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Chondrogenic Progenitors for Cartilage Repair and Osteoarthritis Treatment

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The challenge of injury to the articular cartilage of the joints is the inability of the tissue to effectively self-regenerate. Accordingly, most clinical cartilage repair strategies have focused on use of exogenous cells and/or materials to fill in localized acute defects. Problems still to be overcome using these approaches include attaining seamless integration of repair and host tissue, as well as faithful reproduction of true hyaline cartilage, without which permanent and durable repair is not achieved. A critical consideration in cartilage repair is the nature of the cells expected to do the job. Alternatives to the clinical paradigm of exogenous adult chondrocytes as repair cells need to be developed in order to achieve fully functional articular cartilage repair. Moreover, strategies must be devised to treat the widespread and chronic damage found in osteoarthritis, in which surgical intervention to achieve focal repair is not feasible.

Accumulating evidence demonstrates the existence of stem-like cells, possessing chondrogenic potential, residing within or adjacent to the articular cartilage. For example, a localized population of highly proliferative cells expressing progenitor markers is present in the perichondrium at the border of the growth plate and has been suggested to represent a stem cell- like niche for articular cartilage renewal [1]. Several studies have identified the superficial and/or middle layers of the articular cartilage as regions enriched in a mesenchymal stem cell- like population consisting of proliferating cells which express mesenchymal progenitor markers [2-5]. FACS sorting has been used to isolate mesenchymal progenitor cells from normal and/or osteoarthritic articular cartilage [4,6,7] and in *in vitro* differentiation assays have demonstrated chondrogenic, adipogenic and osteogenic potential by isolated progenitors [3,4,6,7]. Superficial zone progenitors may have an inherent and desirable bias towards differentiation into permanent articular cartilage, as isolated superficial zone progenitors underwent chondrogenic differentiation *in vitro* without concomitant expression of collagen type X, a marker of growth plate cartilage and hypertrophic maturation diagnostic of osteoarthritic disease [3]. Progenitor cells expressing mesenchymal stem cell markers have also been identified deep in the articular cartilage, as highly migratory cells associated with capillary invasion into the calcified zone past the tidemark [8], a characteristic of severe osteoarthritis. These cells were not observed in normal cartilage [8]. The migratory progenitor cells were found to possess enhanced *in vitro* chondrogenic potential relative to osteogenic or adipogenic lineages [8]. Mesenchymal progenitor cells have also been isolated from non-cartilage tissue in the joint including the synovium and fatpad [9], with the synovium-derived cells having greater chondrogenic differentiation potential than the adipose-derived cells [9].

The existence of multiple endogenous chondrogenic progenitor cell populations in the joint and articular cartilage is exciting in terms of offering potential endogenous cell sources for cartilage repair. However, it is apparent that none of these endogenous progenitor populations are sufficient by themselves in halting osteoarthritic progression. The relative content and distribution of superficial and middle zone progenitors has been found to be similar in normal and osteoarthritic cartilage [4], although the profile of progenitor markers expressed by the cells differed [10]. This suggests that the presence of disease may alter endogenous progenitor populations and compromise their ability to accomplish self-repair. Consistent with this possibility, mesenchymal progenitors isolated from osteoarthritic cartilage underwent spontaneous osteogenic differentiation *in vitro* which was not observed in normal adult cartilage [11]. It is also possible that endogenous progenitors, and particularly the highly migratory cells associated with vascular invasion in osteoarthritis, may be part of a response to cartilage damage aimed to provide a temporary rather than permanent repair. For instance, surgical procedures such as micro fracture, which allow progenitors from the subchondral bone marrow to enter the articular cartilage, result in formation of fibro cartilage rather than hyaline cartilage [12]. The chondrogenic potential of bone marrow mesenchymal stem cells is further compromised by donor age [13]. Alterations in the local environment of the joint may also reduce the chondrogenic potential of endogenous progenitors. High levels of inflammatory cytokines are present in osteoarthritic or acutely injured joints, and treatment of mesenchymal progenitors with diseased synovial fluid reduces their *in vitro* chondrogenic differentiation potential [14,15].

Novel approaches for articular cartilage repair may lie in strategies to enhance the effectiveness of resident chondrogenic progenitors by promoting progenitor recruitment, expansion or chondrogenic differentiation. Endogenous progenitors may be recruited to regions of damage via signals which induce cell homing. Remarkably, TGFβ-3 released by a bioscaffold is sufficient, in the absence of exogenous cells, to induce cartilaginous resurfacing of the joint *in vivo* [16], and also induces recruitment of adipose-, synovium- and mesenchymal-derived progenitors into scaffolds *in vitro* while promoting cartilage characteristic gene expression [17]. Exogenous factors may be introduced into the joint with the goal of promoting chondrogenic differentiation by endogenous progenitor cells in the superficial zones. Intra-articular injection of BMP [18] or hyaluronan (reviewed in [19]) may be particularly promising in this regard as both agents possess well-established pro-chondrogenic activities, and both also promote formation of hyaline cartilage, instead of fibrocartilage, by progenitor cells from bone marrow in joints subjected to microfracture [20-22].

