

Updates on cells and cytokines

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Biologic activities of IL-1 and its role in human disease

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The role of the polypeptide proinflammatory cytokine IL-1 family represents a group of proteins that have contrasting and synergistic biologic responses. IL-1 α and β and their precursor forms are heavily involved in the enhancement of inflammation and host defense. Within this family of gene products, there is also a naturally occurring receptor antagonist, IL-1ra, as well as a family of receptor proteins that have differential signaling functions and activities. The study of these proteins in human disease, including allergic disease and type 1 hypersensitivity responses, has led to a better understanding of the underlying general inflammation associated with these syndromes and has provided opportunities to look at new forms of intervention in allergic disease and asthma. (*J Allergy Clin Immunol* 1998;102:344-50.)

IL-1 is actually a family of 3 proteins, IL-1 α , IL-1 β , and the IL-1 receptor antagonist (IL-1ra), which is an antagonist that has no agonist activity compared with the first 2 family members.¹⁻³ IL-1 α and β are both synthesized as precursors. They are then reduced in size of the precursors, which are 31-kd to 17-kd mature forms, that have the greatest biologic impact. These mature forms of IL-1 α and β are potent enhancers of immune responses but also very potent inducers of acute phase responses and inflammation. They also have a wide variety of effects in immunity, inflammation, and host defense. The identification of IL-1ra as a potential antagonist leads to some very interesting possibilities for clinical intervention with cytokine antagonists that have only begun to be explored in terms of their efficacy. This review will also touch on the 2 forms of the IL-1 receptor (IL-1RTI and IL-1RTII).

The IL-1 family represents 3 peptides (IL-1 α , IL-1 β , and IL-1ra or IL-1 γ).^{4,5} Despite the minimal sequence

Abbreviations used

ICE: IL-1 β -converting enzyme

IL-1ra: IL-1 receptor antagonist

PG: Prostaglandin

similarity (~25% amino acid homology), IL-1 α and β have similar biologic activities, and all 3 proteins interact with similar affinities to the 2 IL-1 receptors.⁶ Type I receptors have been found on T cells, fibroblasts, endothelial cells, hepatocytes, and numerous other cells. Type I receptors have an extensive cytoplasmic domain and, following ligand binding, transduce the biologic effects attributed to IL-1.⁷ These are in contrast to Type II receptors, which have been identified on B cells, neutrophils, and bone marrow cells and which have a short intracellular domain. The *capture* and sequestration of IL-1 by these inactive Type II receptors may subserve an antiinflammatory function and hence are sometimes referred to as *decoy* receptors. Type II receptors are thought to function as the precursor for the soluble IL-1 binding factors, which antagonize IL-1 activity when shed.^{7,8} The capacity of IL-1ra to bind to the Type I (proinflammatory) IL-1 receptor without transducing biologic activities is the basis for its capacity to function as an antiinflammatory cytokine antagonist. IL-1 is primarily produced by cells of the mononuclear phagocytic lineage, but it is also produced by endothelial cells, keratinocytes, synovial cells, astrocytes, osteoblasts, neutrophils, glial cells, and numerous other cells. IL-1 production may be stimulated by a variety of agents, including endotoxins, other cytokines, microorganisms, and other antigens. Both IL-1 α and β are synthesized without a hydrophobic leader sequence as a less active 31-kd precursor.⁹ The mechanism for IL-1 secretion is unknown, but it is dependent on its cleavage by a specific converting enzyme into the active 17-kd form and may use ABC transporters with unique signal recognition particles.

One of the most important biologic activities of IL-1 is its function as a lymphocyte activating factor. T_{helper}-cell activation requires the interaction of antigen-MHC complex with the T-cell receptor. However, an additional, noncognate signal is also required for optimal T-cell

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activation and proliferation, and this is generally provided by IL-1. IL-1 enhances the production of T lymphocyte-derived cytokines, such as IL-2, as well as IL-2 receptors. In the absence of IL-1, either no immune response or a state of tolerance develops. In addition to these effects on T lymphocytes, IL-2 can augment B-cell proliferation and increases immunoglobulin synthesis. IL-1 synergizes with various colony-stimulating factors to stimulate early bone marrow hematopoietic progenitor cell proliferation. IL-1 administration produces a bone marrow-derived neutrophilia.

