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Migration of local progenitor cells as therapeutic target in knee osteoarthritis

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Abstract:

The identification of mesenchymal progenitor cells in bone marrow and various joint related tissues like cartilage or synovial tissue renders the cell-biologic systems on which the pathogenetic concepts of osteoarthritis have been developed more complicated by introducing a novel cellular player. The progenitor cells could have different implications in the osteoarthritic process but their precise role is not known so far. For bone marrow derived mesenchymal stromal cells (MSC) the capacity to migrate in response to various chemoattractive factors and to differentiate into the chondrogenic phenotype has been shown. Their potential role in tissue repair may further include the secretion of trophic factors and a certain immunomodulatory function. Migration activity of cartilage-derived cells has also been shown by different approaches. The emerging concept of motile chondroprogenitor cells present within synovial joints might lead to novel therapeutic strategies. Therefore, local mesenchymal progenitor cells may become a future therapeutic target in patients with early stage degenerative joint disease.

Key words: Osteoarthritis, mesenchymal progenitor cell, mesenchymal stroma cell, chemotaxis, cell migration

Introduction

Osteoarthritis as the major degenerative disease of articular cartilage is characterized by a progressive loss of functional cartilage tissue associated with a limited inflammatory reaction and changes in peri-articular and subchondral bone tissue. Its pathogenesis involves multiple factors and the research has mainly been focused on chondrocytes as cellular mediators of the disease [1,2]. The chondrocytes are responsible for keeping the balance between anabolism and catabolism of the extracellular matrix and become metabolically activated during the early stages of the disease trying to compensate for an increase in matrix degradation. In late stage osteoarthritis they show focal proliferation and phenotypic alterations implicating both

"de-differentiation" to a more immature phenotype as well as "terminal differentiation" characterized by the expression of collagen type X and osteogenic markers [3].

Articular cartilage is characterized by low intrinsic repair capacity. One major reason is an insufficient recruitment of cells with chondrogenic potential based on the low cell content of cartilage, its special extracellular matrix keeping embedded chondrocytes in a stationary and non-proliferative stage and its avascular nature preventing access to multipotent progenitor cells and creation of a provisional matrix (e.g. blood clot) via the vascular system.

Tissue derived multipotent cells within synovial joints

During the last decade bone marrow derived mesenchymal stromal cells (MSC) have gained increasing interest because of their multipotency for differentiation into various phenotypes including cartilage. Multipotent cells with chondrogenic differentiation potential have also been identified in several joint related tissues such as synovial tissue [4-6], synovial fluid [7], articular cartilage [8-11], infrapatellar fat [12], trabecular bone [13] and periosteal tissue [14]. Interestingly, in some pathological situations like osteoarthritis or joint trauma with hemarthrosis increased amounts of these tissue-derived progenitor cells seem to be present in joint-related tissues or synovial fluid [8,15]. Nevertheless, they represent minor subpopulations of the respective tissues and they are less characterized than bone marrow-derived MSC so far. For cell-biologic characterization usually the multipotency for differentiation into the osteogenic, adipogenic and chondrogenic phenotype, the presence of characteristic sets of cell surface markers (e.g. STRO-1, CD9, CD44, CD54, CD73, CD166) as well as the absence of hematopoietic markers (e.g. CD14, CD34, CD45) are used [16,17]. In chondrocyte cultures the relative number of cells expressing some of these markers increases during extended cultivation [11] and it is not finally clarified whether this process is caused by so-called chondrocyte "de-differentiation" or preferential amplification of progenitor cells [18,19]. Nevertheless, the expression level of some of these markers has been postulated to characterize cartilage-derived cells with increased chondrogenic potential [20]. The chondrogenic differentiation potential of synovium-derived MSC-like cells was reported to be higher than that of bone marrow derived MSC in vitro [21]. However, differentiated cells from the synovial membrane failed to form stable cartilage after ectopic implantation in vivo [22], which may be explained by missing influences of the local environment of a synovial joint.

