Original Article

Interleukin-1 Receptor Antagonist And Their Roles In Different Diseases

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Abstract

The interleukin 1 receptor antagonist (IL1Ra) family of molecules now includes one secreted isoform (sIL1Ra) and three intracellular isoforms (icIL1Ra1, 2, and 3). Extensive evidence indicates that the sole biological function of sIL1Ra seems to be to competitively inhibit IL1 binding to cell-surface receptors. Although intracellular IL1Ra1 may be released from keratinocytes under some conditions, the intracellular isoforms of IL1Ra may carry out additional as yet poorly defined roles inside cells. Maintenance of a balance between IL1 and IL1Ra is important in preventing the development or progression of inflammatory disease in certain organs. Both the secreted and intracellular isoforms of IL1Ra contribute to maintenance of this balance. An allelic polymorphism in intron 2 of the IL1Ra gene (IL1RN*2) predisposes to the development or severity of a variety of human diseases largely of epithelial cell origin. Both the impaired production of IL1Ra and the overproduction of IL1â are related to the presence of this allele. Restoration of the balance between IL1Ra and IL1 through a variety of approaches is a therapeutic goal in specific chronic inflammatory diseases.

Keywords: IL1Ra, Acute Phase Protein, CNS.

INTRODUCTION

The interleukin-1 receptor antagonist (IL-1Ra) is the first described naturally occurring specific receptor antagonist of any cytokine or hormone-like molecule. The IL-1-inhibitory biologic activity of this material was first described in the early 1980s, with the cloning and properties of recombinant IL-1Ra described in 1990. Published reviews on IL-1Ra have emphasized the biochemical properties of this unique cytokine, the mechanisms of its production, and the characterization of both in vitro and in vivo effects (**1**).

Structure nd Production

The identification of different isoforms of IL-1Ra suggests that this cytokine, and the IL-1 family in general, may play complex roles in biology. Studies on the transcriptional regulation of IL-1Ra, on polymorphisms in the IL-1Ra gene, and on the crystal structure of IL-1Ra are beginning to clarify how this unique cytokine is produced and how it functions. The extensive in vitro investigation of IL-1Ra is now being extended to in vivo studies, allowing a more complete picture to emerge of the regulation and characteristics of this cytokine in a full biologic environment **(2, 3).**

Crystal Structure and Mechanism of Action

The possible mechanism whereby IL-1Ra binds to IL-1 receptors with avidity nearly equal to the two agonists, yet which fails to activate cells. Both types I and II IL-1 receptors are members of the Ig superfamily and possess three Ig-like domains in the extracellular portions. The extracellular domains were enzymatically cleaved and were present as soluble receptors both in the pericellular environment and in the circulation (**4**).

Soluble type II IL-1 receptors bound IL-1_ much more avidly than IL-1Ra and may function as inhibitors of IL-1 action in vivo. In contrast, soluble type I IL-1 receptors bound IL-1Ra almost selectively. Thus, soluble type I IL-1 receptors might bind exogenously produced IL-1Ra in vivo and block or neutralize its natural anti-inflammatory actions. The results of early studies indicated that IL-1_ and IL-1Ra possess an identical _-pleated sheet structure and that residues in the common open-faced surface of both molecules bind to the same site on the type I IL-1 receptor. However, IL-1_ interacted with two additional sites on the receptor, a _-bulge between strands 4 and 5 and a region around aspartic acid at residue. These interactions were thought to be responsible for the difference in biologic activity between IL-1_ and IL-1Ra. The results of more recent sitedirected mutagenesis studies confirm these conclusions. Site A on the side of the _-barrel structure in type I IL-1 receptors bound all three ligands; however, site B in the open end of the _-barrel bound both IL-1 _ and IL-1_ but not IL-1Ra (**2)**.

