Commentary

Physiologic role of interleukin-1 receptor antagonist

William P Arend and Cem Gabay*

University of Colorado Health Sciences Center, Denver, Colorado, USA, and *University Hospital of Geneva, Geneva, Switzerland

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Abstract

Recent studies have described the spontaneous development of arthritis or vasculitis in IL-1 receptor antagonist (IL-1Ra) knockout mice bred on specific and different genetic backgrounds. The levels of both secreted and intracellular isoforms of IL-1Ra produced in the rheumatoid joint or in the arterial wall may not be adequate to effectively inhibit the excess amounts of locally produced IL-1. Thus, an imbalance between IL-1 and IL-1Ra may predispose to local inflammatory disease in particular tissues in the presence of other as yet unknown genetically influenced factors.

Keywords: interleukin-1, interleukin-1 receptor antagonist, rheumatoid arthritis, vasculitis

Introduction

The IL-1 family includes two agonists, IL-1α and IL-1β, and a naturally occurring receptor antagonist, IL-1Ra. IL-1Ra is produced locally in various tissues in response to infection or inflammation, and is present in high levels in the circulation secondary to hepatic production as an acute-phase protein [1]. Multiple isoforms of IL-1Ra have been described: a 17-kDa form secreted from monocytes and other cells as variably glycosylated proteins of 22–25 kDa, and at least three intracellular molecules [2,3]. The first described intracellular isoform of IL-1Ra (icIL-1Ra1) predominates in epithelial cells and fibroblasts, and is a delayed product of transcription in monocytes. The role in physiology of secretory IL-1Ra (sIL-1Ra) appears to be to inhibit competitively the local inflammatory effects of IL-1. Although icIL-1Ra isoforms may be released from dying cells and may also function as receptor blockers, other possible functions of icIL-1Ra isoforms inside cells may exist [3].

The results of two recent studies of IL-1Ra knockout mice [4,5] further the hypothesis that maintenance of a balance between IL-1 and IL-1Ra may be important in preventing the development of inflammatory diseases. Horai *et al* [4] described the spontaneous development of inflammatory arthritis in IL-1Ra knockout mice bred on the BALB/cA background, with many features resembling rheumatoid arthritis (RA) in humans. In contrast, an arterial inflammatory disease resembling polyarteritis nodosa (PAN) spontaneously developed in IL-1Ra knockout mice bred on a MFI × 129 background [5]. These fascinating observations pose questions about the possible pathophysiologic consequences of an imbalance between IL-1 and IL-1Ra in inflammatory disease in the joints or vessel walls in humans.

CIA = collagen-induced arthritis; icIL-1Ra = intracellular IL-1 receptor antagonist; IL-1Ra = IL-1 receptor antagonist; GCA = giant cell arteritis; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; sIL-1Ra = secretory IL-1 receptor antagonist; TGF = transforming growth factor; TNF = tumor necrosis factor.

Interleukin-1 and its receptor antagonist in inflammatory arthritis

The role of cytokines in RA, and the rationale for inhibition of IL-1 and tumor necrosis factor (TNF)-α in this disease have been extensively reviewed [6,7]. Much evidence indicates that both of these proinflammatory cytokines are overproduced in the rheumatoid joint and are key mediators in both inflammation and tissue destruction. The demonstrated success of the therapeutic administration of inhibitors of IL-1 and TNF-α offers further support for the importance of these cytokines in the rheumatoid disease process. However, much less is known about the importance and role of natural mechanisms to counteract the effects of IL-1 and TNF-α in the joint, and whether an imbalance in these mechanisms may predispose to the development of RA. Endogenous inhibitors of IL-1 and TNF-α include their respective soluble receptors; IL-1 effects may be further blocked by IL-1Ra.

The results of studies in animal models of arthritis suggest an important anti-inflammatory role for endogenous IL-1Ra. Lipopolysaccharide-induced arthritis in rabbits markedly worsened after administration of a neutralizing antibody to IL-1Ra [8]. Furthermore, arthritis in numerous animal models was significantly ameliorated after treatment with IL-1Ra, suggesting that the level of production of endogeneous IL-1Ra was inadequate to counteract the effects of local IL-1 fully [3]. Collagen-induced arthritis (CIA) exhibited an earlier onset and more severe course in mice rendered genetically deficient in production of all isoforms of IL-1Ra, whereas the opposite pattern was observed in mice transgenic for sIL-1Ra [9]. Studies on the temporal production of various cytokines in CIA indicated that peak IL-1β mRNA levels in synovial tissue were observed within the first week after the onset of arthritis, whereas levels of IL-1Ra mRNA continued to rise for weeks later [10]. Recent work in our laboratory (Gabay C *et al*, unpublished data) demonstrated that the mRNA for both sIL-1Ra and icIL-1Ra1 were found in the inflamed synovium after the second week of CIA, paralleling the resolution of acute arthritis. The amounts of IL-1β mRNA decreased after day 15, with the cytokine balance being in favor of IL-1Ra. These observations suggest that both sIL-1Ra and icIL-1Ra1 may play important anti-inflammatory roles in CIA in mice.