Although the existence of a small subpopulation of progenitor cells within joint-related tissues is well established, their potential role in osteoarthritis is not known so far. Their increased frequency in late stage disease may indicate a proliferative response preserving the progenitor phenotype or recruitment from surrounding tissues or the vascular system (e.g. pericytes). On the other hand "de-differentiation" of originally fully differentiated chondrocytes to a multipotent progenitor cell phenotype cannot be excluded so far. Based on morphological parameters and the capacity to synthesize different matrix proteins three subpopulations of cells have been described in late stage of osteoarthritic cartilage: preserved chondrocytes continually undergoing degeneration, degenerated cells which are subsequently degraded and fibroblastoid cells which increase in number and do not seem to be primarily influenced by the disease process [23]. The origin and phenotype of these cells is not clear so far and further studies are needed to clarify whether these cells which do not primarily synthesize collagen type II but high levels of decorin and biglycan could contribute to repair processes within cartilage.

Migration of mesenchymal progenitor cells

The principle possibility of local recruitment of cells with chondrogenic potential into non-osteoarthritic full and partial thickness defects of cartilage is indicated by several previous in vitro and in vivo studies. In rabbits intra-articular infusion of bFGF for one day was able to stimulate cartilage repair in full thickness defects [24]. Other studies using the implantation of chondrogenic matrices that contained TGF-ß1 indicated that in full thickness defects vascular invasion from the bone marrow finally leads to an osteogenic tissue covered by a more or less fibrous layer [25]. Therefore, strategies using structural and functional barriers have been tested leading to an improvement of the resulting cartilage repair tissue [25,26]. In human patients with cartilage defects bone marrow cells saturating a collagen type I/III membrane after microdrilling therapy were shown to proliferate and to be multipotent for differentiation into the osteogenic, adipogenic and chondrogenic lineage in vitro [27]. Recruitment and subsequent chondrogenic differentiation of mesenchymal repair cells into a partial thickness defect was reported for a minipig model. In these studies the defect was filled with a fibrin matrix containing free and liposome-encapsulated TGF-ß1 and the recruitment of repair cells seemed to occur from the synovial membrane [28,29]. Besides bone marrow and synovial tissue cells with chondrogenic capacity might also be recruited from the adjacent cartilage. Current data supporting the hypothesis that cells derived from articular cartilage (chondrocytes or progenitor cells) might possess the possibility to move have been reviewed recently [30].

In vitro, it has been shown that enzymatic treatment increases cell density at wound edges of bovine cartilage [31] and that cells expressing α-smooth muscle actin can grow out from human osteoarthritic cartilage after collagenase treatment [32]. The outgrowth of cells with chondrogenic potential has been observed in bovine cartilage – most efficiently from the deeper regions in immature animals [33]. In addition, in vitro outgrowth of repair cells from minced cartilage into resorbable polymer scaffolds and subsequent formation of a cartilage like tissue after ectopic implantation in SCID mice and transplantation into articular cartilage defects in goats was described [34]. All these studies were performed with models of cartilage defects in non-osteoarthritis joints. Therefore, the situation may be different in a local environment of degenerative joint disease. This notion is supported by Frenkel et al. [35], who found that proinflammatory cytokines and NO inhibited bovine chondrocyte migration in a three-dimensional matrix. It has been suggested that the local formation of chondrocyte clusters may partly reflect cell migration processes and that many chondrocytes within the tissue displayed elements of motile cells, including numerous filopodia and cytoskeletal rearrangements [36]. In the respective zones elevated expression of pleiotrophin has been described [37] and this heparin-binding matrix proteoglycan has recently been found to stimulate not only proliferation but also migration of chondrocytes in vitro [38]. The respective phenotype of these migrating cells - either progenitor or fully differentiated - deserves further studies. The observation that in neonatal cartilage motile chondrocytes synthesized collagen type II indicates that chondrogenic differentiation does not primarily exclude cell motility [39].

The cell-biologic processes underlying mesenchymal stem cell recruitment to damaged tissues are just beginning to be elucidated. Since the current knowledge concerning the mesenchymal stem cell niche is highly limited, processes involved in the mobilization from this environment are largely unknown so far. As shown in Table 1, for isolated bone marrow derived MSC various growth factors and chemokines have been identified that stimulate directed migration in vitro [40-47]. More recently, an important role of cell surface receptors for matrix proteins e.g. CD44 and the integrin-ß1 subunit as well as for several matrix proteins like fibronectin, vitronectin and collagen type I has been described [48-51].

