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Editorial

Treatment of Osteoarthritis by Gene and Cell Therapy: A Clinical Reality?

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Editorial

Osteoarthritis (OA) is a highly prevalent degenerative disease of the whole joint for which there is no definite cure. OA affects millions of people worldwide, becoming one of the most costly diseases of our societies, showing the urgent need for new, improved therapeutic regimens.

OA is a very complex condition with many risk factors associated with its incidence, including aging, trauma, metabolic and mechanical conditions, genetic background, and epigenetic regulation [1-6]. OA is mainly characterized by a slow, progressive, and irreversible degradation of the articular cartilage, with a loss of its major extracellular matrix (ECM) components (proteoglycans, type-II collagen) and concomitant changes in the subchondral bone, synovium, and other joint tissues (meniscus, tendons, ligaments) [3,7]. Disturbances in the cartilage homeostasis play determining roles in the pathogenesis and progression of OA. Proinflammatory cytokines (IL-1, TNF-α) and adipokines (leptin, adiponectin, resistin) locally produced by the inflamed synovium, infrapatellar fat pad, osteophytes, or by the chondrocytes themselves may all contribute to the pathophysiology of OA [1,8].

The chondrocytes, the unique cartilage-forming cells, have received particular attention for their potential implication in the progression of the disease. In normal adult cartilage, these cells are terminally differentiated, with low proliferative and metabolic activities. In early OA, instead, the chondrocytes undergo pathological changes in these activities and in their gene expression profiles, displaying transient proliferative responses and synthesis of matrix-degrading enzymes and of unnatural ECM molecules (type-X, type-III, and type-VI collagen, type-IIA procollagen, tenascin, decorin) as an attempt at repair, but further ondergoing an arrest in production of the key ECM components, a decline in responsiveness to reparative stimuli, cell senescence, and structural degeneration that can not be compensated by the invasion of regenerative cells from vascular compartment as the adult cartilage is devoid of vascularity.

Diverse pharmacological treatments and surgical interventions are available to manage the progression of OA, yet none can definitely and completely reproduce an original hyaline articular cartilage, with its natural structure and functions (gliding of the articulating surfaces in the joint, protection of the subchondral bone from mechanical stress.). This is particularly problematic for patients that are too young to undergo partial or total joint replacement.

Strategies based on the use of gene and cell therapy may offer powerful, new tools to promote the durable, effective reconstruction of an original cartilage surface in human OA [9,10]. These approaches are particularly adapted for the long term treatment of a slow, progressive disorder like OA compared with the application of recombinant factors that display very short pharmacological half-lives. Active investigation is ongoing to test the potential benefits of combining gene and cell therapy using cells relevant of the disease pathology (differentiated chondrocytes, bone cells, synoviocytes, meniscal fibrochondrocytes, tenocytes, ligament cells; progenitor cells such as from the bone marrow, adipose tissue, synovium, muscle, induced pluripotent stem cells…) and diverse candidate genes displaying metabolic, proliferative, chondroprotective, or chondroregenerative activities (growth and transcription factors, matrix-producing enzymes, signalling molecules, inhibitors of inflammation, antisense approaches) [9,10]. The choice of an adapted gene transfer system is also of the utmost importance for an effective and lasting treatment of OA by allowing for high and prolonged levels of expression of the candidate sequence due to long-term progression of this disorder. Different types of gene vehicles are available to date (classical nonviral, adenoviral, retro-/lentiviral, herpes simplex virus vectors), but those derived from the replication-defective, non-pathogenic human adeno-associated virus (AAV) recently emerged as the best suited constructs due to their low immunogenic and remarkable high efficacy to transduce all cells relevant of the OA pathogenesis for extended periods of time *in vitro*, but most remarkably *in situ* and *in vivo* when the cells are in their natural environment [11-38], especially in experimental models of OA *in vivo* [28,33,34]. Most notably, such cell- and gene-based procedures are currently tested in human clinical trials to examine the tolerability and efficacy of the treatment in patients [39,40], showing the strong value to address the question of OA therapy by molecular technologies in the affected world population.

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