CHAPTER 2

NITRIC OXIDE SYNTHASE AND CYCLOOXYGENASE INTERACTIONS IN CARTILAGE AND MENISCUS

Relationships to joint physiology, arthritis, and tissue repair

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Abstract: Rheumatoid arthritis and osteoarthritis are painful and debilitating diseases with complex pathophysiology. There is growing evidence that pro-inflammatory cytokines (e.g., interleukin-1 and tumor necrosis factor alpha) and mediators (e.g., prostaglandins, leukotrienes, and nitric oxide) play critical roles in the development and perpetuation of tissue inflammation and damage in joint tissues such as articular cartilage and meniscus. While earlier studies have generally focused on cells of the synovium (especially macrophages), there is increasing evidence that chondrocytes and meniscal cells actively

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contribute to inflammatory processes. In particular, it is now apparent that mechanical forces engendered by joint loading are transduced to biological signals at the cellular level and that these signals modulate gene expression and biochemical processes. Here we give an overview of the interplay of cytokines and mechanical stress in the production of cyclooxygenases and prostaglandins; lipoxygenases and leukotrienes; and nitric oxide synthases and nitric oxide in arthritis, with particular focus on the interactions of these pathways in articular cartilage and meniscus.

1. **INTRODUCTION**

Rheumatoid arthritis (RA) and osteoarthritis (OA) are frequent and important diseases with complex pathophysiology. There is convincing evidence that cytokines (e.g., IL-1 and TNF), prostaglandins (PG), and nitric oxide (NO) play critical roles in the development and perpetuation of inflammation and cartilage and meniscus damage in RA and OA. While earlier studies have generally focused on cells of the synovium (especially macrophages), there is increasing evidence that cells in cartilage (chondrocytes) and meniscus (fibrochondrocytes) contribute to these processes. We now realize that mechanical force affecting cells is transduced to biological signals that modulate gene expression and biochemical processes. Here we give an overview of the interplay of mechanical stress, cyclooxygenases (COX) and PG, nitric oxide synthases (NOS) and NO, and cytokines in arthritis. We focus on cartilage and meniscus studies. We also refer the reader to some other recent pertinent reviews [1–5].

2. **NO AND NO SYNTHASES**

The simple gas NO has many important physiologic and pathologic functions [6]. These include roles in host resistance to tumors and microbes, regulation of blood pressure and vascular tone, neurotransmission, learning, and neurotoxicity, carcinogenesis, and control of cellular growth and differentiation [6, 7]. In the presence of oxygen, NO rapidly (seconds) is converted to nitrite and nitrate, substances which are generally not bioactive (8 for review). NO binds with high affinity to iron in heme groups of proteins such as hemoglobin (Hb) and guanylyl cyclase; Hb is a very effective quencher of NO action. NO also reacts with O$_2^-$, and SOD prolongs NO life by eliminating O$_2^-$. On reacting with O$_2^-$, NO may form peroxynitrite (ONO$^-$), a very reactive molecule. In addition to these NO-related species, S-nitrosothiols (formed by coupling of NO to a reactive cysteine thiol) are very important regulators of physiology and pathology, playing roles in signaling and modulating of cellular and enzyme function [6].

NOS converts L-arginine to L-citrulline and NO (Figure 1). Three forms of the enzyme nitric oxide synthase are encoded by three different genes. Neural NOS (nNOS or NOS1) and endothelial cell NOS (eNOS or NOS3) are constitutive enzymes, demonstrating low level, constant transcription of mRNA. The enzymatic actions of NOS1 and NOS3 are modulated by regulation of cytoplasmic calcium levels, with agents inducing increases in calcium, with subsequent binding