REVIEW

Interleukin-1 in Disease

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Abstract. As outlined in this review, the inflammatory cytokine interleukin-1 (IL-1) mediates a number of pathological processes associated with disease. To prove a role for IL-1, a variety of modalities have been used to block the production and/or activity of IL-1. These include agents which inhibit or reduce 1) IL-1 transcription and/or synthesis, 2) the processing of pro-IL-1 β into its mature forms, 3) the secretion of IL-1 β , 4) the activity of IL-1 using neutralizing anti-IL-1 antibodies or 5) soluble (extracellular) IL-1 receptors, 6) the ability of IL-1 to bind to its receptors using receptor blockade, 7) the availability of surface receptors using agents which down-regulate receptor expression or (8) agents which affect IL-1-mediated signal transduction. Some of these modalities have already entered clinical trials. Clearly, the therapeutic advantage of reducing the activity of IL-1 resides in preventing its deleterious biological effects without interfering with host defense and homeostasis. For example, blocking IL-1-induced prostaglandins is one target in treating inflammatory diseases. Drugs inhibiting cyclooxygenase have well-known toxicities because they block the normal physiologic synthesis of prostaglandins in many tissues such as platelets and gastric lining cells. Blocking IL-1, in contrast, reduces only that portion of prostaglandin synthesis due to elevated IL-1, sparing the synthesis of prostaglandins necessary for physiologic homeostasis. A similar case can be made for endogenous nitric oxide. Thus, there is a unique pharmacological advantage to blocking IL-1 in disease. (Keio J Med 43 (3): 131–136, September 1994)

Key words: cytokines, soluble receptors, receptor antagonist, host defense

Introduction

Interleukin-1 (IL-1) consists of two structurally related polypeptides: IL-1 α and IL-1 β , each of which has a broad spectrum of biological activities. There is a third structurally related IL-1 molecule, IL-1 receptor antagonist (IL-1Ra) which inhibits the activities of IL-1. Among the properties of IL-1 (α and β) are the ability to induce fever, sleep, anorexia, and hypotension. IL-1 stimulates the release of pituitary hormones, increases the synthesis of collagenases, resulting in cartilage destruction, and stimulates prostaglandin production, leading to a decrease in pain threshold. IL-1 also has been implicated in destruction of beta-cells of the islets of Langerhans, growth of acute and chronic myelogenous leukemia cells, inflammation associated with arthritis and colitis, and development of atherosclerotic plaques.

IL-1 actions can be direct on specific target tissues or

indirect as an effector molecule. However, most activities of IL-1 are indirect. An example is the effect of IL-1 in the septic shock syndrome in which infection leads to the synthesis and release of large amounts of IL-1 that induce hypotension via the induction of platelet activating factor (PAF), prostaglandins (PG) and nitric oxide (NO). Another example of IL-1 as an effector molecule is autoimmune disease in which IL-1 contributes to tissue destruction because of its ability to stimulate collagenases and prostaglandins and induce bone resorption.

In most autoimmune diseases, T lymphocytes and not IL-1-producing phagocytic cells are the critical determinants of disease. The various treatments such as cyclosporine affect T-lymphocytes rather than mononuclear phagocytes. Any reduction in IL-1 production associated with immunosuppressive therapies is likely secondary to reduced T-lymphocyte stimulation of IL-1-producing cells. Reducing the production of IL-1 in autoimmune diseases reduces the inflammatory effects

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of IL-1 on target tissues such as the synovium, pancreatic islet cells or intestinal lining cells.

Inhibition of Synthesis of IL-1

IL-1 is rapidly synthesized by nearly every nucleated cell. Monocytic phagocytes when stimulated by microbial products produce the largest amounts of IL-1 per cell. A number of drugs, cytokines and other substances inhibit IL-1 production. Their action is not specific, however, since the production of other cytokines is usually inhibited as well. These agents may act at the level of transcriptional inhibition (corticosteroids) or translation inhibition (the dual inhibitors of cyclooxygenase and lipoxygenase). Targeting of specific nuclear transcription factors such as NF κ B or AP-1 are being investigated.

