Does Osteoblast to Adipocyte Differentiation Play a Role in Osteoarthritis?

Heide Siggelkow*

Department of Gastroenterology and Endocrinology, University of Göttingen, Robert-Koch-Str. 40, D-37075 Göttingen, Germany

ENDOKRINOLOGIKUM Göttingen, Von-Siebold-Str. 3, D-37075 Göttingen, Germany

Abstract: The plasticity of mesenchymal stem cells (MSC) is of major interest for diagnosis and therapy of bone diseases. Interactions between osteoblasts and adipocytes seems are involved in the pathogenesis of osteoporosis. This review is intended to elucidate a link between osteoarthritis and the differentiation of MSCs towards the adipocytic or osteoblastic lineage. Viewing osteoarthritis as a systemic disease, recent data underline the importance of the nuclear receptor peroxisome proliferator activated receptor gamma (PPARγ) in its pathogenesis. In contrast to the increase in fat mass in osteoporosis, in OA, there is evidence of a decrease in PPARγ signaling with increasing severity of OA. Therefore, not the differentiation of osteoblasts to adipocytes, but the development from adipocytes to osteoblast might be a mechanism relevant to the pathogenesis of osteoarthritis.

Keywords: Osteoarthritis, adipogenesis, osteogenesis, transdifferentiation, thiazolidindione, PPARγ.

MESENCHYMAL STEM CELLS

The plasticity of differentiation from mesenchymal stem cells or multi-potent stromal cells (MSCs) is a hot topic in stem cell research. In responce to specific culture conditons, multiple mesenchyme-derived cell types, such as osteoblast, chondrocytes, adipocytes, and myoblasts [1-5] can originate from these cells. A large number of reports have indicated that there is not only the differentiation to either lineage, but also a specific amount of dedifferentiation and even transdifferentiation potential into the other lineages even until late in the development of a specific phenotype [6-9]. In addition, MSCs possess the capacity to cross-lineage differentiation into epithelial cells and lineages derived from the neuroectoderm [10]. Although molecular mechanisms or genetic reprogramming are suggested to cause the remarkable plasticity of MSCs, new findings propose that the ability of MSCs to alter the tissue microenvironment *via* secretion of soluble factors may contribute to tissue repair more significantly than their capacity for transdifferentiation [10].

The development of a specific phenotype is thought to be under transcriptional control. MSCs give rise to myocytes, under the control of MRFs and MEF2 [11], to adipocytes under the control of C/EBP, and and PPAR [12-18] and to chondrocytes under the control of Sox5, -6 and -9 [19] and STAT1 [20]. Runx2 is essential for osteoblast differentiation and is also involved in chondrocyte maturation. Osterix (Osx) acts downstream from Runx2 to induce mature osteoblasts that express osteoblast markers, including osteocalcin [21].

*Address correspondence to this author at the Department of Gastroenterology and Endocrinology, University of Göttingen, Robert-Koch-Str. 40, D-37075 Göttingen, Germany; Tel: 0551-396301; Fax: 0551-392063; E-mail: hsiggel@med.uni-goettingen.de and ENDOKRINOLOGIKUM Göttingen, Von-Siebold-Str. 3, D-37075 Göttingen, Germany;
E-mail: heide.siggelkow@endokrinologikum.com

ADIPOGENESIS AND OSTEOBLASTOGENESIS

The regulation and interaction in the development of osteoblasts and adipocytes is of major interest in the pathogenesis of osteoporosis to date. Various clinical studies show that the decrease in bone volume associated with osteoporosis and age-related osteopenia is accompanied by an increase in bone marrow adipose tissue [22-25]. A number of *in vitro* studies support the hypothesis that a high degree of plasticity exists between adipocytic and osteoblastic pathways [6, 22, 23, 25, 26], based on the lineage-specific marker expression. For example, it has been shown that osteocalcin (Oc) positive-osteoblasts were capable of dedifferentiation and transdifferentiation into cells of another developmental lineage at the single cell level [6, 7]. Activation of adipogenesis in mice by rosiglitazone led to a decrease in osteoblast number and an increase in marrow fat cells supporting the close interaction between both differention pathways [27].

PATHOGENESIS OF OSTEOARTHRITIS-SYSTEMIC OR LOCAL DISEASE

The MSCs responsible for osteoporosis related transdifferentiation of osteoblasts and adipocytes is thought to take place physically mainly in the bone marrow, a space near the bone metabolic unit where osteoblasts produce matrix and differentiate into osteocytes. However, MSCs are present in many adult tissues including bone marrow and trabecular bone as well as adipose and muscle. But how should adipocytes and osteoblasts play a role in osteoarthritis (OA), a disease physically happening in the joint?

