The polypeptide cytokine interleukin-1 (IL-1) affects nearly every tissue and organ system. IL-1 is the prototype of the pro-inflammatory cytokines in that it induces the expression of a variety of genes and the synthesis of several proteins that, in turn, induce acute and chronic inflammatory changes. IL-1 is also the prototypic “alarm” cytokine in that it brings about increases in a variety of defense mechanisms, particularly immunologic and hematologic responses. Most studies on the biology of IL-1 have been performed in animals, but particularly immunologic and hematologic responses. Most studies on the biology of IL-1 have been performed in animals, but human subjects have recently been injected with recombinant IL-1 and the results confirm the two fundamental properties of IL-1 as being both a mediator of disease as well as of host defense. However, in either situation, over or continued production of IL-1 leads to debilitation of normal host functions; therefore, reduction of IL-1 synthesis or its effects becomes a target of therapy in many diseases. In this review, the structure, gene expression, synthesis, and secretion of IL-1 are described. In addition, the two IL-1 surface receptors, possible signal transduction mechanisms, various biologic activities, and production of IL-1 during disease states are discussed. Similarities and differences between IL-1, tumor necrosis factor, and IL-6 are presented. Although various agents for reducing the synthesis and/or for antagonizing the effects of IL-1 have been proposed, the recent cloning of a naturally occurring IL-1 receptor antagonist (IL-1ra) has opened new experimental and clinical approaches. The ability of this IL-1ra to block the triggering of IL-1 receptors in animals without agonist effects has reduced the severity of diseases such as hemodynamic shock, lethal sepsis, inflammatory bowel disease, experimental arthritis, and the spontaneous proliferation of human leukemic cells. © 1991 by The American Society of Hematology.

INTERLEUKIN-1 (IL-1) is the term for two polypeptides (IL-1α and IL-1β) that possess a wide spectrum of inflammatory, metabolic, physiologic, hematopoietic, and immunologic properties. Although both forms of IL-1 are distinct gene products, they recognize the same cell surface receptors and share the various biologic activities. With the exception of skin keratinocytes, some epithelial cells, and certain cells in the central nervous system, significant amounts of mRNA coding for IL-1 are not observed in health in most other cells. However, there is a dramatic increase in IL-1 production by a variety of cells in response to infection, microbial toxins, inflammatory agents, products of activated lymphocytes, complement, and clotting components. In some diseases, notably myeloid leukemias, the IL-1β gene appears to be spontaneously expressed. Its name as an interleukin, which means “between leukocytes,” is misleading because IL-1 is synthesized not only by leukocytes but by other cell lineages as well; furthermore, IL-1 effects are not restricted to leukocytes but rather are manifested in nearly every tissue. IL-1 is thus a “cytokine” and this term is used to connote that the sources and actions of IL-1 (and related polypeptides) include several different cell types. IL-1 belongs to a group of cytokines with overlapping biologic properties. These are tumor necrosis factor (TNF) and IL-6. IL-1, TNF, and IL-6 share the ability to stimulate T and B lymphocytes, augment cell proliferation, and to initiate or suppress gene expression for several proteins.

IL-1 was originally described in the 1940s as a heat-labile protein and found in acute granulocytic exudate fluid, which, when injected into animals or humans, produced fever. At that time, it was was called endogenous pyrogen.1 It had a molecular weight between 10 and 20 Kd and an isoelectric point of 7.1. In the 1970s, human and rabbit endogenous pyrogens were purified to homogeneity23 and shown that only 30 to 50 ng/kg of the purified material produced fevers in rabbits. Due to small amounts of the purified protein, amino acid sequences for endogenous pyrogen was not determined, but studies demonstrated that endogenous pyrogen did more than cause fever. These concepts were supported by the work of Ralph Kamp-schmidt. When injected into animals, endogenous pyrogen caused decreases in plasma iron and zinc levels, produced neutrophilia, induced the appearance of a colony-stimulating activity, and triggered the synthesis of hepatic amyloid A protein. “Lymphocyte activating factors,” described by Gery and Waksman as well as Fritz Bach, were macrophage products that augmented thymocyte proliferation to mitogens. It was subsequently demonstrated that homogeneous, purified endogenous pyrogen also augmented T-cell responses to mitogens and hence “lymphocyte activating factor” appeared to be a property of the endogenous pyrogen molecule. The ability of a macrophage product to act as “lymphocyte activating factor” resulted in the name interleukin; on the other hand, IL-2 was the term given to a T-cell product that stimulated T-cell responses without the requirement of mitogens. Several substances originally described for their biologic activities have been identified as IL-1. These are leukocytic endogenous mediator,6 mononuclear cell factor,9 catabolin,9 osteoclast activating factor,10 hemopoietin-1,11 lymphocyte proliferation promoting factor of neutrophils,12 melanoma growth inhibition factor,13 and tumor inhibitory factor-2.14