The production of IL-1 during the immune response produces a spectrum of changes associated with various illnesses. Interaction of IL-1 with the central nervous system is responsible for producing fever, lethargy, slow wave sleep, anorexia, and the release of corticotrophin-releasing factor. An IL-1 hepatocyte interaction inhibits production of *housekeeping* proteins (eg, albumin) and stimulates in turn the synthesis of acute phase response peptides (eg, amyloid peptide, C-reactive peptide, and complement). To provide the amino acids for this new protein synthesis, IL-1 stimulates the catabolism of muscle. IL-1 activity in joints stimulates synovial cell proliferation, cartilage and bone resorption, and collagen deposition. These effects of IL-1 on muscles and joints contribute to the myalgias and arthralgias associated with illness. IL-1 stimulates endothelial cell adherence of leukocytes through the upregulation of intercellular adhesion molecule. IL-1 also acts on blood vessels to induce vasodilation, contributing to the hypotension of septic shock. Much of the proinflammatory activities of IL-1 relates to its ability to induce arachidonate metabolism with many eicosanoids, such as prostaglandin E₂ and leukotriene B₄, functioning as second messengers. IL-1 induces synthesis of additional cytokines, including TNF, IL-6, GM-CSF, and, as a positive feedback mechanism, additional IL-1. Finally, like TNF, IL-1 is directly cytotoxic to cancerous and virus-infected cells. TNF and IL-1 share numerous biologic activities, the major distinction being that TNF has no direct effect on lymphocyte proliferation.

The IL-1 receptor antagonist (IL-1ra or IL-1 γ) is secreted naturally in inflammatory processes. Its production is upregulated by many cytokines, including IL-4, IL-13, TGF- β , and IL-1 itself. Production of IL-1ra is thought to modulate the potentially deleterious effects of IL-1 in the natural course of inflammation. IL-1ra has been used experimentally as an antiinflammatory agent. In rabbits IL-1ra prevents death from LPS-mediated septic shock and modulates immune complex-induced colitis.¹⁰

STRUCTURE AND FUNCTION RELATIONSHIPS

The structural and functional characteristics of the IL-1 family are undoubtedly linked because the genomic organization of IL-1 clearly demonstrates that not only the 3 genes that code for IL-1 α , IL-1 β , and IL-1ra are on the long arm of human chromosome 2 but also the 2 genes for the IL-1 receptors (IL-1RTI and IL-1RTII). In humans IL-1 α , IL-1 β , and IL-1ra are found on the long arm of

chromosome 2 distributed over 430 kd. In addition, IL-1RI and IL-1RII genes also localize to chromosome 2. The genomic organization of IL-1 α and IL-1 β are quite similar in terms of intron and exon structure, although their promoters differ significantly for promoter control of the representative cytokine genes. For example, in the IL-1 α promoter there is no TATA box motif, and inducible gene expression involves a proximal promoter and 4.2 kB upstream region that appear to be targets for induction induced by phorbol esters in most stimulated cells.⁶ The IL-1 β promoter contains a clear TATA box, which represents a typical motif of inducible genes, but the regulatory region extends over several thousand base pairs upstream from the transcriptional start site. IL-1 β gene expression is regulated at several levels. Studies have shown that sequences in the IL-1 β promoter may be controlled with proximal promoter elements that bind various nuclear factors, including nuclear factor β A (NF β A) and nuclear factor β 1 (NF β 1) and nuclear factor β 2 (NF β 2), and recently sequences of NF β A were found to be similar to that of the transcription factor Spi.1(PU.1), a well-established nuclear factor in cells of myeloid and monocyte lineage. Requirements of Spi.1(PU.1) for IL-1 β gene expression impart tissue specificity because not all cells constitutively express this transcription factor. Human blood monocytes that constitutively express Spi.1(PU.1) are exquisitely sensitive to gene expression for IL-1 β , as well as IL-1ra and TNF.^{11,12}