Agents that reduce the transcription or translation of IL-1 are dependent on the type of stimulation of the cell being employed. For example, using endotoxin as a stimulus, interferon- γ (IFN γ) enhances IL-1 translation whereas using IL-1 itself as a stimulant of IL-1 production, IFN γ inhibits IL-1 synthesis.^{1,2} Another example is the effect of cyclooxygenase inhibitors. Using endotoxin as a stimulus, indomethacin enhances IL-1 translation whereas using IL-1 itself as a stimulant of IL-1 production, indomethacin inhibits IL-1 synthesis.³ Histamine, which increases cyclic AMP through the H₂ receptor, enhances IL-1-induced IL-1.³ In fact, increases in cyclin AMP are likely the mechanism by which PG augment IL-1-induced IL-1 production. The effect of histamine is at the level of translation and not transcription. Thus, this mechanism may explain, in part, the efficacy of non-steroidal anti-inflammatory agents.

Inhibition of the proteolytic cleavage of the precursor of IL-1 β

This is a mechanism for reducing IL-1 activity. IL-1 is first synthesized as a larger, precursor molecule. The precursors for IL-1 α and β have molecular weights of 31,000 Da, but, unlike most proteins, both forms of IL-1 lack leader sequences that enable a precursor proteins to be cleaved to "mature" sizes. For both forms of IL-1, the mature sizes are 17–22,000 Da. Most IL-1 α remains in the cytosol where it may function more as an autocrine or juxtacrine messenger rather than as an extracellular mediator. There is also evidence that the precursor of IL-1 α is transported to the surface of the cell where it has been identified as "membrane" IL-1. Surface-bound IL-1 α precursor is biologically active.

On the other hand, a considerable amount of IL-1 β is transported out of the cell where it can enter the circulation. Various mechanisms for transport include exocytosis from vesicles, active transport via multiple drug

resistance carrier proteins, "leakiness" or following cell death. Unlike the IL-1 α precursor, the IL-1 β precursor requires cleavage for optimal biological activity. Several common enzymes (cathepsin G, elastase) will cut the IL-1 β precursor into smaller and more active forms. However, one particular protease appears highly specific for cutting the IL-1 β precursor from 31,000 to 17,500, its most active form.^{4,5} This enzyme is known as the IL-1 β converting enzyme (ICE). ICE is a member of the cysteine protease family. ICE does not cleave the IL-1 α precursor. Blocking ICE with ICE specific substrate inhibitors reduces the amount of mature IL-1 β produced by activated monocytes.⁴

Neutralization of IL-1 Activity

Neutralizing antibodies to IL-1 β reduce endotoxin-induced fever in animals⁶ and decrease the proliferation of monocytic leukemia cells *in vitro*.⁷ Although antibodies to IL-1 have potential clinical value, most attention has focused on the development of soluble IL-1 receptors in order to neutralize IL-1.

Soluble Receptors as a Strategy for Reducing IL-1 Activity

There are two IL-1 cell surface receptors (IL-1R). The type I IL-1R (IL-1RI) is found on most cells and appears to be important for transducing IL-1 activity. The type II IL-1 receptor (IL-1RII), is found primarily on neutrophils, monocytes, bone marrow cells and B-lymphocytes. The two IL-1R are members of the immunoglobulin superfamily and their binding sites for IL-1 are structurally similar. The IL-1RI receptor has a cytoplasmic segment and a higher affinity for IL-1 α than IL-1 β , whereas IL-1RII receptor has a short cytoplasmic segment and a higher affinity for IL-1 β than IL-1 α . Soluble receptors are the extracellular portions of the receptors that are cleaved from the cell surface. The function of the type II receptor appears to one of binding IL-1 without transmitting a signal. As such, it acts as a "decoy" for the type I receptor and reduces the activity of IL-1.⁸

Soluble IL-1RI and IL-1RII act like antibodies in that they specifically bind IL-1 and thereby prevent IL-1 binding to its receptors on cells. For example, administration of soluble IL-1RI receptors to mice with cardiac allografts increased graft survival and decreased lymph node swelling.⁹ This benefit of blocking IL-1 action is likely to be the result of decreased inflammation rather than immunosuppression. Early studies in humans suggest that soluble IL-1RI receptors can be administered safely and that they block inflammation. Since they are a component of the naturally occurring receptor, they are unlikely to elicit an immune response to a foreign

antigen.