Considerable interest has focused on IL-1 as a mediator in disease and in the production of the systemic “acute-phase” responses. A single injection of 10 to 100 ng/kg of either IL-1 form into experimental animals results in fever, neutrophilia, increased circulating levels of colony-stimulating factors, IL-6, hypozincemia, hypoferremia, increased hepatic acute-phase protein synthesis, decreased albumin, anorexia, sleep, adrenocorticotropic hormone (ACTH).
release, and other manifestations of the response. At higher doses (5 μg/kg), IL-1 induces hypotension and leukopenia. Recent Phase I clinical trials of intravenously administered IL-1 (10 ng to 1 μg/kg) have confirmed the systemic effects of IL-1 reported in animal, particularly fever and hypoten-

Circulating levels of IL-1 are elevated in a variety of clinical situations and, together with similarly elevated levels of TNF and IL-6, correlate with the severity of some diseases, suggesting that these cytokines participate in the host response to or development of illness. Production of IL-1 in tissues is thought to contribute to local effects such as fibrosis, tissue matrix breakdown, or the influx of inflammatory cells. Although there are clear indications for the use of IL-1 in stimulating stem cells, radiation protection, or in increasing host resistance to infection or inflammation, this review will be primarily concerned with the production and biologic activities of IL-1 as it contributes to the pathogenesis of certain diseases. In addition, naturally occurring molecules that antagonize the action of IL-1 and reduce severity of disease will be discussed.

**GENOMIC ORGANIZATION, PROTEIN STRUCTURE, TRANSCRIPTION, TRANSLATION, SECRETION, PROCESSING, AND MEMBRANE IL-1**

*Genomic organization of IL-1.* Two IL-1 cDNAs were cloned in 1984; IL-1β was cloned from human blood monocytes and IL-1α was cloned from the mouse macrophage line P388D. These two forms correspond to the two forms of endogenous pyrogen and lymphocyte activating factor that were described by their distinct isoelectric points; IL-1β has a pI of 7.2 and IL-1α a pI of 5.3. Subsequent to the description of these two cDNAs, IL-1α or β has been cloned in the human, cow, rabbit, rat, and mouse. The entire genomic sequences for each IL-1 form have also been reported; the human IL-1β gene is 7.8 kb and the human IL-1α is 10.5 kb. Each gene contains seven exons coding for the processed IL-1 mRNA. A nearly identical organization exists for the mouse IL-1β gene. Each gene contains nucleotides of the glucocorticoid receptor, but there are no phorbol myristate response elements. The 3’ end contains a 7 nucleotide repetitive motif shared by other endotoxin-inducible cytokines; these sequences may cause mRNA instability that is “stabilized” by endotoxin. The genes for IL-1β and IL-1α are located on chromosome 2.

The two forms of IL-1 are initially synthesized as 31-Kd precursors (pro-IL-1). Neither form contains a signal peptide sequence that would ordinarily indicate a natural cleavage site for the N-terminus. This fact makes IL-1 a unique cytokine. Pro-IL-1 is cleaved by proteases generating a carboxyl terminal 17-Kd peptide, called “mature” IL-1. Mature IL-1α and β are unquestionably the biologically active forms, whereas pro-IL-1β has been reported to be partially active. Pro-IL-1α is phosphorylated and has been reported to be biologically active.

**Structural analysis of IL-1.** Structural analyses suggest that the N-terminus of pro-IL-1α is more conserved than that of IL-1β. Within the various animal species of mature IL-1β, the sequence of amino acids is conserved in the range of 75% to 78% whereas the α sequence is conserved 60% to 70%. Comparison between the β and α forms of IL-1 within each species, however, shows that the amino acid homology is only 25%. Although both IL-1β and α have glycosylation sites, glycosylation by expression in yeast has not increased specific activity over that of the nonglycosylated form.