The 2 forms of IL-1 are initially synthesized as 31-kd precursors of pro-IL-1. Neither form contains a single peptide sequence that would ordinarily indicate a natural cleavage site for the N terminus. This fact makes IL-1 a unique cytokine.⁶ Pro-IL-1 is cleaved by proteases generating a carboxyl terminal 17-kd peptide termed mature IL-1 α or IL-1 β .⁶ These mature cytokines are unquestionably the biologically active forms, whereas pro-IL-1 β is only partially active. Pro-IL-1 α is phosphorylated and is reported to be biologically active because the pro-piece of pro-IL-1 α has been found to localize to the nucleus and to have DNA-binding capacity. Structural analysis of these 2 cytokines show significant homology between mature IL-1 α and β (25%). Both IL-1 α and β have glycosylation sites. However, glycosylation by expression in yeast has not increased specific activity over the unglycosylated form.

IL-1 α , IL-1 β , and IL-1ra all bind the same receptors, yet only IL-1 α and β are able to trigger such receptors. Pro-IL-1 α , which is active, is not processed from pro-IL-1 α intracellularly. Pro-IL-1 α may have important activities as an autocrine growth factor for a wide variety of cell lines, including keratinocytes, murine T_{H2}-type T-cell lines, and clones, as well as epithelium and thymocytes. Pro-IL-1 α , however, when released can be cleaved by extracellular proteases to yield the more active, mature form of 17-kd IL-1 α .¹³ IL-1 β , however, is less active, although not completely inactive in its pro-IL-1 β form, and activity of the intracellular protease known as IL-1 β converting enzyme (ICE) cleaves the pro-IL-1 β to the mature 17-kd IL-1 β as release and synthesis of mature

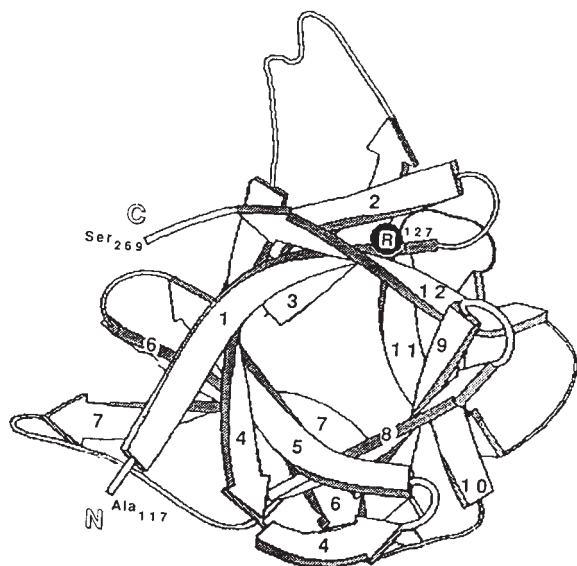


FIG 1. Schematic representation of the IL-1 β crystal structure showing position of the Arg¹²⁷→Gly¹²⁷. Adapted from Gehrke L, Jobling SA, Paik LSK, McDonald B, Rosenwasser LJ, Auron PE. *J Biol Chem* 1990;265:5922-5.

IL-1 β is done in the extracellular compartment. A tremendous amount of interest concerning the ICE enzyme has been generated because ICE and ICE homologous found in other species have been associated with mechanisms of apoptosis.^{14,15} The relationship of IL-1 to ICE is of great interest because perturbation of ICE-dependent functions may influence not only production and generation of proinflammatory cytokines, such as IL-1, but also the generation of signals for apoptosis in immune and inflammatory cells, such as macrophages and T cells.