A naturally occurring soluble form of an IL-1 receptor has been identified in body fluids.¹⁰ This soluble IL-1 receptor is generated by proteolytic cleavage of the extracellular portion of the type II receptor. It specifically binds IL-1 and therefore prevents IL-1 binding to IL-1 receptors on cell surfaces. Low levels of this soluble receptor are found in the circulation of healthy subjects. It has been found in the synovial fluid of patients with rheumatoid arthritis and supernatants from stimulated peripheral blood mononuclear cells. Its concentrations in the circulation are increased in patients during acute reactivation of rheumatoid arthritis.

Blocking IL-1 Receptors

In animals, administration of antibodies to IL-1 type I receptors reduces inflammation and anorexia due to endotoxins and other inflammation-inducing agents.¹¹ However, considerable information has accumulated pertaining to the blockade of IL-1 receptors using the naturally occurring IL-1Ra.^{12,13} This IL-1 antagonist belongs to the IL-1 gene family, it is produced by the same cells, and it has the same molecular size of mature IL-1 and is structurally related to it. Similar to the findings on IL-1, IL-1Ra is not present in peripheral blood monocytes or plasma from normal subjects but is found in the keratinocytes of the skin and in neuronal cells. IL-1Ra binds to cellular IL-1 receptors but this binding does not initiate any biological response. Lacking biological activity, it can be given in doses sufficient to occupy IL-1 receptors and therefore prevent *bona fide* IL-1 from binding to these same receptors.

Since both IL-1Ra and soluble IL-1R are specific inhibitors of IL-1, any modification of disease with the use of these agents would indicate a role for IL-1 in that

particular disease. In fact, administration of IL-1Ra to animals, like administration of soluble IL-1R, reduce the severity of inflammation and some pathologic processes and improves survival. Examples of reduction in the severity of disease or its manifestations associated with IL-1 blockade are shown in Table 2.

IL-1Ra appears to be a pure receptor antagonist. In a Phase I trial in normal subjects, plasma IL-1Ra concentrations of 25 to 30 mg/ml caused no symptoms or changes in vital signs and did not alter white blood cell counts or routine biochemical and endocrinologic tests.¹⁴ These results are consistent with the concept that IL-1 does not play an important role in normal physiologic homeostasis.

IL-1Ra has been given to human subjects injected with endotoxin. In this model, there is an associated neutrophilia and transient reduction in the proliferation of mononuclear cells to mitogens. In these volunteers, IL-1Ra was administered intravenously at 1, 5 or 10 mg/kg over 3 hours. The endotoxin associated neutrophilia and transient reduction in the proliferation of mononuclear cells to mitogens was reversed by IL-1Ra.¹⁵ However, this was observed only at the 10 mg/kg dose.

Blocking IL-1 in the Septic Shock Syndrome

The mechanism of IL-1-induced shock appears to be its ability to increase mediator molecules such as PAF, PG and NO. These substances are potent vasodilators and induce shock in experimental animals. Blocking the action of IL-1 prevents the synthesis and release of these

Table 1 Reducing IL-1 Activity

Strategy	Agents ¹⁾
Reduced Production	Corticosteroids; ω -3 fatty acids; NSAIDs, CO/LO inhibitors; TGF β ; IL-4; IL-10; IL-13
Decreased Processing	Inhibition of specific IL-1 convertases (ICE)
Neutralization	Anti-IL-1 antibodies; soluble IL-1 receptors
Receptor Blockade	Anti-receptor antibodies; receptor antagonists
Downregulation of Type I Receptor	TGF β ; IL-1
Upregulation of Type II Receptor	IL-4

1) Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; CO/LO inhibitors, cyclooxygenase/lipoxygenase inhibitors; TGF β , transforming growth factor β ; ICE, IL-1 converting enzyme.

