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Suppression of osteoarthritis via molecular engineering of an aggrecan mimetic

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ABSTRACT

Osteoarthritis (OA) progresses via a feed-forward cycle in which inflammation leads to the up-regulation of catabolic enzymes that cleave the extracellular matrix (ECM) components. Fragments of ECM molecules hyaluronic acid and collagen type II further stimulate inflammation. The degradation of aggrecan is a critical early event in OA due to aggrecan's ability to protect other ECM components from degradation and support the compressive strength of cartilage. Characterized herein is an aggrecan mimic's (mAGC) ability to replace the functions of native aggrecan and halt the progression of OA. We examine mAGC in both ex vivo cartilage tissue models and in vivo animal models. Aggrecan-depleted cartilage plugs had only ~30% of the compressive strength of intact plug. mAGC was able to diffuse into the cartilage tissue and restore the compressive strength to 90% of the intact healthy cartilage. Depletion of aggrecan also resulted in an increase in catabolic gene expression by chondrocytes that was further amplified with additional inflammatory stimuli. Treatment with mAGC resulted in chondrocyte gene expression of catabolic enzymes at the same lower levels as healthy intact cartilage, both with and without inflammatory stimulation over 21 days. Intact cartilage plugs exposed to osteoarthritic synovial fluid resulted in high degradation of ECM components as measured by release into the culture media over an 8-day period. A single pretreatment with mAGC decreased this degradation to levels similar to those in healthy cultured controls. Further, inflammation and catabolic enzymatic gene expression was lowered in treated plugs to near healthy levels, even in the presence of the inflammatory and enzyme-rich synovial fluid. The data indicates that by providing robust protection against degradation and restoring the mechanical environment, the pro-inflammatory signals that cause upregulation of the degrading enzymes are decreased. In an aggressive rat model, mAGC was able to keep catabolic enzyme levels closer to healthy levels, preserve the proteoglycan content of cartilage tissue, and decrease bone loss when compared with untreated controls. In a nontraumatic guinea pig model, mACG suppressed the progression of OA. This study provides the ground-work for development of an intra-articular therapy that reduces fragmentation of key extracellular matrix components and restores the mechanical environment of the cartilage tissue, resulting in decrease in inflammation and catabolic enzyme production. The therapy has the potential to promote a healthy environment for future tissue regeneration.