The interaction of the two IL-1 agonists with site B is thought to be responsible for induction of biologic responses in target cells. More detailed information on the structure of the IL-1 ligands was obtained using NMR spectroscopy and X-ray crystallography. The detailed crystal structures of complexes of soluble type I IL-1 receptors and IL-1 or IL-1Ra were recently described. Both ligands bound to the soluble receptor with 1:1 stoichiometry, and the three Ig domains of the receptor were wrapped around both ligands. The receptor binding regions in IL-1_ and IL- 1Ra previously identified by site-directed mutagenesis interacted with all three domains of the receptor. However, in IL-1Ra the charged region corresponding to the IL-1_ trigger site (Lys at positions 92-94) did not interact with the third domain of the soluble type I IL-1 receptor. A truncated receptor consisting of domains 1 and 2 bound IL-1 _ and IL-1_ with low affinity but bound IL-1Ra with high affinity. Thus, domain 3 was necessary to achieve high-affinity binding with the two IL-1 agonists, in addition to generation of agonist activity (**2)**.

The identification and characterization of a second subunit of the IL-1 receptor complex, the IL-1 accessory protein (IL-1R AcP), has further clarified the biochemistry and biology of the IL-1 system. The IL-1R AcP is a 570-amino acid protein of the Ig superfamily and possesses limited homology to both types I and II IL-1 receptors. The accessory protein formed a complex with either IL-1 _ or IL-1_ and the type I IL-1 receptor, but IL-1Ra failed to form this complex. The observation that IL-1 _ but not IL-1Ra led to an aggregation of the type I IL-1 receptors at the cell surface, which was associated with induction of biologic responses, was due to formation of a complex with the IL-1R AcP. Cell lines that did not express the IL-1R AcP failed to demonstrate responses to IL-1; these responses were restored by transfection of the cDNA for the accessory protein. Thus, the conformational changes induced in the ligand-receptor complex by tight binding of the IL-1 agonists to domain 3 of the receptor, not seen with IL-1Ra, may allow a secondary interaction of this complex with the IL-1R AcP. Although the IL-1R AcP molecule itself did not bind the IL-1 agonists, association of IL-1R AcP with the ligand-receptor complex led to a fivefold increase in the affinity of binding of IL-1 to the receptor. Signal transduction in responding cells appeared to require intact cytoplasmic domains of both the receptor and IL-1R AcP (**5)**.

Role in Biology

In spite of extensive studies on IL-1 over the past two decades, the important roles that this cytokine may play in normal biology remain unclear. Furthermore, whether the function of IL-1Ra is solely to regulate the agonist effects of extracellular IL-1 in normal biologic processes or in pathophysiological conditions also is unknown. Studies on the tissue distribution of IL-1Ra and on the functional consequences of overexpression or an absence of expression of IL-1Ra in transgenic or knockout mice, respectively, may clarify some possible roles of this cytokine in normal biology. Lastly, intracellular IL-1Ra may carry out unique biologic functions within the cells that produce it **(6)**.

IL-1Ra as an Acute Phase Protein

Results of clinical studies have described elevated IL-1Ra levels in the peripheral blood of patients with sepsis, chronic rheumatic diseases, and following surgical trauma. In children with juvenile chronic arthritis, peripheral blood IL-1Ra levels were found to correlate with IL-6 levels. Furthermore, injection of humans with IL-1 or IL-6 led to a rapid rise in blood IL-1Ra levels. Since IL-1 and IL-6 are known to regulate the production of acute phase proteins (APP) by the liver, such as C-reactive protein, this observation suggested that IL-1Ra may behave as an APP (**7)**.