Table 2 Reduction in Severity of Disease by Blocking IL-1¹⁾⁻³⁾

Death in Mice and Rabbits from Endotoxin
Death in Newborn Rats from <i>Klebsiella pneumoniae</i>
Shock in Rabbits and Baboons from <i>E. coli</i> or <i>Staphylococcus epidermidis</i>
Arthritis in Mice and Rats
Inflammatory Bowel Disease in Rabbits
Onset of Spontaneous Diabetes in the BB Rat
Hypoglycemia and CSF Production in Mice Following Endotoxin
Proliferation and CSF Production of Acute Myeloblastic and Chronic Myelogenous Leukemia Cells
Neutrophil Accumulation in Inflammatory Peritonitis
Sciatic Nerve Regeneration in Mice
Graft vs Host Disease in Mice
Endotoxin-induced Pulmonary Inflammation in Rats
Heart Allograft Rejection
Experimental Autoimmune Encephalomyelitis
Anorexia during the Inflammatory Response in Mice

1) Data are compiled, in part, from references.^{12,13,46} 2) Abbreviations: BB, bio-breeding; CSF, colony stimulating factor. 3) These studies used IL-1Ra to block IL-1, except for heart allograft rejection and experimental autoimmune encephalomyelitis where soluble IL-1 receptors were employed^{9,47} and in reducing anorexia associated with inflammation where antibodies to the IL-1 receptor were used.¹¹

mediators. In animals a single intravenous injection of IL-1 decreases mean arterial pressure, lowers systemic vascular resistance and induces leukopenia and thrombocytopenia.^{16,17} In humans intravenous administration of IL-1 also decreases blood pressure rapidly and doses of 300 ng/kg or greater may cause severe hypotension.¹⁸

There have been two clinical trials testing the efficacy of IL-1Ra in patients with the sepsis syndrome. The first trial compared 4 groups 25 patients each, placebo and three doses of IL-1Ra infused over 72 hours. The two highest doses of 1 or 2 mg/kg/hr (5 or 10 grams over 72 hours) revealed a significant reduction in 28 day mortality compared to placebo. The mortality rate in the placebo group was 44% and the reduction in the two groups of patients treated with IL-1Ra was 40 and 63%, respectively ($p = 0.015$).¹⁹

The study was expanded to 900 patients at 63 hospitals in 8 countries. This Phase III study was double-blinded, placebo controlled and tested the two doses of IL-1Ra (1 and 2 mg/kg/hr for 72 hours). Analysis of 893 patients revealed a mortality rate of 34% in the placebo group, 31% in patients receiving 1 mg/kg/hr and 29% patients treated with 2 mg/kg/hr ($p = 0.22$). However, patients from the study were analyzed separately according to the severity of their disease upon entry as assessed by APACHE II (acute physiologic and chronic health evaluation) scores with a high risk of mortality ($>24\%$). In this subgroup, treatment with the high dose of IL-1Ra was statistically significant. In this high risk mortality group (595 patients), mortality in the placebo group was 45%, 37% in the group treated with 1 mg/kg/hr and 35% in patients receiving 2 mg/kg/hr (22% reduction in mortality, $p = 0.032$, Wilcoxon).²⁰

These data support laboratory and animal studies demonstrating that blockade of IL-1 is effective as the severity of disease increases whereas in less severe models, blocking IL-1 receptors has little or no effect.^{21,22} It also confirms previous studies that high circulating levels of IL-1Ra (>20 mg/ml) are required for IL-1 receptor blockade *in vivo*.²³

Blocking IL-1 in Inflammatory Diseases

The best evidence that IL-1 contributes to the pathogenesis of inflammatory disease can be found in studies of animals with acute, immune complex-mediated colitis in which blocking IL-1 action with IL-1Ra reduces the severity of acute inflammation and decreases eicosanoid concentrations in affected bowel.²⁴ A likely mechanism for these is that blocking the action of IL-1 reduces the amount of IL-8 that is produced in the inflamed bowel as it does in peripheral blood monocytes *in vitro*.²⁵ The increased production of IL-1 and IL-8 in tissue specimens from patients with inflammatory bowel disease appears to come from mononuclear cells in the lamina propria of

the bowel wall. Based on these results, clinical trials of IL-1Ra have been initiated in patients with ulcerative colitis.