Migration within 3-dimensional matrices crucially depends on a well coordinated regulation of adhesion and de-adhesion. In this context e.g. MMP-2, MT1-MMP and TIMP-2 have been implicated in migration of bone marrow derived MSC [52]. For tissue derived mesenchymal progenitor cells, however, it is not known whether the implicated mechanisms are the same. Respective studies on the migratory capacity of cartilage tissue-, synovial tissue- and synovial fluid- derived progenitor cells from osteoarthritic patients have not been published so far. Moreover, the influence of environmental conditions within articular joints deserves further investigation since a chemoattractive effect of synovial fluid on bone marrow derived MSC has recently been shown [53].

There is increasing evidence that within synovial joints local recruitment of cells with chondrogenic potential from different tissue sources might be possible and may occur to a certain extent in osteoarthritis. This leads to the question why these progenitor cells within osteoarthritic joints do not contribute more efficiently to repair processes. That may be a matter of quantity or of inhibitory environmental mechanisms including the presence of pro-inflammatory cytokines or NO [35]. Even a systemic depletion or functional alteration of mesenchymal progenitor cells has been discussed to be implicated in the pathogenesis of osteoarthritis [54]. This was based on the observation of reduced chondrogenic and adipogenic activity of bone marrow-derived mesenchymal stem cells in patients with advanced osteoarthritis [55]. In contrast, the chondrogenic potential of bone marrow-derived mesenchymal stem cells was recently described to be independent of age and osteoarthritis etiology [56]. Overall, the functional role of mesenchymal progenitor cells in synovial joints and their surrounding tissues and their possible implication in the pathogenesis of osteoarthritis clearly deserves further investigation.

The underlying molecular mechanisms supporting local recruitment and differentiation of distinct subpopulations of chondroprogenitor cells, which are largely unknown so far, may bear the key for novel therapeutic approaches. Based on the current knowledge, mesenchymal progenitor cells might not only provide a cell source for synthesis of cartilage matrix proteins - but could also represent a source of trophic factors [57]. Such a “supportive” function still has to be shown for mesenchymal progenitor cells derived from joint tissues. Recently, an immunomodulatory function of bone-marrow-derived MSC has been described based on an antiproliferative effect on T and B lymphocytes, dendritic cells and natural killer cells [58]. Therefore, cell-therapy with allogenic MSC is currently studied for a number of autoimmune-driven diseases and graft versus host disease. In animal models of collagen type II induced rheumatoid arthritis MSC reduced responses of T-cells and prevented tissue damage [59,60]. So far it is not known whether mesenchymal progenitor cells residing in cartilage or synovial tissue also have immunomodulatory properties. For the entire stromal cell population derived from synovial tissue and articular cartilage, however, a similar immunosuppressive effect has been described recently [61]. Currently, there are no data available with respect to the consequences of local application of bone marrow derived MSC on the chronic inflammatory process in OA.

Conclusions and perspectives

The presence of MSC-like cells in joint-related tissues raises further questions. It renders the biologic systems on which the major pathogenetic concepts of osteoarthritis have been developed more complicated by introducing a novel cellular player, which could have different implications within the disease process. On the other hand such a concept might lead to novel therapeutic approaches. Therefore, mesenchymal progenitor cells of synovial joints may become a future therapeutic target in patients with early stage degenerative joint disease.

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Table 1:

Chemoattractive factors for bone marrow derived MSC:

Factor	Assay	References
PDGF-AA, PDGF-AB, PDGF-BB	Boyden chamber assay	[42] [40]
IGF-I/II IGFBP5	Boyden chamber assay	[44]
BMP-2 BMP-4	Boyden chamber assay	[40]
VEGF-A PlGF	Boyden chamber assay	[43]
CCN1/CYR61 CCN6/WISP3	Boyden chamber assay	[62]
bFGF	Boyden chamber, Scratch assay	[46]
CXCL8/IL-8	Boyden chamber assay	[45]
CXCL12/SDF-1	Matrigel Chemoinvasion Assay	[47]
HGF	Boyden chamber assay Scratch assay Matrigel Chemoinvasion Assay	[63] [47]
Wnt3a	Migration through ECM coated filter	[64]