancer factor-2 interacting transcriptional repressor/histone deacetylase 9c | MITR/HDAC9c | ↑ | ↓ | [30] |
| Nuclear factor I–C | NFI-C | ↑ | ↓ | [31] |
| Lysine (K)-specific demethylase 6A | KDM6A | ↑ | ↓ | [32] |
| Bmi1 polycomb ring finger oncogene | Bmi1 | ↑ | ↓ | [33] |
| Msh homeobox 2 | Msx2 | ↑ | ↓ | [34] |
| Transcriptional co-activator with PDZ-binding motif | TAZ | ↑ | ↓ | [25] |
| Heme oxygenase (HO)-1 | HO-1 | ↑ | ↓ | [35] |
| Secreted protein acidic and rich in cysteine | SPARC | ↑ | ↓ | [36] |
| Farnesoid X receptor | FXR | ↑ | ↓ | [37] |
| NAD-dependent deacetylase sirtuin-1 | Sirt1 | ↑ | ↓ | [38] |
| Peroxisome proliferator-activated receptor-γ | Ppar | ↓ | ↑ | [7,39,40] |
| Serpin peptidase inhibitor, clade F (alpha-2 antiplasmin, pigment epithelium derived factor), member 1 | SERPINF1 | ↓ | ↑ | [41] |
| SRY (sex determining region Y)-box 2 | Sox2 | ↓ | ↑ | [42] |
| Enhancer of zeste 2 polycomb repressive complex 2 subunit | EZH2 | ↓ | ↑ | [32] |
| Transducing-like enhancer of split 3 | TLE3 | ↓ | ↑ | [43] |
| S100 calcium binding protein A16 | S100A16 | ↓ | ↑ | [44] |
| Neuropeptide Y (NPY) receptor 1 | Y1 receptor | ↓ | ↓ | [45] |
| Thymosin, beta 4, X chromosome | Tmsb4x | ↓ | ↑ | [46] |
| Chemerin/cognate receptors CMKLR1 | Chemerin/CMKLR1 | ↓ | ↑ | [47] |

belongs to the Notch/Serrate/Delta family of developmental molecules [48]. The extracellular domain of Dlk1 is proteolytically cleaved by tumor necrosis factor alpha converting enzyme: ADAM17/TACE to produce a circulating fragment named fetal antigen 1 (FA1) [48,49] and this extracellular domain or FA1 is thought to mediate the biological activity of Dlk1/Pref-1 [50].

Dlk1/Pref-1 gene was cloned from a 3T3-L1 gene cDNA library and named preadipocyte factor 1 (Pref-1), and the human homolog termed Delta-like or dlk (homologous to invertebrate homeotic proteins, including Delta, and Notch in *Drosophila*) was isolated from human small cell lung carcinoma cell line [51]. It was also cloned from human neuroendocrine tumor (pheochromocytoma) cDNA library under the name pG2, a gene cloned because of its differential expression in human pheochromocytomas versus neuroblastomas [52]. Around the same time, the soluble extracellular part of Dlk1 was isolated from the amniotic fluid of pregnant women and pregnant mice and named FA1 [53]. FA1 is present in all biological fluids including urine, serum and cord serum suggesting an endocrine function [54].

During embryonic development, Dlk1/Pref-1 is highly expressed by many tissues including the pituitary gland, pancreas, lungs, adrenal cortex, placenta, the proximal tubules of kidneys and mesodermally-derived tissues including chondroblasts, and skeletal myotubes [55–57]. The expression of Dlk1/Pref-1 in the postnatal period is limited to the hormone producing cells in the pituitary gland, pancreatic islets, adrenal glands and testis [56] as well as in mono-aminergic neurons in the CNS [58]. In addition, Dlk1/Pref-1 is expressed in bone marrow microenvironment by osteoprogenitors present on the endosteal bone surfaces [10], by B-cells [48] and as recently demonstrated by our group by CD4 and CD8 T-cells [59]

Dlk1/Pref-1 exerts regulatory effects on cell differentiation fate during development as illustrated by the presence of a variety of defects e.g. growth retardation, obesity and skeletal malformations in Dlk1/Pref-1-null mice and in humans with the syndrome of maternal uniparental disomy (mUPD) (in which dlk1 gene is silent; mUPD12 in mice, mUPD14 in humans) [60,61]. Dlk1/Pref-1 is a negative regulator of adipocyte differentiation and fat mass in vitro and in vivo [62] and its levels are regulated in multiple differentiation processes including neuroendocrine differentiation [56], hematopoiesis [63], osteogenesis and chondrogenesis [12] as well as during muscle [64] and liver regeneration [65]. Studies performed by a number of groups including ours revealed a role of Dlk1/Pref-1 in determining BMSC differentiation fate which will be discussed in the following sections.

### *Dlk1/Pref-1 and tissue-specific stem cell differentiation*

The original studies of Dlk1/Pref-1 have focused on its role as a negative regulator of adipogenesis. Using the preadipocytic 3T3-L1 cell line, where Dlk1/Pref-1 is constitutively expressed, its levels decreased during adipocyte differentiation and its constitutive overexpression inhibited adipocyte differentiation [66]. These results were complemented with generation of transgenic mice overexpressing the soluble form of Dlk1 (i.e. FA1) under the aP2 or albumin promoter. The mice displayed reduced fat mass [62] while Dlk1/Pref-1 deficient mice displayed increased adipose tissue formation [61].

We overexpressed Dlk1/Pref-1 in hBMSCs and observed inhibition of differentiation into osteoblastic and adipocytic [10] as well as chondrocytic cells [67]. Interestingly, Dlk1/Pref-1 inhibited differentiation of MSC downstream of C/EBPβ during adipocytic differentiation and Cbfa1/Runx2 during osteoblastic differentiation of MSC suggesting that Dlk1/Pref-1 maintains MSC in progenitor state [10]. This role has also been described in a number of differentiation and regenerative processes in different tissues. High expression levels of Dlk1/Pref-1 were found in MRL mouse blastema cells during ear wound healing [68], in liver progenitor (ductal, oval) cells during liver regeneration following injury [65], satellite cells during muscle regeneration [69] as well as hematopoietic progenitor proliferation [70].

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