Both cultured human hepatocytes and the human hepatoma cell line HepG2 produced sIL-1Ra in response to stimulation with IL-1 and IL-6. This production was increased by dexamethasone, consistent with the enhancing effects of glucorticoids on production of APP. The HepG2 cells contained only the sIL-1RamRNAand not the icIL-1RamRNA, consistent with the results of earlier studies with a liver cDNA library. In addition, transfection studies indicated that only the sIL-1Ra promoter was active in the HepG2 cells. Lastly, transfection experiments with the cloned sIL-1Ra promoter indicated that the response to IL-1 and IL-6 in HepG2 cells was mediated by NF-_B and

C/EBP (NF-IL-6) elements in the sIL-1Ra promoter, identical to other APP. These results may explain the earlier clinical observations of elevated blood levels of IL-1Ra in various diseases and may indicate a unique role in biology for this cytokine (**8, 9)**.

Possible Function of Intracellular Variants

Regulation of the effects of IL-1 in the cell microenvironment would appear to be the major biologic role of extracellular sIL-1Ra. Although icIL-1Ra may be released from dying or dead cells, the fact that at least two isoforms of intracellular IL-1Ra have been maintained during evolution suggests that they may be involved in additional functions inside cells. The results of cell fractionation studies in our laboratory indicated that intracellular IL-1Ra in both monocytes and neutrophils remained primarily in the cytoplasm **(10)**.

In addition to its role as an extracellular cytokine, IL-1, presumably IL-1_, likely plays an internal autocrine role as well. IL-1 _ binding to plasma membrane type I IL-1 receptors led to internalization of the receptor ligand complex with eventual nuclear localization. Intracellular IL-1 _ may play a role in cell growth and differentiation as treatment of human endothelial cells with an IL-1 _ antisense oligodeoxynucleotide prevented senescence and prolonged the in vitro lifespan **(2).**

Furthermore, mature IL-1 _ delivered directly into the cytoplasm of EL4 thymoma cells by transfection was biologically active in induction of IL-2 production, suggesting a possible role for intracellular IL-1 _ that did not require the N-terminal propiece or plasma membrane IL-1 receptors. The results of studies indicated that the constitutive expression of high levels of intracellular IL-1 _ in scleroderma fibroblasts was due to enhanced transcription and, most importantly, determined the fibrogenic phenotype of these cells . Lastly, the 33-kDa intracellular precursor of IL-1_ inhibited Fas-mediated apoptosis by acting as a competitive substrate for IL-1_ converting enzymes (ICE) required for apoptosis (**11)**.

Whether icIL-1Ra influences any of these purported activities of intracellular IL-1 is not known. Intracellular IL-1Ra reportedly exhibits an intrinsic autocrine role in two different experimental systems. Ovarian cancer cells possessing high levels of icIL-1Ra displayed impaired IL-1-induced IL-8 and GRO mRNA expression in comparison to cells that did not produce icIL-1Ra. This effect of icIL- 1Ra was not secondary to blockade of plasma membrane receptors for IL-1 but appeared to be mediated by destabilization of the chemokine mRNA. In studies from our laboratory, high levels of both constitutive and cytokine induced icIL-1Ra in keratinocyte cell lines and in transfected fibroblasts were associated with decreased plasma membrane expression of ICAM-1 **(12)**.

IL-1RA IN DISEASE

Although the role of IL-1Ra in normal physiology remains to be further clarified, the use of specific neutralizing antibodies has demonstrated the importance of endogenous IL-1Ra as a natural anti-inflammatory protein in animal models of disease. In addition, the pattern of endogenous IL-1Ra expression in some human diseases has been described, with the clear implication that this molecule may be an important element of host defense in the human as well. The administration of recombinant IL-1Ra has clarified the role of IL-1 in animal modelsof disease and has established a foundation for clinical trials using the recombinant protein in human diseases. Finally, the delivery of IL-1Ra by gene therapy in animal diseases has led to the first trials of gene therapy with the IL-1Ra cDNA in patients with rheumatoid arthritis (**13)**.

Role of Endogenous IL-1Ra in Host Defense

Studies on the presence of IL-1Ra in animal models of disease and in human diseases have been summarized in earlier reviews. Additional publications over the past few years have indicated that although IL-1Ra is produced locally in tissues during active disease and can be measured systemically, the local balance of net biologic function remains in favor of the agonists IL-1_ and IL-1_. As an example, evidence regarding the importance of IL-1 and tumor necrosis factor (TNF)-_ in rheumatoid arthritis has been reviewed (**14)**.

