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REVIEW ARTICLE

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The role of nitric oxide in arthritic joints: a therapeutic target?

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Abstract Nitric oxide (NO) is produced by many cell types in the joint, and its expression is delicately regulated. Depending on its concentration and cellular origin, NO appears to have both pro- and anti-inflammatory potential in the joint. Constitutively expressed nitric oxide synthase (NOS) produces small amounts of NO, which is essential for normal physiological homeostasis. However, inflammatory stimuli such as endotoxins, cytokines, and growth factors promote inducible NOS (iNOS) expression, initially as an anti-inflammatory response, and catalyse a high output of NO. Excessive NO can amplify inflammatory pathways and contribute to the development and maintenance of arthritis. Consequently, proper regulation of NO synthesis can lead to a novel therapeutic approach for inflammatory joint diseases. Further careful study will be necessary to develop new drugs to regulate the NO pathway and to determine the dosage, timing of administration, and duration of treatment in order to avoid both undesirable immunostimulatory effects and immunosuppressive effects.

Key words Nitric oxide · Rheumatoid arthritis · Osteoarthritis · Therapeutic target

Introduction

In 1987, endothelium-derived relaxing factor (EDRF)[1] is first determined to be a short-lived free radical, nitric oxide (NO).[2,3] NO is generated from the oxidation of a guanidino nitrogen of L-arginine[4] by three distinct NO synthase (NOS) groups of enzymes: intracellular free-calcium-dependent constitutive NOS (neuronal cNOS, NOS1, and endothelial cNOS, NOS3), and calcium-independent and inducible NOS (iNOS, NOS2). Constitutively expressed NOS produces small amounts of NO (picomole–nanomole), which are essential for normal physiological homeostasis such as cardiovascular or neuronal functions.[5] However, inflammatory stimuli such as endotoxins, cytokines, and growth factors induce iNOS expression, initially as an anti-inflammatoric response, and catalyse a high output of NO (micromole).[6–8] Excessive NO can amplify inflammatory pathways and damage the surrounding cells and tissues as well as the NO-producing cells themselves. Consequently, proper regulation of NO synthesis can lead to a novel therapeutic approach to inflammatory joint diseases.

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Cellular origin of NO in the joints

Recently, increased production of NO in serum or joint fluid has been reported in inflammatory joint diseases.[9–12] Farrel et al.[9] first reported enhanced NO concentration in serum and synovial fluid of patients with rheumatoid arthritis (RA) and osteoarthritis (OA). Subsequently, the intra- and extra-articular cellular origins of iNOS have been identified as synovial fibroblasts,[13] synoviocytes,[14] both circulating and synovial tissue monocytes/macrophages,[13,15] endothelial cells,[14] chondrocytes,[16] and osteoblasts (for a review, see Evans and Ralston[17]). Depending on its concentration and cellular origin, NO appears to have both pro- and anti-inflammatory potential in the joint,[18] so it has been called a "double edged sword"[19] or "Jekyll and Hyde".[20]

NO and synovial inflammation

McInnes et al.[13] demonstrated that synovial membrane cultures from RA and OA joints spontaneously produce NO. Grabowski et al.[21,22] showed that $CD68^+$ macrophages in the synovial lining layer, and to a lesser extent fibroblasts,

are predominant sources of iNOS. In contrast, no evidence of iNOS was detected in noninflammatory synovium. NO production of synoviocytes was up-regulated by in vitro stimulation with a combination of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and lipopolysaccharides (LPS).[14]

Catabolic effects of NO

Synoviocytes and macrophage cell lines produce high concentrations of TNF-α in response to the NO donor s-nitrosoacetyl penicillamine.[13] In addition, several reports have demonstrated the pro-inflammatory roles of NO, potentiation of IL-1 and TNF-α release by leucocytes,[23] the stimulation of angiogenic activity by monocytes,[24] and the increase in vascular permeability.[25] Neovascularization and increased vascular permeability are a major pathology in inflammed synovium. Clinically, NOS activity correlates with the tender and swollen joint counts in patients with RA.[15] In vitro, NO production is significantly correlated with the growth-promoting effect of vascular endothelial cell growth factor (VEGF), but not with that of fibroblast growth factor-2 (FGF-2).[26] The angiogenic effects of VEGF were blocked by the NOS inhibitor L-NMMA. Moreover, NO produced by endothelial cells interacts with neutrophils to produce lipoxin A_4 and superoxide radicals, leading to significant toxicity to the endothelial cells.[27]