Modification of the extracellular matrix and increased chondrocyte proliferation are characteristics of osteoarthritis typically considered to be part of the disease pathology. Paradoxically, stimulation of

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these processes may be useful in promoting targeted migration of progenitors to damaged sites [23], or may promote expansion or prime subsequent chondrogenic differentiation by resident progenitor pools [5]. For example, transient treatment of mixed host/donor cartilage explants with the pro-inflammatory cytokine IL1-β caused matrix remodeling via induction of matrix catabolic activity, but ultimately enhanced integration between the two tissues [24]. Moreover, surprisingly, blocking matrix metallo protease activity has been found to suppress chondrogenic differentiation of mesenchymal stem cells *in vitro* [25]. Further, transient stimulation of β-catenin signaling, a signal typically associated with osteoarthritic progression [26], instead caused thickening of the articular cartilage *in vivo* [27] and increased proliferation of isolated superficial zone progenitors *in vitro* while promoting subsequent differentiation of the cells towards permanent articular cartilage *in vivo* [5].

Strategies to augment the response of endogenous progenitor populations to cartilage injury may involve not only exogenous factors, but also exogenous progenitor cells. In particular the potential use of mesenchymal stem cells for treatment of articular cartilage damage has been intensely investigated (reviewed in [28-30]). Outcomes from studies in which progenitor cells including mesenchymal stem cells were implanted or injected into damaged joints in animal models [31-36] or humans [37,38] have been encouraging, however, the mechanisms by which the exogenous progenitor cells restore cartilage integrity and/or function are poorly understood. Intriguingly, a recent study examining articular cartilage repair by human embryonic stem cell-derived chondrocytes, which were implanted into full thickness focal defects in rat articular cartilage *in vivo* and monitored using a human-specific antibody, revealed gradual replacement of the human cells with rat cells during repair of the defect region [39]. This suggests the exogenous chondrocytes provide paracrine signals which can enable the endogenous host tissue accomplish cartilage repair. Signals from the host tissue may in turn influence differentiation by exogenous progenitors introduced into the damaged cartilage or joint. The injured or osteoarthritic joint is classically considered hostile due to the presence of inflammatory cytokines in the joint fluid. However, the local microenvironment adjacent to the damaged cartilage may provide access to chondrocyte-produced pro-chondrogenic factors that may positively influence chondrogenic potential of engrafted exogenous cells. Indeed, while intra-articular injection of human embryonic stem cells leads to teratomas which ultimately destroy the joint, when introduced as implants directly into a focal defect the cells instead form cartilage [40]. Mutually beneficial interactions between progenitors and chondrocytes have also been shown. For instance, chondrogenesis in co-cultures of mesenchymal stem cells and articular chondrocytes is mediated by progenitor-stimulated chondrocyte proliferation, in conjunction with chondrocyte-stimulated progenitor cell differentiation into the chondrocyte lineage [41]. In addition, participation of mesenchymal progenitors in repair of articular cartilage was accompanied by strong induction of collagen type II staining around both host and transplanted cells [36]. Thus, exogenous progenitor cells may function in promoting cartilage repair through interaction with endogenous chondrocytes or chondrogenic progenitors, in addition to themselves serving as a supplemental source of cells for reconstruction of damaged cartilage.

In order to exploit the potential of exogenous signals and cells in cartilage repair strategies, means for efficient delivery and retention of the factors or cells at the region of damage will need to be devised. This may be achieved for localized defects via direct surgical implantation of bioscaffolds, with or without incorporated factors or cells. Alternate approaches such as direct injection into the joint will be required for treatment of non-focal osteoarthritic lesions [42]. A non-invasive approach would be preferable for the patient and convenient for the health care provider even for local damage due to acute injury. Clinical trials are underway to evaluate the safety and efficacy for osteoarthritis treatment of direct intra-articular injection of recombinant BMP [43], or of genetically-modified chondrocytes expressing TGF-β1 [44]. Encapsulation of growth factors or genetically-transduced cells releasing such factors, in biomaterial microspheres is also being investigated as a way to achieve sustained delivery into the joint [45-47]. Several studies in which mesenchymal progenitor cells were labeled and tracked following direct intra-articular injection in damaged or osteoarthritic joints have demonstrated presence of labeled cells within the tissues of the joint including the surface and interior regions of the articular cartilage [32,33,48,49]. In one study injected mesenchymal stem cells were found to repopulate fibro cartilage and synovium but not articular cartilage [31]. However, the cells were found to attach and populate deep fissures of human osteoarthritic cartilage explants, and subsequently formed a regenerated cartilage surface *in vitro* [50]. Thus physical as well as molecular cues may promote graft-host tissue integration. Incorporation of exogenous progenitors into the articular cartilage may be enhanced by increasing the number of injected cells [51], or by co-injecting them with hyaluronan [36]. One novel approach for targeting injected cells to damaged articular cartilage utilized iron-labeled synovial-derived progenitors which were injected into the joint and homed to the damaged region via implantation of an intra-articular magnet [52].

This issue of Rheumatology: Current Research is focused on chondrogenic progenitor responses to cartilage injury. These encouraging studies suggest the field can expect exciting progress in utilization of exogenous signals or progenitor cells for cartilage repair, as well as development of strategies to enhance repair by endogenous chondrogenic progenitors already present in articular cartilage. Importantly, these approaches may offer new promise for treatment of cartilage injury and osteoarthritis.

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