Mature IL-1 β has been crystallized, and its tertiary structure has been analyzed at a resolution of 2 and 3 nm (Fig 1). The 3-dimensional analysis shows 12 β -strands held together by hydrogen bonds. Computerized molecular modeling of IL-1 α from the primary sequence also has identified similar structures. The tertiary structure is similar to a tetrahedron, the interior of which is filled with conserved hydrophobic side chains. Similarly well-conserved amino acids are on the surface of the molecule. Two amino acids have greater than 35% of the side chains accessible to solvent, including a glutamic acid at position 212 and a proline at position 234.^{9,16} The glutamic acid could be critical for biologic effects because selective destruction of glutamate residues results in dramatic loss of biologic activity.^{9,16} The overall folding of the 12 β -strands is similar to that found in a soybean trypsin inhibitor, but there is no IL-1 biologic activity in that molecule. A similar kind of tetrahedron crystal structure has been associated with the cytokine IL-18 and at one time was used to explain some overlap of some functions between IL-18 and IL-1.

IL-1ra, in contrast to IL-1 α and β , is synthesized with a leader peptide that allows normal patterns and mecha-

nisms of protein secretion. Keratinocytes and epithelial cells, however, have an alternative form of IL-1ra termed *intracellular IL-1ra* that lacks a leader peptide and hence remains intracellularly where it is constitutively produced and regulates intracellular activities in keratinocytes and epithelial cells. One of the functions of the intracellular form of IL-1ra may be to block the intracellular accumulation of IL-1 α and pro-IL-1 α that may have autocrine growth activities. Unlike IL-1 α and IL-1 β , the secreted and intracellular forms of IL-1ra do not possess any agonist activity even when added to biologic systems at a 10⁶-fold increased concentration. Crystal structure analysis of IL-1ra complexes shows that IL-1ra contacts with the domains of the IL-1 receptor in a similar manner to both IL-1 α and β , and a couple of these contact points can be differentiated in terms of potential contact points that are activating the various IL-1 receptors. At present there are 2 primary IL-1 receptors that have been identified. The type 1 receptor, which codes for an 80-kd protein, and the type 2 receptor, which has a much smaller intracellular chain and codes for a protein of 67 kd. The cytosolic portion of the shorter IL-1RII makes that cytokine receptor a more likely candidate for a decoy receptor that will bind up and inhibit the activities of the IL-1 α and β that might be present in the milieu in which the cell finds itself.

There are also reports of accessory molecules that will coalesce with both IL-1RI and IL-1RII in enhancing signal transduction. These accessory proteins associated with the IL-1 receptor have recently been associated with IL-18 binding in experiments that have delineated the IL-18 receptor. Materials, presumably through transcriptional activity, that upregulate IL-1 receptor type I surface expression include phorbol esters, prostaglandin E₂ (PGE₂), dexamethasone, epidermal growth factor, IL-2, and IL-4. In cells that synthesize PGE₂, IL-1 upregulates its own receptor through PGE₂. However, when PGE₂ synthesis is inhibited, IL-1 downregulates IL-1 receptor expression in the same cells. TGF- β and IL-1 downregulate surface expression of IL-1 receptor type I on T cells, but in the case of T_{H2} lymphocytes, IL-1 downregulates the IL-1 receptor type I surface expression and is associated with a decrease in mRNA half-life for the IL-1 receptor type 1. The type II receptor can be upregulated by IL-1 itself, as well as dexamethasone and IL-4. Upregulation of this type of RII receptor is clearly related with downregulation of overall biologic effects of any mature form of IL-1 because the IL-1RII acts as a decoy receptor. Table I summarizes a comparison of the various members of the IL-1 family.

BIOLOGIC EFFECTS

The biologic effects and function of IL-1 involve systemic and local effects that have influence on immunologic properties, including T-cell activation, increased IL-2 receptor expression, synergy of IL-1 and IL-6 for IL-2 synthesis and other T-cell growth factor activities, and the activation of B cells by means of induction of IL-4 and synergy with other B-cell stimulating cytokines, including IL-4 and IFN. Synergy with IL-2 and IFN is

