Gene therapy for orthopaedic diseases; how to deliver?

Laura Creemers

Department of Orthopedics, University Medical Center Utrecht, Utrecht, the Netherlands

Gene therapy is a promising strategy in orthopaedic disease, especially nonintegrating and/or non-viral approaches; In most cases, temporary modulation will be sufficient for treatment, in contrast to oncological or genetic disease. Also widespread diseases such as osteoarthritis and chronic low back pain related to intervertebral disc (IVD) degeneration are in principle amenable to gene therapy. Several molecular targets involved in disease progresssion or symptom generation have been identified, which can be targeted much more specifically by antisense therapy than by –if available- small molecule inhibitors. Moreover, the growing body of evidence for the role of epigenetic modulation in health and disease suggests the possibility to use miRNA delivery to positively modulate cell phenotype in the joint or IVD. Also, plasmid DNA encoding regenerating genes can be delivered to this end.
As cartilage and the IVD are non vascularised tissues, however, systemic delivery of gene expression modulators is in most cases not feasible. Routes to take towards genetic modulation in the joint and IVD will therefore consist either of treating cells to be transplanted, before or during transplantation, or by local delivery to resident cells. Both anatomical structures are accessible for local injection and the associated diseases are in general local in nature. Even then, transport to resident cells of the cartilage and IVD may pose some challenges, given the tight extracellular matrix surrounding these cells. The use of smart delivery tools and gene modulating agents hold promise to overcome this barrier.