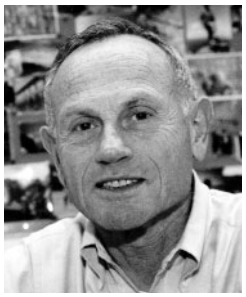
Editorial

Retinoids and Rexinoids for the 21st Century: A Brave New World for Arthritis



Rheumatoid arthritis (RA) is a chronic autoimmune disease in which joints are progressively and irreversibly destroyed, primarily by the action of matrix metalloproteinases (MMP)[1]. These are a family of at least 24 enzymes that are active at neutral pH and that have the major function of modeling and remodeling the extacellular matrix in normal physiology and in the pathogenesis of disease[2]. The overproduction of at least 2 members of this family, the collagenases MMP-1 and MMP-13, by fibroblasts lining the rheumatoid joint and neighboring articular chondrocytes, results in the degradation of cartilage, tendon, and bone[1,2].

The disease afflicts more than a million people worldwide, most of them women, and there is no cure[1,3]. The cost to the economy is hundreds of millions of dollars in lost wages and medical expenses[3]. A wide array of medications is used to treat this disease, including aspirin, nonsteroidal antiinflammatory drugs, specific antibodies directed toward tumor necrosis factor-α (TNF-α) and its receptor, glucocorticoid hormones, and some anti-cancer therapies such as methotrexate and cyclophosphamide[1,3,4]. Most of these do not stop joint destruction. Encouragingly, the TNF-α antagonists have shown some suppression of joint destruction, at least within a limited timeframe[1,3,4]. In addition, glucocorticoids suppress MMP gene expression, thereby limiting joint destruction[1,3,4]. These compounds act at a transcriptional level, but like many other therapies, however, their longterm usage may be associated with significant toxicities.

Another approach is inhibiting the enzymatic activity of MMP, which has been a major therapeutic goal in cancer, since tumor invasion and metastasis would potentially be curtailed[5,6]. Nonetheless, despite promising preclinical studies, human trials have almost uniformly been disappointing, showing little or no efficacy, and enthusiasm for blocking enzyme activity has waned[5,6]. An article by Beehler, *et al* in this issue of *The Journal*[7] reintroduces the transcriptional approach to inhibiting MMP gene expression by testing a novel vitamin A analog (retinoid), and describes the ability of this compound to inhibit the progression of clinical disease in animal models of arthritis.

At physiologic concentrations, vitamin A and its metabolites affect the expression of many genes, especially during embryogenesis and development, where they control morphogenetic events (reviewed in[8,9]). In contrast, pharmacologic doses of synthetic retinoids have therapeutic effects in a number of disorders, such as acne, psoriasis, leukemia, and some head and neck cancers[8-10]. The discovery more than 20 years ago that retinoids could inhibit the synthesis of several members of the MMP family[11-13] sparked initial interest that these compounds might be therapeutically useful in RA.

Indeed, several studies that quickly followed these early reports produced promising results[14-16]. In 3 different rat models of RA (collagen-induced arthritis, adjuvant arthritis, and streptococcal cell wall-induced arthritis), in which 13-*cis*-retinoic acid or 4-hydroxyphenyl retinamide were orally administered to the animals, all showed a decrease in collagenase levels. In 2 of the models (adjuvant arthritis and streptococcal cell wall-induced arthritis), the retinoids also suppressed clinical symptoms of the disease[15,16]. However, similar to results in the present study with all-*trans*-retinoic acid, collagen-induced arthritis was not suppressed[14], possibly because a different profile of inflammatory mediators contributed to the pathology of this model. Nonetheless, these early experiments were hopeful, and it has been disappointing that this potential avenue of therapy has not been further explored[17].

In the 1990s, we began to understand the molecular mechanisms by which retinoids exert their effects on gene expression[9,12,13]. Retinoic acid receptors (RAR), which bind all-*trans*- and 9-*cis*-retinoic acids, and retinoid X receptors (RXR), which bind 9-*cis*-retinoic acid and their specific subtypes, α, ß, and γ, were identified as members of the steroid superfamily of nuclear receptors. A role for retinoids as hormones with substantial effects on gene expression was

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confirmed. In most cases, retinoids target genes through RAR/RXR heterodimers that interact with specific retinoic acid response elements (RARE) in the promoters of these genes. In the absence of ligands for RAR/RXR heterodimers, or in the presence of certain antagonists, these target genes are repressed. This repression results from the recruitment of complexes containing histone deacetylases that are tethered to RARE through co-repressors. Consequently, histones are deacetylated, chromatin is compacted, and gene expression is silenced. Alternatively, in the presence of ligand, transcription becomes activated. Upon ligand binding, the co-repressor is destabilized, followed by a conformational change in the receptors that allows co-activators to bind and chromatin to decondense. However, these mechanisms are probably not functional for the MMP; with the exception of MMP-11 (stromelysin-3), the promoters of the MMP lack RARE[12,13].