TABLE I. The IL-1 and related protein family

Cytokine	1° Source	Activity	Size	Secretion	Leader chromosomal	
					Sequence	Locus
IL-1 α	MØ	2+	31-kd precursor	Extracellular proteases	–	2q
		4+	17-kd mature			
IL-1 β	MØ	1+	31-kd precursor	ICE	–	2q
		4+	17-kd mature			
IL-1ra	MØ	4+	23-kd apparent	Usual pathway	+	2q
icIL-1ra	Epithelium	4+	17-kd actual		–	2q
IL-1RTI	Many cells	4+	80 kd	Membrane bound	+	2q
IL-1RTII	Many cells	1+	67 kd	Membrane bound	+	2q

also seen in natural killer-cell activity, and IL-1 itself is important in expressing both lymphokine and cytokine gene expression within immune cells, as well as cytokine receptor mRNAs. IL-1 also has significant biologic properties related to its proinflammatory activity. These include the induction of fever, slow wave sleep, anorexia, and neuropeptide release. Gene expressions for complement, liver proteins, and adhesion molecules on endothelial cell activation are all prominent. Adhesion molecule expression is thought to play a role in the accumulation of inflammatory cells at sites of tissue injury, and neutrophil and eosinophil priming have both been attributed to IL-1 activity, as well as actual blood neutrophilia. Hypotension, myocardial suppression, septic shock, and death all can be physiologic responses to overwhelming expression of IL-1 and other proinflammatory cytokines. IL-1 itself has actually been associated with cyclooxygenase and lipoxygenase gene expression; synthesis of metalloproteins, collagenases, osteoblast, and osteoclast activation; and specific cytotoxicity mediated against β -islet cells.¹⁷⁻²⁶

There are a number of protective effects of IL-1 related to both cancer and infection, and therefore certain bacterial infections and other diseases may mediate protection from proinflammatory and infectious complications of IL-1 overproduction. A summary of IL-1 biologic effects is presented in Table II.

IL-1 AND DISEASE

Because of its many, varied, and multiple biologic effects, IL-1 may also play a significant role in the mediation of a number of inflammatory diseases. These disease-related responses relate to some of the basic biologic functions of IL-1. Therefore IL-1 may play a major role in the development and maturation of a number of cell lineages derived from bone marrow precursors. For example, hematopoiesis and the role of hematopoietin 1 identified subsequently as both mature forms of IL-1 α and β have been important in the significant generation and full maturation of the red cell series of blood cell differentiation. IL-1 also synergizes with a number of factors, including GM-CSF and IL-3, to generate both neutrophil and macrophage cell line lineages for the devel-

TABLE II. IL-1 biologic effects

•Systemic effects
Fever, shock, hypotension, stimulation of HPA axis, neutrophilia, hypoferrinemia, hyperlipidemia, hypoalbuminemia
•Local effects
Angiogenesis, fibrosis, neutrophil influx, chemokine induction
•Immunologic effects
Enhanced T and B cell stimulation, enhanced lymphokine synthesis, enhanced antibody production (adjuvant effect)
•Inflammatory effects
Mediates shock, arthritis, colitis, insulinitis and thyroiditis in inflammatory disease; increases adhesion molecules on endothelium; enhances release of arachidonate products, prostanooids, and eicosanoids

opment of these hematopoietic white cells. Therefore hematologic diseases, including leukemia, may be very dependent on either the activity of IL-1 or the inhibition of IL-1 for the disease to take place, and evidence has suggested that IL-1 has played a role in acute myeloblastic leukemia, chronic myelogenous leukemia, chronic leukemia, and multiple myeloma. The mechanism of IL-1 in each of these different hematopoietic diseases may be slightly different, but IL-1 is important in these particular disease states.²⁷⁻³⁰

IL-1 has also played a role in the biology of cancer cells and solid tumors. Evidence in both mice and human models suggests that IL-1 may have effects on either enhancement or inhibition of malignant cell growth and proliferation either in vivo in mouse models or in vitro with cell lines. Tumor biology and the ability of IL-1 to synergize with IFN- γ in generation of natural killer cells and cytokine-activated killer cells have also focused interest on the role of IL-1 in oncology. IL-1 has profound effects on endothelial, smooth muscle, vascular, and myocardial cells and therefore in a wide variety of vascular disease, including atherosclerotic vascular disease in which macrophage activation and presumed production of IL-1 have been well established.³¹⁻³⁵ IL-1 itself is an important mediator of shock in relation to either sepsis or cardiogenic shock, and the toxicity of IL-1 in humans has additive and synergistic toxicities with TNF. This has led to a number of studies examining the

