Mechanisms of joint destruction in rheumatoid arthritis

HUGO E. JASIN

Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, University of Arkansas for Medical Sciences, and Veterans Administration Hospital, 4301 West Markham, Little Rock, AR, 72205, USA

Abstract: We review the mechanisms involved in irreversible cartilage damage in inflammatory arthritis, in the context of experimental work carried out by members of the Department of Orthopedics, Yokohama City University School of Medicine, in the author’s laboratory. The importance of the superficial layer of cartilage, and the phenotypic differences between superficial and deep chondrocytes with respect to nitric oxide production are emphasized. In addition, we describe some of the consequences resulting from the interaction of nitric oxide and reacting oxygen radicals at the cartilage surface.

Key words: rheumatoid arthritis, inflammation, cartilage

Introduction

In this review, we describe the pathogenic factors involved in tissue damage in chronic inflammatory joint diseases in general, and in rheumatoid arthritis, in particular. Much of this work has been carried out in collaboration with many members of the Department of Orthopaedics, Yokohama City University Medical School.

Mechanisms of irreversible cartilage damage in rheumatoid arthritis

Loss of joint function in rheumatoid arthritis is the result of the irreversible damage to the articular cartilage as a direct consequence of the sustained chronic inflammatory process. The mechanisms operative in cartilage damage in rheumatoid arthritis are not completely understood. However, it is likely that the inability of chondrocytes to maintain tissue integrity, as a result of cell death and metabolic abnormalities induced by factors secreted by cells in inflamed synovium, invasive pannus, and synovial fluid play a major role in the process of cartilage destruction. In addition, proteolytic enzymes and other factors from pannus cells and synovial fluid acting directly on the cartilage matrix also contribute to the destructive process. At the present time it is not possible to single out any of the many factors known to be operative in the rheumatoid joint as mainly responsible for the irreversible damage; it is likely that the concerted action of many of the factors acting over a protracted period of time are responsible. Synthesis and degradation of cartilage macromolecules in normal adult tissue is probably a tightly regulated process, since the chemical composition of adult cartilage matrix remains fairly constant and only changes slowly with advancing age. Thus, cartilage matrix degradation in pathologic conditions could result from a decrease in the rate of macromolecule synthesis, an increase in the rate of proteoglycan and collagen breakdown, or a combination of both processes. Matrix proteoglycan is highly susceptible to degradation by various proteolytic enzymes, such as cathepsins, elastase, and metalloproteinases. This macromolecule is the component most readily lost in pathologic conditions. However, proteoglycan is also rapidly restored by chondrocytes, so that irreversible damage is thought to occur only when collagen fibers are degraded, since this structural component cannot be replaced in a manner that would maintain the integrity of this tissue. There is good evidence suggesting that active proteolytic enzymes may be responsible for degradation of the matrix proteoglycans. However, the collagen type II fiber appears to be relatively resistant to enzymatic attack and the rheumatoid synovial fluids usually lack active
collagenase due to the presence of excess inhibitors. Thus, it is likely that collagen degradation may be due to collagenase secreted by activated chondrocytes and fibroblastic pannus.

Recent studies from our laboratory have shown that collagen type II (CII) on the intact articular surface of cartilage is partially protected from binding by anti-collagen antibodies. The protective surface material was found to be at least partly protein in nature, not present in synovial fluid, non-covalently bound to the underlying intercellular matrix, and synthesized by resident chondrocytes. Additional studies showed that the surface material was unexpectedly sensitive to in-vivo degradation in a rabbit model of acute inflammatory arthritis, and in vitro it was sensitive to degradation by activated polymorphonuclear leukocytes, and neutrophil elastase. Moreover, we have shown that the intact cartilage surface does not sustain cell adhesion, whereas elastase-treated cartilage explants reconstituted with fibronectin did. Further studies indicated that components extracted from the surface of cartilage inhibited human fibroblast cell adhesion to fibronectin-reconstituted cartilage, and that the small proteoglycans in inhibited human fibroblast cell adhesion to fibronectin-reconstituted cartilage, and that the small proteoglycans fibromodulin (FM) and decorin were mainly responsible for the inhibition of cell adhesion to fibronectin and collagen. FM was shown to inhibit adhesion by interfering with the interaction of the cell-binding domain of fibronectin with the arginine-glycine-aspartic acid (RGD) receptor on the fibroblast membrane.