Blocking IL-1 in Acute and Chronic Myelogenous Leukemia

IL-1 is a growth factor for acute and chronic myelogenous leukemia cells. Although IL-1 β mRNA cannot be detected in peripheral blood cells or bone marrow aspirates from normal subjects, it can be detected in cells from patients with acute myelogenous leukemia.²⁶ In addition, these leukemia cells produce an IL-1-like activity²⁷ as do chronic granulocytic leukemia cells of the juvenile type.²⁸ These results do not necessarily implicate IL-1 as a cause of these leukemias. However, antibodies to IL-1 β significantly reduce the spontaneous proliferation and colony formation of these cells *in vitro*,⁷ and IL-1Ra and an IL-1 inhibitor from human M20 leukemia cells similarly decrease the proliferation and colony formation of leukemic cells.^{26,29,30} Anti-IL-1-based therapy may be useful to inhibit or synchronize the growth of the leukemia cells so that they become more vulnerable to chemotherapeutic agents.

The IL-1 specific precursor-converting enzyme is found in large amounts in myelogenous leukemia cells.⁵ One approach to reduce the action of IL-1 in myelogenous leukemia therefore would be to prevent the proteolytic cleavage of the IL-1 precursor to an active form.

Does blocking IL-1 impair host defense mechanisms?

Patients with sepsis have plasma levels of IL-1 β in the range of 250–500 pg/ml and rarely over 1 ng/mg.³¹ In some studies in this patient population, there is a direct correlation between the level of plasma IL-1 β and mortality.³² However, plasma concentrations of 30 mg/ml of IL-1Ra (representing a 10,000 fold molar excess) sustained over three days in humans with the septic shock syndrome is associated with improved survival. In healthy human subjects, these same concentrations sustained over 3 hours appear to be without detectable detrimental effects including tests of immune responses.^{14,15} This is consistent with *in vitro* experiments in which blocking IL-1 did not diminish the response of human T-cells to antigens.³³ Although there are no long term human data available at the present time, blocking IL-1 is likely to be safe, at least in the short term. Since the treatment of some IL-1-mediated diseases may require prolonged use, the question arises whether sustained blockade of IL-1 will weaken host defense mechanisms.

On the other hand, there is no dearth of experimental data illustrating a role for IL-1 in boosting natural host

defense mechanisms. For example, IL-1 protects the early stem cells against radiation damage,³⁴ can act as an adjuvant³⁵ and improves survival of granulocytopenic mice with lethal *Pseudomonas* infection.³⁶ How can IL-1 improve survival while blocking IL-1 may accomplish the same endpoint? Thus, small amounts of IL-1 produced in disease are necessary for maintaining natural host defenses, whereas high amounts of IL-1 are lethal. In some animal models of infections, blocking IL-1 increases mortality.^{37,38} Clinical evidence supports this concept. In some patients with sepsis, there is a statistically significant correlation with survival and production of IL-1 whereas failure to produce IL-1 is associated with death.^{31,39} However, blocking high levels of IL-1 as occurs in disease will reduce inflammation and the severe consequences of this cytokine. It is presently unclear whether total blockade of IL-1 is advisable or even achievable in the clinical setting.

Differential Production of IL-1 and IL-1Ra

The production of IL-1 and IL-1Ra is differentially regulated even in the same cell, although the same cell synthesizes both cytokines.⁴⁰ For example, in a cell stimulated with endotoxin, the expression of the IL-1 β gene takes place before IL-1Ra.⁴¹ In addition, triggering of the receptor for immunoglobulin on the monocyte stimulates IL-1Ra but not IL-1 production. In human subjects injected with a small amount of endotoxin, levels of IL-1Ra are 100-fold greater than IL-1 β .⁴² In contrast, unlike endotoxin, *Borrelia burgdorferi* induces more IL-1 β than IL-1Ra⁴³ and the expression of IL-1Ra in acute myelogenous leukemia cells is suppressed whereas IL-1 β is produced spontaneously.²⁶

Other cytokines may also contribute to the balance of IL-1 and IL-1Ra production during disease. For example, IL-4, transforming growth factor- β and IL-10 have the interesting property of increasing the synthesis of IL-1Ra but at the same time decreasing the synthesis of IL-1.⁴⁴ The efficacy of these cytokines in various inflammatory diseases may include their ability to regulate the balance of the agonist to the antagonist. A special example of this balance exists in the skin. Skin keratinocytes contain large amounts of IL-1a which remain within the cell. A form of IL-1Ra is found in 10-100-fold higher concentrations in the keratinocytes. This intracellular IL-1Ra may be serving a role as an anti-inflammatory agent buffering the inflammatory properties of IL-1 released from the skin following injury.⁴⁵

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