

Matrix Catabolism in Arthritis: Priming the Guns with Oncostatin M



Cytokines such as tumor necrosis factor (TNF) and interleukin 1 (IL-1) have long been at the forefront as “guns” in inflammatory arthritis: they are effective in inducing destructive catabolic matrix metalloproteinase (MMP) release by resident connective tissue cells of the synovium, cartilage, and bone, and they are delivered by armies of immune and inflammatory cells that invade synovium and fluid of affected joint tissues¹. More recent data also implicate IL-17 in mediating similar activation of catabolic mechanisms. Clearly, other cytokines may also participate in the pathophysiology of these tissues *in vivo* through different mechanisms, and we suggest that the macrophage/T cell/neutrophil product oncostatin M (OSM) is critical in priming connective tissue cells for robust responses to IL-1, TNF, and IL-17 *in vitro* and *in vivo*.

Reduction in symptoms of pain and swelling of inflamed joints in rheumatoid arthritis (RA), although in large part controlled by nonsteroidal antiinflammatory drugs and/or steroid therapy, is not tightly coupled to control of the destruction of joint tissue. Inflammation of RA joints involves numerous sets of molecules (eicosanoids, adhesion molecules, cytokines and chemokines, RANK/RANKL among others); however, catabolism of cartilage and bone in joint disease is a prime end effect of both rheumatoid and osteoarthritic disease. The direct effectors of catabolism include activated enzymes, primarily of the MMP family (particularly MMP-1, MMP-13, and aggrecanase in joint tissues)^{2,3}; moreover, mechanisms for generation and control involving endogenous inhibitors such as the family of TIMP (tissue inhibitor of MMP)⁴ have been the subject of extensive work over several years.

Osteoarthritis may also involve IL-1 and TNF mediation of MMP and aggrecanase expression^{5,6}. Where targeting immune T and B lymphocytes that initiate autoimmune mechanisms in RA has been difficult due to lack of specific methods, targeting acute inflammation symptoms and effector mechanisms of extracellular matrix catabolism has been and is currently a reasonable tack for treating established disease.

The establishment of therapies devised to block TNF or IL-1 has been well documented in animal models of arthri-

tis. These have been translated to the clinic, where TNF blockade therapy in particular, either antibodies to TNF or soluble TNF receptor moieties, has been established as effective^{7,8} in a proportion of patients. However the action of such regimens may not include consistent amelioration of joint destruction, let alone repair of affected cartilage, bone, and synovial tissue. Further, a subset of patients are not responsive at all. Lack of efficacy in patient subpopulations may be a result of relatively late administration of anticytokine therapy, since early subclinical rheumatoid or osteoarthritis is not easily identifiable at present. Certainly the relative success of TNF or IL-1 blockade therapy has instilled confidence in the success of targeting such molecules as an approach, and fuels further investigations of novel cytokine therapies and/or combination approaches.

Targeting IL-1 and TNF in combination therapy would be predicted to be more effective than either alone⁹, since IL-1 blockade (IL-1 receptor antagonist) showed success in preclinical trials in animal models and some success in clinical trials. However, a recent limited clinical trial of TNF and IL-1 blockade did not show predicted increased efficacy and led to increased side effects (infection). Combination therapies for RA patients using TNF blockade and methotrexate (MTX) clearly have an advantage over either treatment alone¹⁰. Although the method(s) by which MTX acts in RA patients is still not clear, one assumes it is different than IL-1 or TNF blockade, since MTX does not show such properties *in vitro*. This supports the notion of increased efficacy of combination treatments that target different mechanisms of action.

The control of chronic inflammation is unclear certainly in human disease, and studies have explored various angles in hematopoietic, immune, and effector function regulation. Elucidating the mechanisms of chronic inflammation awaits clarification of the interplay between various molecules, including cytokines and target cells, and evolution over the time course of disease development, including latter stages of destruction of the normal extracellular matrix of synovium, cartilage, and bone. The success of existing approaches in animal models may not reflect similar efficacy in human subjects due to differences between species in

mechanisms of inflammatory networks or differences in pharmacological properties of compounds, or due to a lack of precise animal model equivalents of the human disease. Therefore searching for new animal models and systems that allow testing of certain activities of new compounds/biologicals will provide additional information with which to create rational approaches with drug or anti-cytokine therapy. The development of genetic systems to overexpress cytokines, either in transgenic animal models or using transient gene induction methods, will allow further study of the assessment of the MMP and their respective inhibitors in extracellular matrix catabolism *in vivo*.

Over the last few years, investigations have indicated the possible role of other cytokines in the interplay within the development of chronic arthritis. Animal models of RA such as collagen-induced arthritis (CIA) or adjuvant-induced arthritis have been widely used to test the efficacy of anti-cytokine therapy. Thus, in addition to the success of targeting TNF or IL-1, inhibition of IL-15, IL-17, IL-18, and IL-23 has been shown to be effective in ameliorating disease parameters in such models¹¹⁻¹⁴. The role of the IL-6 family of cytokines¹⁵ has also come to front stage as mediators of pathology, and IL-6 receptor blockade has shown success in clinical trials¹⁶.

Among the IL-6 family of cytokines¹⁵, oncostatin M is particularly interesting^{6,16}. OSM synergizes with other cytokines (IL-1, TNF, IL-17) in inducing the production of MMP by chondrocytes and synovial cells *in vitro*¹⁷⁻²⁰. Although OSM in isolation regulates TIMP in synovial fibroblasts and chondrocytes *in vitro*^{17,18,21}, its effect in concert with IL-1, TNF, and IL-17 results in a net catabolic balance of MMP activity in synovial fibroblasts and chondrocytes/cartilage. OSM also induces a transformed-like growth phenotype of murine synovial fibroblasts *in vitro*²² and induces IL-6 *in vitro* and *in vivo*. Intraarticular overexpression of OSM induces pannus-like joint pathology in mice and induces similar pathology in IL-6 knockout (KO) mice, and IL-6 does not have such effects *in vitro* or *in vivo* in transient systems^{22,23}. However, effects of OSM are modulated in IL-1 KO mice, indicating important interplay between OSM and IL-1 in mouse models. Further, this suggests that unique activities of OSM, including the capacity to synergize with low concentrations of IL-1 or TNF, might mediate such responses. Although overexpression of OSM also results in periosteal-layer bone apposition, recent work has indicated that local overexpression of combinations of either IL-1 or TNF with OSM^{24,25} dramatically alters the balance of MMP and TIMP levels in mouse cartilage *in vivo*, and that this interaction correlates with cartilage tissue destruction.

Collectively, these results strongly support the potential of targeting cytokines such as OSM that act by "priming" connective tissue cells to allow robust responses to IL-1, TNF, or IL-17. Antibodies to OSM have been shown to dra-

matically reduce the inflammation and the connective tissue catabolism in mouse CIA²⁶, and may do so by regulating synergistic activities between OSM, IL-1, TNF, and possibly other cytokines. To this end the mouse mutated in the OSM receptor-beta gene²⁷ or the OSM ligand will be useful in testing the importance of OSM, although this is yet to be examined comprehensively. Inhibition of cytokines including IL-1 or TNF and their synergistic effects with other cytokines will allow more effective control of joint destruction and debilitation/morbidity of patients. Additional targeting of OSM may provide a means to this end in modulating the ability of cells to respond to low amounts of IL-1 or TNF in MMP production, thus reducing the action of such established powerful cytokines on extracellular matrix catabolism.

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