Protective effects of NO

It should be noted that low amounts of NO are protective and anti-inflammatory for diseased synovium. NO suppresses mitogen-stimulated T-cell proliferation,[28] monocyte chomotaxis,[29] leukocyte adhesion,[30] and mast cell reactivity.[31] NO also inhibits the synthesis of IL-6 and prostaglandin E_2.[32] IL-18 is a novel cytokine which is expressed in RA synovium, and might play a crucial part in promoting the synovial inflammation.[33] IL-18 production in primary synovial cultures and purified synovial fibroblasts was up-regulated by IL-1 and TNF-α. NO release is up-regulated by IL-18, and conversely blocks the processing of proIL-18 into a biologically active cytokine through inhibition of the IL-1β-converting enzyme (ICE). In addition, NO inhibits expression of cytokine-induced adhesion molecules, such as VCAM-1 and E-selectin, by human endothelial cells.[34]

NO and cartilage damage

Chondrocytes are believed to be a major cell source of NO,[35] which contributes to the degradation of articular cartilage itself. The overexpression of iNOS by chondrocytes from RA and OA joints can result from the diffusion of increased levels of inflammatory cytokines, including interleukin-1 (IL-1), TNF-α,[36] IL-17, and IL-18,[37] into cartilage via synovial fluid. The protective and anabolic effects of NO have also been reported elsewhere.[38] In contrast, NO production by chondrocytes in response to these catabolic cytokines, as well as LPS or presumably abnormal mechanical stress,[39] has been shown: (1) to inhibit the synthesis of proteoglycan and type II collagen,[40] (2) to increase the susceptibility to oxidant injury,[41] (3) to stimulate matrix metalloproteinase (MMP) production and activation,[42,43] (4) to inactivate tissue inhibitor of metalloprotease (TIMP),[44] (5) to downregulate IL-1 receptor antagonist expression,[45] (6) to interfere with chondrocyte migration and attachment to fibronectin, probably via inhibition of actin polymerization and β1 integrin signaling,[46,47] and (7) to induce apoptosis.[48–51]

NO and chondrocyte cell death

Blanco et al.[48] first demonstrated that NO is the primary inducer of apoptosis in human articular chondrocytes. Interestingly, they indicated that NO protects chondrocytes from oxygen radical-induced necrosis. NO production and chondrocyte apoptosis in a rabbit OA model (anterior cruciate ligament transection) was reported by Hashimoto et al.[52] They showed that the prevalence of apoptotic chondrocytes was significantly correlated with the levels of nitrite and histological OA grade, suggesting that NO production may lead to chondrocyte apoptosis during the early phase of OA. In RA cartilage, Kim et al.[53] reported an increased population of apoptotic chondrocytes (3.01%) compared with normal cartilage (0.15%), whereas there was about a 10-fold difference in this rate and the transferase-mediated biotin-dUTP nick end-labeling (TUNEL)-positive cell population (ca.30%). Recently, we found that numerous disintegrating RA chondrocytes were TUNEL-transmission electron microscopy (TEM)-positive, suggesting that a majority of so-called apoptotic chondrocytes may belong to a category other than apoptosis (unpublished data).

The fate of chondrocyte-derived apoptotic bodies or cell fragments is still unknown. They remain within the cartilage matrix without being ingested by phagocytes. It is reported that apoptotic bodies express matrix vesicle-like functional activities, and may take part in the pathological calcification of articular cartilage.[54] However, clinically, cartilage calcification in an RA or OA joint is not often seen except for crystal-related arthropathies. In the late stage of cartilage degradation, these extra-cellular vesicles might be released into the joint, and could promote synovitis.

To date, the regulation mechanism of cell death has not been fully elucidated. The bcl-2 protooncogene is known to protect cells from apoptosis. It is expressed in normal adult and OA cartilage, especially adjacent to OA defects, whereas it decreases in RA cartilage.[55] Further investigation will be needed to discover the interactions of oncogenes such as p53, bax, and p21 which can influence chondrocyte survival.

