Gene Therapy for Articular Cartilage Repair

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Gene therapy offers a promising treatment option for repair of damaged articular cartilage, an unsolved problem in modern orthopaedics. Articular cartilage is a highly specialized tissue composing of chondrocytes and extracellular matrix (ECM). As the gliding surface of joints, healthy articular cartilage allows for smooth and painless joint motion. However, cartilage diseases are most commonly seen due to traumatic injury and degenerative diseases, which cause pain and dysfunction. Due to avascular status, articular cartilage has a very limited capacity for self-repair and regeneration. Current surgical therapeutic procedures for cartilage repair fail to restore a normal articular surface [1-5]. Gene therapy is being developed to generate long-lasting hyaline cartilage by augmenting the reparative activities or preventing the degenerative activities.

Gene therapy is the use of DNA as a pharmaceutical agent to treat disease. The first gene therapy for articular tissues was described to treat human rheumatoid arthritis [6]. Although considerable progress has been made in identifying genes that regulate cartilage differentiation in past 15 years, gene therapy to repair full-thickness cartilage defects is unsatisfactory. Genes used for cartilage repair include growth factor genes, cytokine receptor antagonists and transcription factors. Growth factors improve cartilage repair by stimulating chondrocyte proliferation and improve chondrogenesis [7-12]. Cytokine receptor antagonist IL-1Ra and tumor necrosis factor alpha inhibitor prevent cartilage matrix degradation and reduce inflammation to prevent arthritis [13-17]. Transcription factors are useful in cartilage repair by promoting chondrogenesis or maintaining chondrocyte phenotype [18-20]. Current gene therapy approaches can be achieved by either administering the desired genes into the sites of damaged cartilage, or by transplantation of genetically modified cells into the defects. The selection of gene delivery approaches depends on the need of long-term or short-term expression and the therapeutic expression level of the desired genes.

Multiple gene therapy combined with stem cells and scaffold is desirable and need to be developed for repair of articular cartilage defects. The optimal choice of therapeutic genes for cell-based cartilage repair cannot be simply predicted from observations of individual genes [21]. More efforts need to be made to understand the molecular basis of cartilage differentiation. So far, gene network of cartilage differentiation remains poorly understood, the molecular mechanism and the role of genes during cartilage differentiation are not well defined; the therapeutic genes identified for articular cartilage are very limited. It is still challenging to deliver the therapeutic genes to the damaged cartilage in a safe, efficient manner and express them in a controllable manner. Taking sox9 as an example, the chondrogenic master regulator sox9 is required for MSC commitment and condensation, and chondrocyte differentiation and proliferation. However, Sox9 inhibits transition of proliferating chondrocytes to hypertrophy [19]. Expression level of sox9 is also critical to chondrocyte, low levels of Sox9 overexpression enhanced Col2A1 gene transcription whereas high levels of Sox9 overexpression induced an inhibition of Col2A1 gene expression in chondrocytes [22]. These data suggest that continuous expression of sox9 is not good for hyaline articular cartilage, controllable expression of sox9 will be of particular importance to regeneration of hyaline cartilage. Therefore, efficient delivery and controllable expression of the therapeutic genes, and multiple strategies will lead to complete and durable hyaline cartilage regeneration.

References


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