



The Burden of Human Osteoarthritis: Cell- and Gene-Based Therapies on the Horizon?

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Editorial Note

Osteoarthritis (OA) is a degenerative disease of the entire joint that affects millions of people worldwide, becoming one of the most prevalent and costly diseases of our societies. OA is a particularly complex, disabling condition, as many risk factors have been associated with its incidence (aging, trauma, metabolic conditions, and genetic background) [1-3].

OA is mostly characterized by a gradual, irreversible degeneration of the articular cartilage showing a loss of major extracellular matrix (ECM) components (proteoglycans, type-II collagen), with concomitant changes in the subchondral bone and synovium. Disturbances in cartilage homeostasis are believed to 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 [4,5].

The putative implication of articular chondrocytes (the unique and key cells that form the cartilage) during OA progression has received particular attention in recent times. In normal adult cartilage, the chondrocytes are terminally differentiated cells with practically no proliferative and low metabolic activities. Yet, in early OA, these cells undergo important changes in their activities and in expression patterns, showing 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) seen first as an attempt at repair, but further undergoing an arrest in production of the key ECM components, a decline in responsiveness to reparative stimuli, and ultimately cell senescence and structural degeneration that can not be compensated by regenerative cells in absence of vascularity.

Although several pharmacological treatment options and surgical interventions are currently available to manage the progression of OA, regeneration of the articular cartilage remains an unsolved problem, in particular for patients that are too young to undergo partial or total joint replacement. Most challenging, none of the current interventions has been shown to durably and reliably restore the natural cartilage structure and function in OA.

Options based on the use of cell and gene therapy approaches might be explored as new, powerful tools to allow for a durable, functional repopulation and reconstruction of an original cartilage surface in human OA [6-8]. Such strategies may be well suited to treat a slow and irreversible disorder like OA over time instead of systems based on the application of recombinant factors with relatively short pharmacological half-lives. Active research is ongoing to evaluate the therapeutic benefits of such approaches using various relevant cells (chondrocytes, synovial cells, cells of the surrounding tissues of the joint cavity, progenitor cells) and with different candidate genes with metabolic, proliferative, regenerative (chondrogenic) activities (growth

and transcription factors, matrix-producing enzymes, signalling molecules, inhibitors of inflammation, antisense approaches). Also important for the treatment of OA, the development of effective cell and gene treatments will necessitate that the gene vehicle allows for high and sustained levels of expression of the candidate sequence due to the slow and irreversible progression of this disorder. This might be allowed by different vector classes, among which those derived from the replication-defective, non-pathogenic human adeno-associated virus (AAV), as rAAV appear to be much less immunogenic and more efficient than classical nonviral, adenoviral, and retro-/lentiviral vectors [9-13]. Most remarkably, such cell- and gene-based procedures are currently employed in human clinical trials to assess the tolerability and effectiveness of the treatments in cohort of patients [7,14,15], holding great promise to address in a close future the problem of OA in the human population.

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