RHEUMATIC DISEASES

Elevated blood levels of IL-1Ra have been described in patients with juvenile chronic arthritis, polymyositis, systemic lupus erythematosus, and rheumatoid arthritis. The high serum levels in lupus patients were correlated with disease activity and were accompanied by both high IL-1Ra mRNA levels in peripheral monocytes and enhanced IL-1Ra production after culture of these cells on adherent IgG (**15)**.

An important anti-inflammatory role of endogenous IL-1Ra was suggested by observations in patients with knee arthritis from Lyme disease. A higher ratio of IL-1Ra to IL-1_ was present in the synovial fluids of those patients with

acute arthritis who recovered more rapidly than in patients with a more protracted course. These results suggested either that the synovial fluid IL-1Rawas derived, at least in part, from production by cells in the synovial tissue or that the neutrophil-derived IL-1Ra in the fluid phase was able to penetrate the tissue and dampen the inflammation. IL-1Ra protein and mRNA were localized to macrophages in the sublining and perivascular areas in rheumatoid synovial tissue and were present at lower levels in the intimal lining layer **(16)**.

INFECTIOUS DISEASES

Numerous examples have been published of the presence and role of endogenous IL-1Ra in infectious diseases, both in animal models and in human disease. High IL-1Ra levels (up to 55 ng/ml) were described in the plasma of acutely ill patients either after surgery, with adult sepsis, with neonatal sepsis, or presenting with fever of unknown origin subsequently proven to be due to infection, neoplasm, or inflammatory disease **(17)**.

CENTRAL NERVOUS SYSTEM

Many investigators have described the presence of all three members of the IL-1 system in the brain and have explored the role of these cytokines in diseases of the central nervous system. IL-1Ra mRNA was localized in the rat brain by in situ hybridization histochemistry to the paraventricular nucleus of the hypothalamus, hippocampus, and cerebellum. Chronic intracerebroventricular infusion of IL-1_ in rats induced expression of mRNAs for all three ligands of the IL-1 system in the same areas, particularly in cells in close proximity to the microvasculature (17**)**.

Cytokine synthesis and release, particularly of TNF-_ and IL-1_, are thought to mediate tissue damage in focal cerebral ischemia, probably during the reperfusion phase. IL- 1Ra is capable of crossing the blood-brain barrier; thus, protein measured in the brain may be of peripheral or local origin (18**)**.

Plasma IL-1Ra levels were elevated in stroke patients along with other APP, with a direct relationship to the size of the infarct. IL-1Ra mRNA was increased in focal areas in the rat brain after induced ischemia, reaching a maximum at 12 h, somewhat later than the peak presence of IL-1. In addition, in response to systemic inflammation, large amounts of sIL-1Ra mRNA were found only in the anterior pituitary, whereas IL-1_ mRNA was present in many other areas of the brain. These observations suggest that endogenous IL-1Ra production in the brain may play an important anti-inflammatory role in the local response to ischemia as well as in regulation of the neuroendocrine system (19**)**.

LARGE INTESTINE

Endogenous IL-1Ra has also been examined in the large intestine of patients with inflammatory bowel disease (IBD). The expression of IL-1Ra mRNA relative to that of IL-1_ appeared to be low in the colonic tissue of patients with Crohn's disease or ulcerative colitis in comparison to that from patients with inflammation secondary to infection. In further studies, a reduced ratio of IL-1Ra to IL-1_ was observed in colonic tissue from patients with active IBD in comparison to those with self-limited colitis. The importance of endogenous IL-1Ra in host responses to colonic inflammation was demonstrated by the observation that anti-IL-1Ra antibodies led to prolonged intestinal inflammation and increased mortality in a rabbit model of colitis induced by formalin and immune complexes. These results all indicate that a relative deficiency in local IL-1Ra production may predispose to chronic inflammation in IBD **(20)**.