Because IL-1β and IL-1α trigger the same receptors, some regions of each form may contain minimal structural requirements for receptor activation. Four approaches have been used: (1) biologic activity of synthetic subpeptides, (2) effects of antibodies to synthetic subpeptides, (3) site-specific mutagenesis, and (4) X-ray crystallographic analysis. In each experimental approach, T-cells and fibroblasts that express the p80 or IL-1 receptor type I (IL-1RtI) have been used to assess biologic activity or receptor binding. Although IL-1 subpeptides have some biologic activity, their specific activities are low. The carboxyl terminal of the mature IL-1β appears to retain some biologic activity. A subpeptide of IL-1β from 208-240 (amino acid numbers refer to pro-IL-1) possesses sleep and pyrogenic properties but lacks T-cell activation, whereas subpeptide 237-269 antagonizes mature IL-1 effects on T cells. A nonapeptide consisting of residues 163-171 activates T cells, stimulates glycosaminoglycan synthesis, is an adjuvant, and recruits antitumor reactivity in vivo, but lacks pro-inflammatory and pyrogenic properties. A pentapeptide (165-169) is highly exposed and is more potent than the nonapeptide. A 21 amino acid subpeptide of human IL-1β (165-186) exhibits fibroblast activity.

Antibodies to synthetic C-terminal or N-terminal subpeptides reduce biologic activity by affecting the folding of the N-terminal amino acids. These data support other studies (see below) suggesting that both the N-terminal as well as the C-terminal amino acids are involved in receptor-binding events. Monoclonal antibodies (MoAbs) to the human IL-1β subpeptide 165-186 neutralize the biologic activities of the mature IL-1. An MoAb to the IL-1β nonapeptide (163-171) blocks adjuvant but not pyrogenic activity.

Data from site-directed mutagenesis suggests that two cysteine residues in mature IL-1β are required for full activity. The exposed lysines are not critical to biologic activity. In fact, a carboxyl terminal lysine that may be involved with radiolabeling with Bolton-Hunter reagent can be mutated to a cysteine, biotinylated and yet not affect receptor binding nor biologic activity. In general, the various muteins generated by specific amino acid substitutions have not changed the overall structure of IL-1 using circular dichroism or proton magnetic resonance. The effects of site-specific mutagenesis on IL-1 activity and receptor binding have been reviewed. The histidine at position 146 or the single tryptophan in IL-1β is required for biologic and receptor-binding activity. N-terminal mutations have also yielded muteins of IL-1β with altered biologic and receptor-binding data, suggesting that N-terminal amino acids, particularly the arginine at 120, play an
important role in either stabilizing the tertiary structure or by direct interaction with receptor-binding domains. A single point substitution in the human IL-1β of arginine 127 to glycine results in a 100-fold loss in biologic activity on T cells without diminishing receptor-ligand binding. This mutant has the potential to function as an IL-1 receptor antagonist (IL-1ra) (see below).

Attempts to separate the immunostimulatory from proinflammatory properties have yielded several IL-1 muteins. Substitution of arginine to glycine at position 120 of IL-1β results in a mutein that is devoid of any pyrogenic property but retains the ability to stimulate ACTH release. Changing the aspartic acid at position 151 to tyrosine in the mature IL-1α results in loss of prostaglandin E2 (PGE2) induction and fibroblast growth but retention of T-cell responses. This mutein also antagonizes IL-1α and β induction of PGE2 and functions like a receptor antagonist.

Mature human IL-1β has been crystallized and its tertiary structure analyzed at a resolution of 2 and 3 Å. The three-dimensional analysis shows 12 β strands held together by hydrogen bonds. Computerized molecular modeling of IL-1 from the primary sequence also showed a similar structure (Fred Cohen, personal communication, 1987). 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 (glutamic acid at 212 and proline at 234) have greater than 35% of their side chains accessible to solvent. The glutamic acid could be critical for biologic effects because selective destruction of glutamic acid residues results in dramatic loss of biologic activity. The nonapeptide (163-171) corresponds to a loop between β strands 4 and 5. The overall folding of the 12 β strands is similar to that found in soybean trypsin inhibitor, but there is no IL-1–like biologic activity of that molecule.