Recent observations by us and others indicate that there are profound phenotypic differences between superficial and deep articular chondrocytes, in addition to the obvious morphologic disparity. The articular cartilage surface is positioned in the front line of attack in inflammatory joint diseases so that it is exposed very early to the various noxious factors contained in the synovial fluid exudates. With respect to the deep articular chondrocytes, it has been suggested that chondrocyte-derived NO may contribute significantly to the total NO produced in the joint cavity in inflammatory arthritides. Work by us and others indicates that there are significant differences in NO production between activated superficial and deep articular chondrocytes. These differences were not only detectable in terms of oxidant production and NO synthase activity, but also at the transcriptional level, suggesting that this feature represents still another phenotypic difference between superficial and deep cells, in addition to phenotypic differences in morphologic characteristics, synthetic activities, and response to cytokines.

NO and its derivatives have been shown to have both pro-inflammatory and anti-inflammatory activities. The direct effects of NO in inflammatory foci are probably exerted at a short distance from its source, since its half-life in physiologic conditions is only a few seconds. However, nitration products, such as the peroxynitrite ion and S-nitrosothiols, are more stable, and may mediate some of the in-vivo biologic effects attributed to NO. Peroxynitrates are generated by NO and the superoxide ion, which may decompose to yield the hydroxyl radical in the absence of iron as another possible pathway for tissue injury. This radical has been the focus of increased interest as a possible mediator of cytotoxicity. Recent studies have shown that NO stimulates endothelial cell proliferation and that it mediates angiogenesis induced by substance P and prostaglandin E2, effects that may be pertinent to pannus formation in rheumatoid arthritis. Thus, it is possible that NO produced near the articular cartilage surface may mediate both protective and noxious effects in inflammatory arthritis. Pertinent to the former possibility is our recent observation showing that NO is able to inhibit oxygen radical-mediated covalent cross-linking of immune complexes on the cartilage surface. With respect to the possible deleterious effects of NO, recent studies have shown that interleukin (IL)-1-mediated induction of NO synthesis by chondrocytes may induce apoptosis (programmed cell death). However, chondrocyte apoptosis took place only if oxygen radical quenchers were added to the culture, suggesting that superoxide reduced the levels of biologically active NO. Conversely, stimulation of oxygen radical synthesis in the presence of NO synthase inhibitors induced cell necrosis. Moreover, cytokine-stimulated chondrocytes developed increased sensitivity to oxidant injury, which was recently suggested to depend on NO synthesis by these cells. The above observations may explain older studies that demonstrated widespread cell death of chondrocytes in the superficial layers of cartilage in rheumatoid arthritis.

Highly reactive oxygen-derived species (ROS) play important roles in defense mechanisms against infections and in tissue injury in inflammatory reactions. One of the main reactive products generated by activated phagocytic cells is hypochlorous acid (HOCl), formed by the enzyme myeloperoxidase (MPO) acting on H2O2 in the presence of chloride ion. This oxidant is mainly responsible for the intracellular killing of phagocytosed bacteria, and it also plays a role in tissue injury because it mediates oxidative modification of tissue macromolecules, eg, the deamination and decarboxylation of proteins with the formation of aldehydes, sulfhydryl oxidation, and covalent cross-linking. We have previously shown that HOCl is responsible for the covalent cross-linking of proteins, namely IgG, resulting in the generation of immune complex-like aggregates (IC) with phlogogenic capacity. Moreover, IgG aggregates with evidence of oxidative modification have been found in the synovial