OA has traditionally been regarded as a disease of the articular cartilage, with cartilage degeneration and finally erosion as its main, identifying features. Meanwhile, changes in the structure and content of articular cartilage, subchondral bone, synovial membrane, joint ligaments, and tendons have been described [28]. The classical hypothesis regards excess synthesis and release of catabolic factors including proinflammatory cytokines, matrix metalloproteinases (MMPs),

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and nitric oxide, as well as a reduced synthesis of anabolic factors such as insulin-like growth factor 1 (IGF-1) as causative for cartilage damage [29, 30]. However, OA can also be regarded as a systemic disease involving stromal cell differentiation and lipid metabolism [31]. Supporting this hypothesis, generalized changes including muscle weakness [32], weakening of the anterior cruciate ligament [33], and also increasing adiposity [34] have been observed in in-vivo models of OA and in patients. Therefore, OA is considered a complex joint disease involving all joint tissues in disease initiation and progression. Studies supporting this hypothesis include data on increased subchondral bone activity in OA patients with higher uptake in scintigraphic technetium labeled disphosponate preceding detectable cartilage loss [35]. It has been suggested that the progression of articular cartilage degeneration is concomitant with intense remodeling of the subchondral bone and increased bone stiffness, leading to abnormal mechanical stress across the overlying cartilage [36, 37]. In comparison to osteoporosis patients, patients with OA tend to have a higher body mass index together with an elevated rate of bone turnover, resulting in increased bone density [38]. This data is supported by data in animal models showing increased bone density and osteoid volume often more severe than cartilage changes [39, 40], whereas in models with locally induced joint disease, changes in bone and cartilage occur concomitantly [41].

POSSIBLE MECHANISM OF SYSTEMIC DISEASE

Models of locally induced osteoarthritis cannot reflect features of OA as systemic disease. Recently, a systemic model of osteoarthritis was used to overcome this disadvantage. The STR/ort mice spontaneously developed histological lesions resembling those of human osteoarthritis, approx. 85% of male STR/ort mice developing the disease in the medial tibia plateau at age 1 year [42]. The authors used genome wide expression profiling and functional analysis; development and function of connective tissue and lipid metabolism were shown to be the ones most significantly up-regulated and down-regulated, respectively, during OA progression [43]. Based on their results, the authors suggest that peroxisome proliferator activated receptor gamma (PPARγ) signaling is down-regulated during progression of OA and that a shift away from adipocyte formation and towards osteoblast differentiation in MSCs is an important component in this spontaneous OA model. Studies confirming this data definitely show the central role of PPARγ in OA.

PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR GAMMA

PPARγ is a nuclear transcription factor, which was originally identified as the key regulator of adipocyte differentiation. It is also expressed in skeletal muscle, liver, heart, and intestine [44]. PPARγ has also been identified in cells within the vascular and immune systems [45-47]. Besides the extensive data on its function for adipogenesis, PPARγ has been reported to limit inflammation; the PPARγ ligands inhibit macrophage activation as well as the production of inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6 [48, 49]. Similar effects have been reported in T lymphocytes; there is also evidence that PPARγ limits the production of proximal cytokines such as IFN-gamma and interleukin-1 (IL-1) [50, 51]. In addition, the PPARγ agonist can inhibit the production of MMP-13 in human chondrocytes and MMP-1 in human synovial fibroblasts [52, 53]. PPARγagonists have proved to be vasoprotective and have reduced atherosclerosis in mouse models, an effect possibly related to the anti-inflammatory capacities of PPARγ[54].

PPARγ AND OSTEOARTHRITIS

It can be proposed that, PPARγ agonists might exert their therapeutic effects on surgically induced or collagen-induced arthritis through the suppression of these inflammatory mediators [52, 53]. The PPARγ agonist rosiglitazone has recently been shown to exert a positive effect on surgically induced OA in guinea pigs [55]. Thus, the decrease of PPARγ in OA would therefore reflect the decrease in anti-inflammatory activity. This is one possible hypothesis for the link between PPARγ and OA.

A second hypothesis concerns the development of osteoblasts, chondrocytes and adipocytes from MSCs. In the regulation between adipogenesis and osteogenesis, a dominant role is also attributed to the adipogenic transcription factor PPARγ2 [12-18]. There is evidence that activation of PPARγ2 by the antidiabetic drug rosiglitazone stimulates adipogenesis and inhibits osteoblastogenesis in different mesenchymal progenitor models *in vitro* and *in vivo* [56]. Therefore, it is suggested that an early event in the initiation and progession of OA is a preferential shift toward osteoblastogeneis resulting from the downregulation of PPARγ signaling [43]. This would be in accordance with the increase in subchondral bone formation and sclerosis associated with OA disease progression in human and animal models of OA.

ADIPOGENESIS AND OSTEOBLASTOGENESIS IN OA

Interestingly, the interaction of osteoblastogenesis and adipogenesis in OA therefore provides a contrast to the pathogenetic model for age-induced osteoporosis. Recent evidence suggests that the effect of PPARγ is age dependent with increased expression of PPARγ in bone marrow MSCs as age increases [27]. PPARγ activation led to changes in marrow structures and function such as a decrease in osteoblast number, an increase in marrow fat cells, an increase in osteoclast number, and a loss of the multipotential character of marrow mesenchymal stem cells [27]. If upregulation of PPARγ, e.g. by thiazolidindionen, could abrogate OA progression by inhibiting early bone formation, it might induce osteoporosis on the other hand. Presently, it is not known if patients with diabetes mellitus show less OA, but there is evidence for a higher rate of fracture when treated with thiazolidindionen [57-60]. Modulating the activity of the nuclear receptor PPARγ in a tissue and target specific manner might result in different, more selective PPARγagonists [61].

To conclude, the differentiation of osteoblasts to adipocytes does not appear to be the relevant mechanism - this is, rather, the development from adipocytes to osteoblasts that seems to be involved in the pathogenesis of OA. If and how major bone diseases like OA and osteoporosis are linked opens up a fascinating new area of research! Focussing on

the interaction between [36] osteoblast and adipocyte could provide important leads to further discovery.

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