Control of transcription and synthesis of IL-1. The amount of IL-1β mRNA found in stimulated human peripheral blood mononuclear cells (PBMC) is usually 25- to 50-fold greater than the α form. The two forms of IL-1 appear to be under separate transcriptional control. A critical aspect of understanding IL-1 gene expression in a variety of cells is the exquisite sensitivity to endotoxins (bacterial lipopolysaccharides). This is particularly the case with human blood monocytes, which synthesize IL-1 when stimulated by 10 to 20 pg/mL of endotoxin; routine tissue culture media often contain this and greater amounts of endotoxin. To evaluate IL-1 transcription and translation, water and tissue culture media should be subjected to ultrafiltration by hydrophobic membranes to remove exogenous IL-1-inducing substances. Using these conditions, there is no evidence of IL-1β or α gene expression in circulating PBMC of healthy subjects by northern hybridization, in situ hybridization, or polymerase chain reaction. However, adherence of PBMC to glass or polystyrene triggers IL-1β gene expression, but, in the strict absence of endotoxin, gene expression occurs without translation into IL-1 protein. Circulating human blood in plastic tubing at 200 mL/min for 4 hours at 37°C under strict endotoxin-free conditions does not trigger transcription. Numerous reports of “spontaneous” IL-1 production in various disease states such as acquired immunodeficiency syndrome (AIDS) or in the laboratory by infection of mononuclear cells with the human immunodeficiency virus (HIV) are likely artificial because of the endotoxin contamination.

Using endotoxin and other microbial products, transcription of IL-1β mRNA is rapid; in macrophage cell lines, endothelial, smooth muscle, and blood mononuclear cells, endotoxin-stimulated IL-1β RNA transcription is observed within 15 minutes. Following stimulation by endotoxin, peak accumulation of IL-1β mRNA occurs at 3 to 4 hours, is sustained for 6 to 8 hours, and then decreases rapidly. Studies suggest that there is synthesis of a transcriptional repressor as well as increases in the half-life of the mRNA. On the other hand, using IL-1 as a stimulus of its own gene expression, steady state levels are slower to increase and are sustained for 30 hours.

Transcription and translation of IL-1 are distinct and dissociated processes. Transcription without translation can be observed following adherence of blood monocytes to surfaces, or exposure to recombinant CSA, β-glucan polymers, or calcium ionophore, in each case, steady state mRNA levels for IL-1β are comparable with those using 1 ng/mL of endotoxin, but unlike endotoxin, there is no translation of the IL-1 mRNA into protein. The half-life of mRNA is unchanged in using these stimuli, suggesting that accelerated destruction of mRNA is not the explanation for the failure of translation. Cells containing untranslated IL-1 mRNA are “primed,” and small amounts of other stimuli (endotoxin or IL-1 itself) rapidly trigger translation and usually result in more IL-1 synthesis than nonprimed cells. Another stimulus, heat-killed Staphylococcus epidermidis, primarily delivers a translational signal.

Expression of IL-1 gene in health. Are IL-1 genes expressed in health? Studies suggest the presence of IL-1 by immunohistochemical methods in neuro-endocrine tissues such as hypothalamus, pituitary, adrenal chromaffin cells, and peripheral nerves from healthy animals. Similarly, IL-1α staining cells have been described in the epidermis with evidence that this IL-1 is biologically active. Sauder has reviewed the biologic significance of IL-1 in the skin. Because histochemical studies do not evaluate in situ hybridization on the same tissues, it is difficult to ascertain whether the immunoreactive material is IL-1 or a related peptide such as fibroblast growth factor or IL-1 that has been taken up from another tissue. Gene expression has been reported for IL-1β and α in normal mouse tissues but it is unclear whether the RNA is translated into IL-1 protein. Umbilical vein human endothelial cells contain IL-1, but this may be caused by stimulation during labor and delivery. Because transcription and translation of IL-1 are under separate control, how does one interpret in situ hybridization studies of IL-1 in peripheral tissues? In humans, there is no evidence of IL-1β protein in freshly obtained spleen or lymph node cells, but IL-1β was detected in acute adenitis or when stimulated 24 hours in the presence of endotoxin. At this writing, a required production of IL-1 as part of homeostasis in health remains unproven, although there may be some
Role of cyclic adenosine monophosphate (cAMP) in IL-1 production. Using endotoxin or other microbial stimuli, prostaglandins and prostacyclin were initially reported to have little effect on transcription but reduced translation of IL-1. Blocking cyclooxygenase can increase production of IL-1, particularly when cells are stimulated by agents that stimulate large amounts of PGE. PGE-induced suppression of IL-1 translation appears to be via the induction of cAMP. The addition of PGE or dibutyryl cAMP suppresses IL-1 synthesis, and this has recently been confirmed using PGE and phosphodiesterase inhibitors for increasing intracellular cAMP levels. Histamine binding to the type II histamine receptor raises cAMP levels and histamine reduces stimulated when freshly obtained or after they have been stored in tissue explants for 24 hours. Phorbol ester-induced IL-1 synthesis is enhanced by dibutyryl cAMP, whereas in the same experimental model, increased cAMP suppresses LPS-stimulated production. Histamine, which reduces LPS-induced IL-1 synthesis via a cAMP pathway, enhances IL-1-induced IL-1 synthesis and gene expression. However, other studies do not show a significant downregulation of IL-1 synthesis by agents that increase cAMP.

