On the Potential Use of Genetically Modified Mesenchymal Stem Cells to Treat Articular Cartilage Defects
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Damage to articular cartilage, the tissue that allows for a smooth gliding of the articulating surface of a joint (and to withstand high loads), is an unsolved problem, especially following joint trauma [1]. As adult, hyaline cartilage is aneural, avascular, and without a lymphatic drainage, it does not have access to reparative cells that may be brought locally in response to injury. Defects (partial or full-thickness) of the cartilage thus do not heal on themselves and instead, tend to become persistent and progress inevitably, often towards osteoarthritis [2].

Current options for cartilage repair are diverse (narrow-stitching techniques, transplantation of tissue or cells, replacement surgery), yet none can reliably regenerate the natural functions of the cartilage, including its integrity (type-II and not type-I collagen), the adherence of the repair tissue to the surrounding cartilage, and the ability of withstanding mechanical stress over time.

Considerable efforts have been made to improve the repair processes and in particular, the promise of treating cartilage defects by cell- and gene-based approaches has attracted much attention [3-7]. Indeed, administration of candidate genes, rather than recombinant factors with short half-lives, might be a means to promote sustained repair like for disorders showing a gradual progression. The development of strategies using the implantation of genetically modified mesenchymal stem cells (MSCs) as therapeutic platforms might prove beneficial to enhance cartilage repair during surgical procedures. As a matter of fact, MSCs might be better suited for this purpose than committed cells such as chondrocytes that require more invasive methods of extraction and tend to lose their phenotype upon culture. Also, MSCs have the ability to recapitulate lineage transitions originally involved in mesenchymal tissue formation (cartilage, bone, fat tissue), among which a potential for chondrogenesis [8-10]. MSCs further display critical tropic activities and demonstrate, interestingly, a broad panel of immunomodulatory properties. MSCs can be isolated from the bone marrow, bone, adipose tissue, muscle, synovium, peristium, and perichondrium. It is important to note that genetic modification of such cells might also allow to overcome some of the limitations stillassociated with their use, like the large amount of cells needed for application in vivo, the relatively low percentage of which enter proper chondrogenic pathways to produce a functional, reparative tissue, and the decline of lifespan and potency seen in pathological conditions (in OA patients, for instance) [11,12]. For cartilage repair, a challenge will be also to maintain the cells in a prehypertrophic state that avoids premature terminal differentiation, hypertrophy, and ossification [10,13-15].

Genetic manipulation of MSCs to enhance their potency for chondrogenesis and cartilage repair has been attempted using different gene delivery vectors, including nonviral systems as well as adenoviral, retro-/lentiviral, and recombinant adeno-associated viral (rAAV) vectors, without altering their multilineage potential [16-25]. Beneficial effects upon MSC chondrogenic differentiation in vitro have been reported by transfer of gene sequences coding for growth (TGF-β, Bmps, IGF-I, FGF-2) and transcription factors (SOX5, SOX6, SOX9,ZNF145), or signaling molecules (heedgehogs, PTHrP) [6,26,27].

Most remarkably, several experimental studies have evidenced the feasibility of applying genetically modified MSCs (commonly as cell suspensions, three-dimensional cultures, coagulates, in conjunction with biomaterials, or even as tissue grafts) to successfully improve the repair of cartilage defects in vivo using many of the gene candidates cited above [19,21,28-36]. It remains to be seen now whether this approach will meet decisive success in patients, as no known clinical trial is ongoing for the treatment of articular cartilage defects by administration of gene-modified MSCs.

References

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