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ScienceDirect
Joint Bone Spine 74 (2007) 536–539
JOINT BONE SPINE
http://france.elsevier.com/direct/BONSOI/

Clinical-state-of-the-art

Plasticity of osteoprogenitor cells

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Received 6 September 2007; accepted 7 September 2007
Available online 12 October 2007

Abstract

Plasticity is the ability to give rise to cell types whose phenotype is different from that of the source tissue. Osteoblasts originate in progenitors located in the bone marrow or around blood vessels. Marrow stromal cells can differentiate into adipocytes, in part at the expense of osteoblasts. The osteoblast–adipocyte balance is influenced by systemic factors, chiefly hormones, and local factors in the microenvironment, as well as by mechanical loads, which induce or suppress the activity of transcription factors crucial to the differentiation of each cell type. New insights into the molecular mechanisms involved in controlling the osteoblast–adipocyte balance are unlocking doors to a vast array of innovative treatment strategies.

Keywords: Cell differentiation; Stem cells; Marrow stromal cells; Adipocytes; PPARγ

1. Introduction

Until a few years ago, commitment to a cell differentiation pathway was believed to be usually irreversible. Classically, cell differentiation is a process by which a cell acquires a terminal phenotype after going through several intermediate steps. For instance, hematopoietic cells move through a hierarchy of progenitors characterized by increasingly narrow differentiation potentials. Thus, a totipotent cell can differentiate, for instance, into a myeloid or lymphoid stem cell, each of which can give rise to a cell lineage. The lineages are separate, so that one cell type cannot switch to another. In recent years, however, the rapid accumulation of knowledge about stem cells has radically changed our understanding of cell differentiation. The concept of cell plasticity has emerged as a result.

2. Background information on adult stem cells

Indefinite or prolonged self-renewal and an ability to differentiate into several specialized cell types are distinctive characteristics of stem cells. Self-renewal occurs via asymmetric division, which produces one stem cell and one progenitor cell destined to differentiate into a specialized cell. Stem cells fall into two main categories, namely, embryonic stem cells, which originate in the inner part of the blastocyst (4- to 5-day-old embryo), and adult stem cells, which are found in adult tissues. Embryonic stem cells are pluripotent: they can differentiate into any of the more than 200 cell types in the body. Adult stem cells, in contrast, are multipotent, i.e., produce closely related cells. Adult stem cells contribute to adult tissue repair. The differentiation potential of stem cells was thought to be determined early on by the embryological origin of the host organ (ectodermal, mesodermal, or endodermal). Stem cells located in a tissue were believed to produce only the cell types found in that tissue. Furthermore, their self-renewal potential was thought to be limited. According to this view, stem cells found in an ectodermal tissue such as the retina or nervous system are unable to differentiate into cells found in mesodermal tissues, such as muscle cells.

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1297-319X/$ - see front matter © 2007 Published by Elsevier Masson SAS.
doi:10.1016/j.jbspin.2007.09.001

Studies reported between 1997 and 1999 established, however, that adult stem cells could differentiate into cells of different embryonic origin. Adult neural stem cells injected intravenously produced myeloid cells and B and T lymphocytes [1]. In another study, adult neural stem cells co-cultured with myoblasts or injected into skeletal muscle produced skeletal muscle cells [2]. When injected to adult mice, adult hematopoietic cells generated hepatocytes [3] or microglia in the brain [4]. Although these findings have been challenged, they nevertheless constituted a breakthrough in our understanding of cell differentiation.

3. Cell plasticity and osteoblast plasticity

Plasticity is the ability to give rise to cell types whose phenotype is different from that of the source tissue. Orthodox plasticity is the ability to produce cells derived from the same germ layer (e.g., marrow stromal cells differentiating into adipocytes) and nonorthodox plasticity, the ability to generate cells derived from other germ layers (e.g., marrow stromal cells differentiating into neurons). Stem cells can exit their resident tissue, enter the bloodstream, and localize in a tissue that needs repair. Factors must exist that stimulate stem cell mobilization then attract the stem cells to the injured tissue. Such factors have been identified in cardiovascular disease. Conceivably, osteoprogenitors that are not yet differentiated may travel from the marrow of a normal bone to a fracture site [5]. Further studies are needed to confirm this hypothesis.