NOS and COX

Synovial cells from RA patients and chondrocytes from OA patients over-express cyclooxygenase (COX)-2, and produce high levels of prostaglandin (PG) E_2, which is believed to promote joint imflammation and destruction.[56] Endogenous NO release acts in an autocrine fashion to down-regulate IL-1β-stimulated production of IL-6, IL-8, and PGE_2.[57] In OA cartilage explants, the NOS inhibitor L-NMA significantly increases both PGE_2 and MMP-3 production.[58] In a mouse macrophage line, however, L-NMMA blocks both NO and PGE_2 release, indicating the role of NO in COX activation.[59] These data strongly suggest the existance of cross-talk between NOS and COX, which might be different in different cell types, and be finely regulated in vivo.

Inhibition of NO pathway in inflammatory joint diseases

As described above, NO is produced by many cell types in the joint, and its expression is delicately regulated. However, high NO output may amplify the inflammatory pathway and contribute to the development and maintenance of arthritis. Some currently used antirheumatic agents are known to act to down-regulate NO activity (for more information, see the excellent review by Clancy et al.[58]). For direct inhibition of NOS enzymes, McCartney-Francis et al.[60] showed that intravenous administration of N^G-monomethyl-L-arginine (L-NMA), an general inhibitor of NOS, profoundly reduced synovial inflammation and tissue damage as measured by an articular index and reflected in the histopathology of streptococcal cell wall (SCW) fragments in SCW-induced arthritis. Conner et al.[61] reported that adjuvant-induced arthritis (AIA) was suppressed by the NOS inhibitor L-NMA, demonstrating the inhibition of paw swelling and histopathological changes. However, nonselective NOS enzyme inhibitors would totally suppress NO production and could lead to serious cardiovascular and nervous system toxicity if used long term. Thus, a selective inhibitor of iNOS would be beneficial for clinical use. In an OA model, Pelletier et al.[62] used oral treatment with N-iminoethyl-L-lysine (L-NIL), a selective inhibitor of iNOS, and showed decreased production of NO as well as MMP, IL-1β, peroxynitrite, and COX-2. From the results of our preliminary study on a collagen-induced arthritis model, L-NIL significantly decreased the arthritic score, histological score, and nitrotyrosine production in cartilage, but not completely. It should be noted that continuous inhibition of iNOS would lead to serious infectious complications,[63] as seen in iNOS knockout mice.

The transcription factor nuclear factor-kappaB (NF-κB) is a key regulator of inflammatory and immune response.[64] NF-κB is induced by many stimuli, including TNF and IL-1, forming a positive regulatory cycle that may amplify and maintain the process of inflammatory joint disease.[65,66] The activation of NF-κB is implicated in up-regulation of iNOS[67] at the transcriptional level, as well as a variety of proinflammatory mediators including IL-6,[68] IL-8,[69] COX-2,[70] PGE_2,[71] MMPs,[72] and ICAM-1.[73] Marok et al.[74] reported the positive reaction against "activity-specific" antibodies to the Rel-A (p65) subunit of NF-κB in type-A synoviocytes and endothelium from an RA joint. Treatment of synovial cells with N-acetyl-L-cysteine (NAC), an antioxidant agent, inhibited TNF-α-induced NF-κB activation and transcription, and synovial cell proliferation induced by TNF-α.[75] These data strongly suggested that NF-κB can be an effective therapeutic target in arthritis.[76] More recently, effective therapeutic results were reported using inhibitors for NF-κB, NAC,[77] diethyldithiocarbamate,[78] and NF-κB decoy oligodeoxynucleotides as a gene therapy[79] in a collagen-induced arthritis model. Interestingly, an inhibitor of NF-κB, PS-341 treatment, inhibited iNOS protein expression in synovial tissue, as well as serum levels of IL-6 and NO metabolites (nitrate and nitrite) in SCW-induced polyarthritis in rats.[67] These results suggest that an inhibitor of NF-κB might play a role in the inhibition of the NO pathway, leading to the suppression of arthritis. However, NF-κB is also known as an inhibitor of apoptosis in many cell types, while the relation between NF-κB activation and chondrocyte apoptosis is still unknown at present.

In summary, to develop new drugs to regulate the NO pathway, further careful study will be necessary to determine the dosage, the timing of administration, and the duration of treatment in order to avoid both undesirable immunostimulatory effects and immunosuppressive effects.

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