Rheumatoid synovitis also demonstrates an imbalance between production of IL-1α and IL-1Ra. Immunohistologic studies [11] indicated that IL-1 was present in approximately 90% of cells at the cartilage–pannus junction, whereas staining for IL-1Ra was found in less than 10% of the cells. In addition, chondrocytes in the articular cartilage near the pannus contained IL-1α in four out of five RA samples, with approximately 65% of the cells containing IL-1α, whereas IL-1Ra was detected in only one sample, with less than 10% of the cells being positive. IL-1Ra was produced primarily by macrophages in the rheumatoid synovium, with little protein found in fibroblasts [12,13]. The amounts of IL-1Ra produced by cultured rheumatoid synovial tissue were inadequate to inhibit the amounts of IL-1 produced by the same tissue effectively [14,15]. Finally, in recent studies we failed to detect icIL-1Ra1 mRNA or protein in 10 synovectomy samples from eight patients with active RA of long duration, whereas sIL-1Ra mRNA and protein were present in all samples (unpublished observations).

Thus, it appears that endogenous IL-1Ra is certainly anti-inflammatory, but may not reach high enough local levels of production to inhibit early synovitis effectively. Our recent studies (Gabay C *et al*, unpublished data) on CIA in mice suggest that delayed production of icIL-1Ra1 by synovial fibroblasts and macrophages may contribute to resolution of the acute synovitis. An absence or deficiency in synovial cell production of icIL-1Ra1 in some RA patients may predispose to continued active synovitis.

The recent observation of spontaneous development of inflammatory arthritis in IL-1Ra knockout mice further supports the hypothesis that a balance between IL-1 and IL-1Ra is important for maintenance of homeostasis and prevention of disease. Although the absence of IL-1Ra did not affect T-cell and B-cell numbers, the IL-1Ra knockout mice developed autoantibodies such as rheumatoid factors, antibodies to double-stranded DNA, and antibodies to collagen type II [4]. Both IL-1α and IL-1β were constitutively present in normal mouse joints. However, the expression of IL-1β mRNA was elevated twofold to threefold in the joints of IL-1Ra knockout mice before the onset of arthritis, and mRNA for IL-1β, IL-6, and TNF-α were all elevated in the synovium of mice during active arthritis. This finding suggests that the absence of IL-1Ra predisposes to an augmented local production, as well as effect, of proinflammatory cytokines. However, it seems unlikely that arthritis developed spontaneously just because of unopposed activity of the low levels of basal IL-1Ra; other as yet unknown pathophysiologic factors must have been operative as well. Without these other factors, possibly enhancing local IL-1 production, an absence of IL-1Ra may not have been deleterious.

A further analysis of the genetic influences in this model may establish additional mechanisms that, in the presence of an imbalance in the IL-1 system, predispose to arthritis. Early spontaneous development of arthritis was observed only in IL-1Ra knockout mice bred on the BALB/cA background, but not on the C57BL/6J background [4]. However, IL-1Ra knockout mice of the C57BL/6J background developed a high incidence of arthritis after immunization with collagen type II, and knockout mice bred on the DBA/1 background developed more severe CIA than IL-1Ra-producing mice. These findings may indicate that

the anti-inflammatory effects of endogenous IL-1Ra are important in any animal model of arthritis, or that the absence of IL-1Ra may have altered the immune response. Finally, in light of the arguments offered above, it would be of interest to examine whether absence of production of icIL-1Ra1 alone, and not also of sIL-1Ra, would similarly predispose to or worsen arthritis in animal models.

Interleukin-1 and its receptor antagonist in inflammatory vascular disease

In comparison with arthritis, a less firm scientific foundation exists to support the possible involvement of IL-1 and IL-1Ra in inflammatory vascular disease. However, inflammation is thought to be an important component in atherosclerotic vascular disease after mechanical damage to endothelial cells in the intima. Stimulation of foam cells in atheromatous lesions by oxidized lipoproteins is thought to be the responsible mechanism for enhanced local production of IL-1 [16,17]. In turn, IL-1 leads to the production of platelet-derived growth factor, which may stimulate smooth muscle cells and fibroblasts into further participation in pathologic events in the vessel wall.