After the pioneering work conducted in the 1980s by Freidenstein and Owen [6], Pittenger et al. established that adult marrow stromal cells could differentiate in vitro into several cell lines including osteoblasts [7]. However, factors that specifically induce differentiation to adipocytes, chondrocytes, or osteoblasts must be added to the culture medium. Differentiation into osteoblasts, which generates phenotypic characteristics such as alkaline phosphatase and osteopontin production, occurs upon exposure to dexamethasone, β-glycerol phosphate, vitamin C, and 10% serum. The factors needed to produce differentiation into adipocytes are isobutylxanthine, dexamethasone, insulin, and indomethacin. Chondrocytes are produced on a three-dimensional substrate in the presence of TGF-β3, without serum. Osteoblasts can also differentiate in vitro from perivascular cells called pericytes [8]. Isolated mouse adipocytes placed in culture chambers implanted under the skin of rabbits generated either fibrous tissue or bone tissue whose cells produced collagen that underwent mineralization [9]. Taken in concert, these data establish that several cell types previously thought to be terminally differentiated are capable of generating other cell types. Progress has been made in elucidating the molecular basis for switching from one cell lineage to another.

4. Osteoblast–adipocyte interactions

Although bone and fat cells can probably differentiate into each other, whether this capability is present at all times remains unknown. Pioneering studies documented replacement of trabecular bone by fat tissue during aging in humans [10,12] and showed a negative correlation between differentiation of adipocytes versus osteoblasts from cultured marrow stromal cells [11].

Stem cell differentiation depends on the sequential expression of transcription factors specific for each lineage. These transcription factors activate the expression of genes involved in the various steps of the differentiation process. Some of these factors must be present for differentiation to occur, whereas others must be downregulated. Without runx2, osteoblasts fail to develop. Factors involved downstream of runx2 include osterix, dlx5, msx2, and Twist [12]. Briefly, CCAAT/enhancer-binding protein-α (C/EBPα) and peroxisome proliferator-activated receptor-γ (PPARγ) are required for adipocyte differentiation, whereas MyoD is the master gene for myocyte differentiation. Genetic manipulation of cells partly engaged in one lineage, designed to force the expression of a transcription factor for another lineage, leads the cells to differentiate into this other lineage. For instance, forcing the muscle cell precursors C2C12 to express runx2 led to differentiation of the cells into osteoblasts [13], a process known as transdifferentiation.

The numerous factors capable of influencing the adipocyte/osteoblast balance are being actively investigated. Improved knowledge of these factors can be expected to generate a host of new treatment options. An exhaustive review of these factors would be beyond the scope of this paper. Cellular factors include transcription factors, as mentioned above, which serve as switches that allow differentiation to occur either when they are on or when they are off. Systemic hormonal factors and local factors in the microenvironment modulate the induction of the transcription factors.

4.1. Transcription factors

PPARγ activation induces adipogenesis. Interestingly, mice deficient in PPARγ exhibit reduced adipogenesis contrasting with a high bone mass related to increased osteoblastogenesis [14]. In contrast, bone loss and increased bone marrow adipogenesis occur in mice [15] and rats [16] given PPARγ agonists of the glitazone family, which are PPARγ activators used to treat type 2 diabetes mellitus. Data obtained in humans are too scant to conclude that strict reciprocity exists regarding adipocyte and osteoblast differentiation. Nevertheless, vertebral bone loss has been reported in diabetic patients taking the PPARγ activator thiazolidinedione [17].

The AP1 transcription factor complex includes compounds that are critically involved in osteoblast differentiation [18]. Thus, overexpression of DeltaFosB, a member of the AP1 family, in mice, strongly inhibits adipogenesis and increases bone mass continuously until, by 15 weeks of age, the metaphyses contain virtually no visible marrow [19]. Nevertheless, the decrease in adipogenesis and increase in osteogenesis are related to two independent mechanisms [20].

4.2. Systemic/hormonal factors

Studies have investigated whether hormones known to induce bone formation also affect adipogenesis. Estrogens added