LUNG

IL-1Ra production in the lung also has been implicated in modulating local inflammatory diseases. Tissue homogenates and BAL from patients with idiopathic pulmonary fibrosis demonstrated elevated IL-1Ra levels compared with samples from normal controls. The IL-1Ra protein was found in hyperplastic type II pneumocytes, macrophages, and fibroblasts, with the latter cells exhibiting an enhanced production of IL-1Ra in vitro in response to TGF-_. Both IL-1_ and IL-1Ra were present in the bronchial epithelium of patients with asthma, and plasma levels of IL-1Ra increased during acute attacks of asthma. The relative amounts of IL-1Ra and IL-1_ in BAL were thought to be important in neutrophil-induced airway inflammation in patients with pan-bronchiolitis. Low concentrations of the anti-inflammatory cytokines IL-10 and IL-1Ra in the BAL of patients with early acute respiratory distress syndrome were closely associated with a poor prognosis **(21)**.

KIDNEYS

IL-1Ra has also been examined in renal diseases. Studies in normal rats indicated that the kidneys contributed _80% to the clearance of infused IL-1Ra, with either extensive reabsorption and/or metabolism occurring after filtration in the glomeruli. The highest urinary IL-1Ra levels were found in normal children in comparison to those with acute or recurrent pyelonephritis. Elevated plasma levels of IL-1Ra were present in patients with chronic renal failure, reflecting inadequate clearance as well as possibly increased production. Glomerular expression of IL-1Ra mRNA was readily detected in rats with antiglomerular basement membrane antibody-mediated glomerulonephritis. These observations suggest that the ratio of endogenous IL-1Ra to IL-1_ may not be adequate to inhibit inflammation in various forms of acute renal diseases **(22)**.

REPRODUCTIVE SYSTEM

The IL-1 system also may be involved in normal ovarian function as well as in the uterus during pregnancy and delivery. IL-1Ra mRNA was present in whole ovarian extracts. IL- 1Ra was found in both granulosa and thecal cells in developing follicles, with an increase in the levels of IL-1Ra in thecal cells during ovulation. High concentrations of IL-1Ra, up to to 70 ng/ml, were detected in human amniotic fluids. The highest concentrations were present during the third trimester; the major source is probably fetal urine. The amniotic fluid and neonatal urine concentrations of IL-1Ra were higher for female fetuses than for male, and these levels were increased in preterm labor precipitated by intrauterine infection. IL-1Ra production by decidual cells was stimulated by IL-4 and TGF-_, with decidual IL-1Ra possibly playing a negative regulatory role in preterm labor precipitated by intrauterine infection (**23).**

REFRACTORY EPILEPSY

There is a clinical evidence demonstrating an increased production of inflammatory cytokines in association with epileptic seizures**.** In experimental models; interleukin-1beta (IL-1β) appears to be proconvulsant and neurotoxic whereas interleukin-1 receptor antagonist (IL-1Ra) is anticonvulsant and neuroprotective**.** The role of IL-1 is less well defined, but there are some data suggesting that IL-1 acts more as a proconvulsant **(24).**

In humans, the levels of IL-1 and IL-1Ra were increased after epileptic seizures both in cerebrospinal fluid (CSF) and plasma within 24 h after secondarily generalized tonic–clonic **(25)** and focal seizures **(24).**

Indeed, in multiple distinct animal models of epileptogenesis, pharmacologic blockade of IL-1 through the use of the IL-1 receptor antagonist (IL-1RA) reduced seizures and signs of cellular injury **(26),** leading to the proposal that medications for peripheral autoinflammation could be beneficial for intractable epilepsy **(27).**

Conclusion

IL1Ra can be used as a diagnostic marker in a variety of chronic inflammatory diseases.

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