TABLE III. IL-1 and disease

•IL-1 and hematopoietic function
Enhancement of hematopoiesis and erythropoiesis; association with hematopoietic malignancy; acute myelogenous leukemia, chronic myelogenous leukemia, multiple myelomas
•IL-1 and solid tumors
IL-1 produced by malignant cells induces proliferation of some tumor cells ex vivo and in vivo; IL-1 inhibits tumor cell growth ex vivo and induces tumor cell expression and inhibits in vivo metastasis in vivo
•IL-1 and atherosclerotic vascular disease
IL-1 produced by diseased blood vessels; IL-1 produced by endothelial cells, smooth muscle cells, and myocytes
•IL-1 and inflammatory disease
Arthritis, colitis, asthma, Type I diabetes mellitus, multiple sclerosis

role of either IL-1ra or a soluble IL-1 receptor as potential therapeutic interventions in a number of inflammatory diseases.

Other diseases that may have some role with IL-1 include both experimental and natural infection in which infections with staphylococcus and k-lebsiella have been shown to modulate IL-1 production. In models of acute and chronic lung injury, intervention with IL-1ra or soluble IL-1 receptor activity has been shown to enhance recovery from bleomycin-induced interstitial pulmonary fibrosis. In models of metabolic dysfunction, including amyloidosis, muscle protein breakdown associated with fever, the role of IL-1 and LPS involved in corticotropin-releasing factor gene expression in the hypothalamus, and adrenocorticotrophic hormone release as a consequence of either stress or infection. A number of autoimmune diseases, including diabetic models and graft-versus-host disease, as well as islet transplants, all have also been associated with IL-1 activity. Finally, inflammatory bowel disease has been shown to have a clear role for IL-1 in that experimental models of inflammatory bowel sounds have been altered by intervention with anti-IL-1 actions as have models of collagen-induced arthritis. Finally, the role of IL-1 in immediate-type hypersensitivity, allergic diseases, dermatitis, contact dermatitis, atopic dermatitis, and asthma will be dealt with in subsequent portions of this review. Table III summarizes the role of IL-1 in various diseases.

IL-1 AND ALLERGIC DISEASES

IL-1 has had a varied history in terms of its response and modulation of immediate-type hypersensitivity and allergic diseases. In type 1 immediate hypersensitivity, IL-1 has been shown to be involved in generating enhanced basophil-histamine release either directly or indirectly through intermediate induction of IL-1, as well as chemokines.^{21-23,36-47} In addition to this finding concerning the effects of IL-1 on basophil-histamine release, there are also some data to suggest that histamine itself may regulate cytokine gene synthesis. Therefore cyclic nucleotides activated by binding of histamine to

TABLE IV. IL-1 and immediate hypersensitivity and allergic disease

IL-1 and immediate hypersensitivity
• Enhances basophil histamine release with chemokine
• Production is enhanced in cells that bear FcεRI and RceRII (MO, monocytes, dendritic cells, Langerhans cells, mast cells, basophils)
• Participates in late-phase response in skin, nose, and lungs.
IL-1 and allergic disease
• Participates in inflammation in asthma
• Participates in nasal inflammation in allergic rhinitis
• Participates in inflammation in skin (atopic dermatitis, contact dermatitis)