Retinoid repression of MMP gene expression is mediated by other mechanisms, ones that interfere with Fos and Jun, transcription proteins that bind to the activator protein-1 (AP-1) site located in the proximal promoter of most MMP, including the collagenases[12,13]. There may be downregulation of Fos and Jun mRNA, perhaps through inhibition of cell signaling to the promoters of these genes, sequestration of Fos and Jun proteins, and conformational changes in Fos and Jun as a result of direct interactions with RAR/RXR heterodimers. Thus, retinoids and their nuclear receptors may use several seemingly redundant mechanisms to inhibit MMP gene expression.

Nonetheless, the pleiotropic effects of retinoids on many genes have contributed to their reputation as detrimental[8,9]. They are potent teratogens, and thus cannot be given to women who might become pregnant. They have also been associated with suicide in teenagers taking Accutane® (13-*cis*-retinoic acid) for severe acne. In addition, in some experimental systems, they have been linked to an increase in MMP gene expression, rather than to repression. Therefore, the recent development of ligands that target specific RXR/RAR, thereby affecting the expression of certain genes, represents an important step in directing effects on the expression of specific genes[7,9]. These "second generation" compounds have the ability to selectively activate particular signaling cascades and to engage certain RAR/RXR, thereby targeting certain genes, and perhaps avoiding the more general side effects associated with the use of parent retinoids. Thus, the description of a novel synthetic retinoid that decreases the clinical symptoms of RA in 2 animal models, with a concomitant decrease in MMP production in the afflicted joint, is particularly exciting and promising. This retinoid, an RAR α, ß, and γ antagonist, represses AP-1 driven genes, such as the MMP, while all-*trans*-retinoic acid did not[7]. Possibly this retinoid and others similar to it will, like their original counterparts, act synergistically with glucocorticoids[18] or with other new and novel transcriptional inhibitors of MMP[19] to reduce MMP production, thereby providing even more precisely targeted effects on the expression of particular genes. Further, because of this synergism, lower doses of each drug can be used, thus subverting certain effects associated with conventional doses.

The next steps in this important work are determining the molecular mechanism(s) by which this novel retinoid blocks inflammation and MMP gene expression, identifying additional retinoids that might be effective, and extending studies to include other animal models of RA, such as the rabbit. The synovial tissues of rats and mice express only one interstitial collagenase (MMP-13), while the tissues of humans (and rabbits) express MMP-1 and MMP-13[4,7]. Both the early work and the present study indicate that retinoids, including the RAR-selective ligand reported here, can suppress both genes. Nonetheless, it will be essential to document the tissue-specific effects of these new compounds on the collagenases and the other MMP that mediate the pathophysiology of RA.

Another set of related compounds that are totally unexplored in the field of rheumatology is the rexinoids, which are ligands that bind specifically to the 3 RXR, and *not* to any of the 3 RAR[20,21]. RXR are unique in the entire nuclear receptor superfamily by virtue of their ability to form functional heterodimers with many other members of this family, such as the RAR, the vitamin D receptor, the thyroid receptor, the peroxisome proliferator-activated receptor-γ (PPAR-γ), and several others[22]. Thus, selective ligands for RXR have wide potential actions in clinical medicine. Rexinoids are already in clinical use in the field of oncology. They have also aroused a great deal of interest for potential applications in treatment of type II diabetes, by virtue of their ability to potentiate the insulin-sensitizing actions of PPAR-γ ligands, such as the widely used thiazolidinediones, namely rosiglitazone and pioglitazone. PPAR-γ is known to regulate the inflammatory process[23], and the rexinoids will undoubtedly be found to have significant actions in this area as well, especially when used in combination with other ligands of the nuclear receptor superfamily. Most notably, from a practical perspective, rexinoids are much less teratogenic than classical retinoids. Their potential applications in the field of rheumatology should be pursued. Hopefully, these new retinoids for the 21st century will bring a new world to the patients who suffer from this chronic and disabling disease.

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