

Stem Cell Therapy for Bone and Cartilage Defects – Can Culture-expansion be Avoided?

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Skeletal tissues including bone and cartilage experience significant mechanical stresses following normal physical activity. In bone, resultant microcracks are continuously repaired as a result of coordinated activity of osteoblasts, their progenitors – multipotential stromal/stem cells (MSCs) and osteo clasts, the bone-resorbing cells [1]. Physiological cartilage repair mechanisms are less well understood, but could be potentially mediated by MSCs present in cartilage superficial layer [2,3], synovium [4,5] or synovial fluid [6,7].

Significant damages to bone and cartilage can occur as a result of acute injury (trauma) or due to chronic disease (such as osteoarthritis). In acute settings, the last two decades have witnessed a significant advance in tissue engineering approaches to repair bone in cartilage, with the use of scaffolds seeded with large numbers of culture-amplified MSCs. However, more recent research has indicated that loading scaffolds with culture-expanded stem cells may not be absolutely required, and depends on the nature and size of the defect [8,9]. This Editorial will highlight recent advances in bone and cartilage repair strategies based on enhancing the recruitment of endogenous MSCs into the defect areas.

Bone Repair

Fracture is a typical example of acute injury to bone that normally repairs itself. Non-union (failure to repair) commonly occurs when bone loss is too large (a critical-size defect) or when a patient presents with co-morbidities, such as diabetes, smoking, or high blood pressure [10]. The repair of critical-size defects requires the provision of mechanical stability and the presence of sufficient numbers of MSCs and vascular progenitors at the repair site [11].

The first successful tissue-engineering constructs to repair critical size defects in humans were based on culture-expanded bone marrow MSCs seeded on macroporous hydroxyapatite scaffolds [12]. Although they were implanted over a decade ago, the uptake of this technology in general clinical practice remains low; this is most likely due to the requirement of two surgeries (for MSC harvesting and implantation), difficulties in regulating the safety of such complex cellular products and the associated high costs of therapy. Instead, a so called Ilizarov distraction/bone transfer technique remains one of the most common methods for large defect reconstruction [13]. In basic terms, it relies on stabilizing the biomechanics and reducing the distance between the bone ends, followed by a very slow and controlled ‘stretching’ thus allowing a newly-formed callus tissue to be gradually vascularized and remodeled. It is believed that in this technique, the repair cells (MSCs) originate from the neighboring tissues such as periosteum [14]. As an alternative, pieces of autograft bone, containing patient’s own MSCs and a bone scaffold, are placed inside the defect area; the remaining bone void is filled with a so called ‘graft expander’, normally a synthetic scaffold, and mechanically stabilized. Graft material can be additionally loaded with concentrated BM aspirate from the same patient in order to provide additional MSCs [8,15,16].

The success of these empirical surgical approaches suggests that even for very large bone defects culture-expanding MSCs to increase their numbers million-fold may not be necessary. Instead, the provision of correct biomechanical environment seems to be the key, coupled with a scaffold that permits colonization by neighboring tissue-resident MSCs. Potent chemokine molecules such as stromal cell-derived factor 1 (SDF-1/CXCL12) and monocyte-specific chemokine 3 (MCP-3) may facilitate further recruitment of MSCs and subsequent graft vascularization in vivo [17-19]. Similar strategies based on manipulating resident MSCs for cartilage tissue regeneration are illustrated below.

Cartilage Repair

It is well-recognized that cartilage repair critically depends on the depth of a defect; full-thickness (osteochondral) defects that penetrate into the subchondral bone repair much better than partial-thickness (chondral) defects that commonly fail to repair [20]. This difference can be explained by larger numbers of MSCs present in subchondral bone [21,22] as opposed to their relative paucity in cartilage [2,3] or synovial fluid [6,7]. A surgical procedure called microfracture remains the gold standard for the treatment of isolated cartilage defects [23]; in this technique drilling into the subchondral bone plate creates a blood clot that is believed to have two valuable functions: first, it serves as a source of chemokines bringing subchondral bone MSCs to the repair site and second, it acts as a fibrin-based natural scaffold allowing retention, proliferation and chondrogenic differentiation of migrated MSCs [22].

Although it is generally assumed that MSCs residing in subchondral bone cavities are chiefly responsible for cartilage repair following microfracture, other joint-resident MSCs as synovium MSCs [5], synovial fluid MSCs [24] or superficial cartilage MSCs [2,3] could be also involved, particularly since these MSC types are known to possess high chondrogenic potentials [24,25] and to have a direct access to cartilage. Recently, Sharma et al. [26] detected the presence of synovial fluid in the defect areas three weeks after implantation of empty hydrogel-based scaffolds, combined with microfracture, in fifteen patients with isolated cartilage lesions. MSCs injected into the

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joint space have been found in regenerated cartilage and meniscus [27], proving that these MSC could migrate through the fluid and reach the damaged areas of cartilage. Finally, the penetration of host cells into the defect site, 'assumedly from the surrounding marrow and/or synovial spaces', has been eloquently shown in Quintavalla et al. study [28].

How these endogenous MSCs are recruited into cartilage defects remains unclear. In a case of microfracture, a passive release of MSCs from the subchondral bone or the bone marrow is possible; however it is likely to be followed by their active migration driven by a simultaneous release of potent chemokine molecules into the synovial fluid [29]. Recently, several chemokines present in the synovial fluid, such as CCL25, CXCL10 and XCL1 were implicated in these migration processes [30]. Platelet-derived growth factors (PDGFs), concentrated inside the fibrin clot [31] and shown to be chemotactic for MSCs [32], could be also involved. These PDGFs could influence MSC migration, as well as their subsequent proliferation [33], differentiation and matrix synthesis.

It can be envisaged that in principle, similar MSC migration mechanisms could be re-created with the use of 'smart' scaffolds placed in the defect site. In order to develop these new approaches, a better knowledge of the types of chemokines and their corresponding receptors on the surface of different types of MSCs is needed. For example, implantation of scaffolds loaded with TGFβ3 has led to excellent repair, by endogenous cell homing, in a rabbit model [34]. Migration of human synovial MSCs and their infiltration into similar scaffolds was improved with the creation of a stable gradient of SDF-1/CXCL12 [35]. The most recent work from the same laboratory has highlighted 'the need to test multiple cytokines concurrently due to synergistic or antagonistic effects' [36].

MSCs from different tissues possess different migration potentials towards the same chemokine because they express different patterns of the corresponding chemokine receptors [37-39]. Cultured MSCs lose a full repertoire of their chemokine receptors after extensive passaging [37]. Further work is therefore needed to isolate uncultured MSCs from the joint tissues, such as synovium, and to investigate their chemokine receptor expression and the chemokine responsiveness prior to in vitro culture. This knowledge would help to design novel scaffolds, loaded with specific chemokines, in order to attract endogenous MSCs into the sites of cartilage damage.

Conclusion

Recent evidence suggests that manipulating the migration of endogenous MSCs from tissues surrounding bone or cartilage defects could represent a viable alternative to traditional tissue engineering approaches with scaffolds seeded with culture-expanded MSCs. Further work is needed to better understand the in vivo signaling mechanisms responsible for physiological chemokine releases post-injury [40] as well as to study the cellular interactions between migrated MSCs and other cells resident in damaged tissues [41].

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