IL-1Ra was detected in the endothelium of diseased coronary arteries [17], and administration of IL-1Ra inhibited fatty streak formation in the apolipoprotein E knockout mouse [18]. Cultured human umbilical vein endothelial cells stimulated by a variety of conditions were not observed to produce IL-1Ra mRNA or protein in two earlier studies [19,20]. However, in recent studies [21] human umbilical vein endothelial cells stimulated by lipopolysaccharide, phorbol myristate acetate or transforming growth factor (TGF)-β produced icIL-1Ra1 mRNA, and atherosclerotic coronary arteries contained mRNA for both IL-1Ra isoforms, as determined by reverse transcription polymerase chain reaction. Thus, IL-1Ra found in the vessel wall during inflammatory conditions may be derived from infiltrating macrophages or myoepithelial cells, or possibly from endothelial cells, with icIL-1Ra1 possibly being the major isoform produced. However, the results of studies in animal models of atherosclerosis and in patients with coronary artery disease would suggest that the levels of endogenous production of IL-1Ra in the vessel wall may not be sufficient to inhibit the effects of IL-1 produced locally.

The presence of IL-1 in the vessel wall in forms of vasculitis in humans has been examined only in giant cell arteritis (GCA). Temporal artery biopsy specimens from patients with GCA contained mRNA for the macrophage cytokines IL-1β, IL-6, and TGF-β_1, as well as for the T-cell cytokines IFN-γ and IL-2, as determined by reverse transcription polymerase chain reaction [22]. The IL-1β, IL-6, and TGF-β proteins were localized by immunohistochemistry primarily to $CD68^+$ macrophages in the adventitia, in the vicinity of activated $CD4^+$ T cells producing IFN-γ [23]. The IFN-γ-producing $CD4^+$ T cells in the adventitia of temporal artery biopsies in GCA were CD45RO-positive, suggesting a memory phenotype, and a subset of these cells exhibited markers of proliferation [24]. IL-1Ra mRNA or proteins were not examined in these studies.

These findings imply that GCA is mediated by T cells in the adventitia responding to unknown endogenous or exogenous antigens, then activating nearby macrophages to secrete cytokines including IL-1β, leading through unclear mechanisms to eventual damage to the inner media and intima [24]. The possibility exists that the local production of IL-1Ra may be inadequate to oppose the IL-1 effects. Histologic studies on small and medium-sized arteries in nerve and muscle biopsies from patients with PAN [25] indicated a similar predominance of macrophages and $CD4^+$ T cells, although the presence of cytokines in these inflamed vessels was not determined. The implication is that PAN may also be a T-cell-mediated disease, however, involving effector macrophages and possibly local cytokine production.

The spontaneous arteritis described in IL-1Ra knockout mice bred on the MFI × 129 background developed at points in the vasculature subjected to high turbulence or stress, similar to the pattern of lesions in atherosclerosis or PAN, but different from GCA [5]. Homozygous animals died prematurely from consequences of the inflammatory vasculitis, whereas heterozygotes developed small lesions that were not usually fatal. This observation suggests that, in the presence of a partial deficiency in IL-1Ra, the vessel wall is able to heal or contain the lesion. IL-1β was demonstrated in the vessel wall lesions, localized primarily to macrophages often found in association with $CD4^+$ T cells. However, whether IL-1β was present in uninvolved segments of the vessel wall was not examined in these studies. Arteritis has not been found in IL-1Ra knockout mice bred on other genetic backgrounds.

Thus, the description of spontaneous arteritis in IL-1Ra knockout mice suggests that expression of IL-1Ra in the vessel wall, or in the circulation, may be necessary to counteract the potentially injurious effects of local IL-1 production, possibly induced by mechanical damage to the endothelium. Determination of the genetic influences on the development of arteritis in this model, which are acting in combination with a lack of IL-1Ra, may indicate possible predisposing factors in patients with PAN.

Conclusion

An imbalance between IL-1 and IL-1Ra may predispose to inflammatory arthritis and arteritis, in the presence of other as yet unknown genetically influenced factors. Thus, endogenous IL-1Ra may serve an important role in preventing or limiting organ damage under local conditions, leading to excess IL-1 production. Possibly sIL-1Ra, either

present in the circulation as a product of hepatocytes, or produced locally from tissue macrophages, may serve a necessary regulatory function. Alternatively, icIL-1Ra1 production by fibroblasts, macrophages, endothelial cells, or cells of epithelial origin may restore the local cytokine balance in diseased organs. A deeper understanding of the presence and regulation of production of IL-1Ra isoforms, and of their biologic effects on or in specific cells or tissues, may clarify whether a relative imbalance between IL-1 and IL-1Ra plays an important predisposing role in acute and chronic inflammatory diseases in humans.

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Authors' affiliations: William P Arend (Division of Rheumatology, University of Colorado Health Sciences Center, Denver, Colorado, USA) and Cem Gabay (Division of Rheumatology, University Hospital of Geneva, Geneva, Switzerland)

Correspondence: William P Arend, Division of Rheumatology B115, University of Colorado Health Sciences Center, 4200 East Ninth Avenue, Denver, Colorado, 80262, USA. Tel: 303 315 6666; fax: 303 315 5540; e-mail: William.Arend@uchsc.edu