TUMOUR NECROSIS FACTOR AND INTERLEUKIN-1 ARE INVOLVED IN MATRIX DEGRADATION OF HUMAN OSTEOARTHRITIC ARTICULAR CARTILAGE

+Kobayashi, M; *Tchetina, E; **Tanzer, M; **Zukor, D J; **Antoniou, J; ***Feige, U; *Poole, A R. (E-A. R. Poole is a consultant to Amgen Inc.)
+Joint Diseases Laboratory, Shriners Hospitals for Children, Montreal, Quebec, Canada. 514-849-6208, Fax: 514-849-9684, Masakyon99@aol.com

Relevance to Musculoskeletal Condition

Both tumour necrosis factor-alpha (TNF-alpha) and interleukin-1 (IL-1) play important roles in mediating and controlling inflammation in arthritis. This study shows involvement of TNF-alpha and IL-1 in the degradation by chondrocytes of human osteoarthritic (OA) cartilage matrix, and thereby identifies possible therapeutic targets in the treatment of OA.

Introduction

Excessive degradation of type II collagen is commonly observed in osteoarthritic (OA) and rheumatoid arthritic articular cartilages. The net loss of proteoglycan that occurs in the early stage of OA is in part a consequence of disruption of the collagen fibrillar network. Thus, monitoring both collagen and proteoglycan catabolism is important when investigating of matrix degradation.

Our recent studies have demonstrated increased cleavage and denaturation of type II collagen in human articular cartilage in OA (1-4). It is known that TNF-alpha and IL-1 play important roles in the pathogenesis of inflammation in arthritis and can each cause damage to cartilage which is mediated by chondrocytes. There have been reports showing that both TNF inhibitors including soluble TNF receptor type 1 (soluble TNF-RI) and IL-1 receptor antagonist (IL-1ra; anankira) can control chronic inflammation and erosion in rheumatoid arthritis. Other reports suggest upregulation of these cytokines and their receptors in OA cartilage. Cytokines, including IL-1, activate synthesis and release of matrix metalloproteinases such as MMP-13 (collagenase-3) leading to cartilage matrix degradation. These observations together suggest that these cytokines may play a role in cartilage degradation in OA.

The purpose of this study was to determine if soluble TNF-RI and/or IL-1ra can inhibit type II collagen cleavage by collagenases and proteoglycan breakdown in human OA cartilage.

Hypothesis

That TNF-alpha and IL-1 are involved in cartilage resorption in human articular cartilage in OA and that soluble TNF-RI, IL-1ra or their combination can inhibit this degradation.

Materials and Methods

Recombinant human IL-1ra (anakinra) and soluble TNF-RI (PEG sTNF-RI) were from Amgen Inc. Human femoral condylar cartilages were obtained at total knee arthroplasty from 15 patients with OA diagnosed according to the criteria of the American College of Rheumatology. Normal cartilages from 5 patients were obtained at autopsy. All cartilage specimens were cultured as explants in serum-free medium for up to 16 days with or without PEG sTNF-RI (0.1, 0.5 or 1 ug/ml) and/or anakinra (20 or 100 ng/ml).

An immunoassay was used to measure a collagenase-generated type II collagen cleavage neoepitope in cartilage and its release into media (3,4). Proteoglycan glycosaminoglycan (GAG) content (mainly aggrecan) in cartilage and its release into media were also assayed by the dimethylmethylene blue method (5). Cartilage wet weight at day16 was used for normalizing the results.

Gene expressions of MMPs, TNF-alpha, IL-1 and aggrecan were analyzed by RT-PCR using total RNA directly extracted from cartilage explants.

Results

Effects of PEG sTNF-RI and anakinra on type II collagen cleavage by collagenase

In 10 out of 15 patients, increased collagenase activity in OA cartilage (4) was arrested by PEG sTNF and/or anakinra blockade. Among these, 0.5 ug/ml PEG sTNF-RI, 100 ng/ml anakinra, or 0.5 ug/ml of PEG sTNF-RI and 100 ng/ml of anakinra inhibited collagen cleavage down to the normal control levels.

Effects of PEG sTNF-RI and anakinra on GAG content

In 8 out of 15 patients, GAG release was inhibited by these anti-cytokines leading to an increase in cartilage GAG content.

Effects of PEG sTNF-RI and anakinra on gene expressions

RT-PCR analyses have thus far revealed that anakinra down-regulated MMP-1 and IL-1 gene expression and up-regulated aggrecan expression within 4 day explant. There was little detectable expression of MMP-13 and TNF-alpha, and any effects on these genes remain to be established.

Discussion

The results indicate that TNF-alpha and IL-1 can play important roles in cartilage matrix degradation in human osteoarthritic cartilage. Blockade of either these cytokines may offer an opportunity to control cartilage resorption therapeutically in OA cartilage.

Conclusions

1) PEG sTNF-RI or anakinra can inhibit type II collagen cleavage by collagenase in 67% of OA patients.

2) These antagonists can also inhibit aggrecan release in 53% of OA patients and stimulate repair as revealed by increased aggrecan content.

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References


**McGill University, Montreal, Quebec, Canada.
***Amgen Inc., Thousand Oaks, CA.

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