TABLE V. Interventions directed at reduction in IL-1 activity

Pharmacologic
• Inhibitors of lipoxygenation and cyclooxygenation of arachidonic acid
• Steroids
• Dietary omega 3 fatty acids
Biologic
• IL-1ra
• Soluble IL-1RTI or IL-1RTII
• mAbs to IL-1α, IL-1β, or fragments
• Cytokines (IL-4, IL-10, IL-13, TGF-β)

macrophages may regulate the synthesis of not only IL-1β but also TNF-α and IL-6. Therefore H2 receptors on PBMCs and macrophages all have the capability of modulating cytokine synthesis. In animal models of hyperreactive airways disease in guinea pigs and rabbits, as well as in humans, IL-1 has also been shown to be generated in asthmatic airways and may, through its ability to stimulate smooth muscle, generate some degree of bronchoconstriction. The actual administration of IL-1 to animals that are already hypersensitive has not been fully appreciated as yet, but the role of IL-1 in airways hyperresponsiveness and inflammation leaves open the possibility that interference with IL-1 activity through IL-1ra or soluble IL-1 receptor may influence the outcome of asthma. In addition, it has been shown that IL-4 downregulates IL-1 synthesis but upregulates IL-1ra production from human mononuclear cells and macrophages.³⁰ Therefore the antiinflammatory effect of IL-4 in moderating T_{H1}-dependent proinflammatory cytokine expression is of great interest and may play a significant role in models of asthma. IL-1 is thought to play other roles in various kinds of animal models of chronic lung injury. IL-1 and interference with IL-1 have been shown to affect endotoxin-induced neutrophil infiltration in rat lung, and IL-1 receptor antagonist has inhibited antigen-induced pulmonary eosinophil accumulation in airway hyperactivity. In other models of lung injury, bleomycin- or silica-induced pulmonary fibrosis in rats and mice can be ameliorated by anti-IL-1 and/or IL-1ra, and hyperoxy-induced pulmonary hypertension is also modulated by IL-1ra. Carrageenan-induced pleurisy in

rats and mice is also reduced when IL-1 is interfered with, and the decreased albumin leak after systemic endotoxemia and localized fluid leak within the lungs are also moderated by downregulating IL-1.

Skin responses are also affected by IL-1. Keratinocytes and Langerhans cells are capable of producing both IL-1 α and β . In fact, the keratinocyte is a large repository of an intracellular form of IL-1ra. In atopic dermatitis and in atopy in general, IL-1 has been shown to be part of both the early- and the late-phase response within the skin. In animal, as well as human, models of contact sensitivity, IL-1 expression is critical. Finally, IL-1 has been demonstrated in nasal fluid before and after allergen challenge in those individuals who have allergic rhinitis, and therefore IL-1 may play a significant role in allergic rhinitis. The role of IL-1 in immediate hypersensitivity and allergic disease is summarized in Table IV.

POTENTIAL INTERVENTIONS

Intervention with 2 therapeutic modalities has made a significant difference in understanding the role of IL-1 in disease. The broadest experience clearly has been related to the effects of IL-1ra in animal models of disease and in relatively early clinical trials. In addition, soluble IL-1 receptors have been used in both animal and human studies and to examine the alteration in disease related to soluble forms of the IL-1 receptor. There are also potential uses of humanized mAbs that neutralize IL-1 α and IL-1 β activities, as well as IL-1 receptor blockade. The IL-1 receptor antagonist requires a large amount of material to be administered to animals or humans to blunt the effects of IL-1. Because IL-1ra inhibition of IL-1 activity must induce receptor blockade by occupying all receptors, the molar amounts of IL-1ra required to achieve this are significantly higher than molar amounts of IL-1 soluble receptor type I that can inhibit IL-1 before it binds to the surface receptor. A soluble form of the type II receptor should potentially perform better than type I, although the difference between type II and type I soluble receptors may be most mediated by the cytosolic portion of the receptors. IL-1ra has moderated animal models of infection; animal models of metabolic dysfunction; animal models of autoimmune disease; graft-versus-host disease; malignant disease; local and systemic models of inflammation, including the lung injuries mentioned previously; arthritis models; EAE models; and diabetes. In addition, IL-1ra has been tried in various forms of shock, including septic shock and postangioplasty, in animal models of vascular disruption. A summary of IL-1 therapeutic intervention is summarized in Table V.

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