The effects of cAMP on IL-1 synthesis and gene expression are dependent on the type of stimulant and the conditions of cell culture. For example, there are differences in the effects of PGE whether the monocytes are freshly obtained or after they have been adherent for 24 hours. Phorbol ester-induced IL-1 synthesis is enhanced by dibutyryl cAMP, whereas in the same experimental model, increased cAMP suppresses LPS-stimulated production. Histamine, which reduces LPS-induced IL-1 synthesis via a cAMP pathway, enhances IL-1-induced IL-1 synthesis and gene expression. Similarly, PGE, enhances IL-1-induced IL-1 and IL-1-injected IL-1 is reduced by cyclooxygenase inhibitors.

Control of IL-1 transcription and translation is affected by other cytokines. IL-1 is a stimulus of its own gene expression and synthesis in blood mononuclear, fibroblasts, endothelial, and smooth muscle cells. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage-CSF (M-CSF) also stimulate IL-1 production. In the strict absence of endotoxins, interferon-γ (IFNγ) does not stimulate IL-1 transcription or synthesis. In fact, IL-1-induced IL-1 production (either IL-1β-induced IL-1α, or IL-1α-induced IL-1β) is suppressed by IFNγ. The suppression of IL-1-induced IL-1α by IFNγ is at the level of transcriptional activation; IL-1 production by activators of protein kinase C (PKC) is also suppressed by IFNγ. On the other hand, IFNγ augments transcription and the amount of IL-1 synthesized following endotoxin or TNF stimulation. IL-1 transcription is also suppressed by IL-4, IL-6, and transforming growth factor-β (TGFβ). A recently described cytokine (IL-10), a product of T-helper-1 cells, suppresses the transcription of IL-4 and IL-5 and also suppresses LPS-induced IL-1 synthesis.

Activators of cytokine production in a variety of cells also increase the synthesis of products of the lipoxygenation of arachidonic acid and some of these products provide a positive signal for IL-1 gene expression. Corticosteroids suppress IL-1 transcription and synthesis when added before initiation of transcription; they are less effective when added after transcription. Agents that nonspecifically block the lipoxygenase pathway of arachidonate metabolism reduce IL-1. However, using specific inhibitors of the 5-lipoxygenase pathway, IL-1 transcription is unaffected. The 13-lipoxygenase products may be involved in the early events of transcription. Supporting evidence for the importance of lipoxygenase products in the production of IL-1 come from human volunteers taking eicosapentaenoic (N-3) acid fatty acid dietary supplements; a 70% reduction in ex vivo IL-1β and IL-1α total synthesis was observed. These N-3 fatty acids are metabolized to other lipoxygenase products that likely compete with N-6 fatty acid-derived leukotrienes for stimulation of transcription.

Processing of pro-IL-1. The first translation product of IL-1 is the pro-IL-1 31-Kd precursor. Without a clear signal peptide, a considerable amount of the pro-IL-1 that is synthesized remains cell-associated. The localization of cell-associated IL-1 is almost entirely cytoplasmic, not in the endoplasmic reticulum, Golgi, or plasma membrane fraction. There is evidence that cytosolic IL-1 can be localized to nonclathrin coated vesicles and microtubules, or lysosomes. Pro-IL-1α but not IL-1β is phosphorylated at serine 90 and 107 and, presumably, phosphorylated pro-IL-1α would be more resistant to proteolytic cleavage or transport to the extracellular space, although there is no direct evidence for this explanation. The half-life of cell-associated IL-1α is 15 hours, whereas that of IL-1β is 2.5 hours.

The amount of IL-1 that is “secreted” depends upon the cell type and the conditions of stimulation. The monocyte/macrophage appears to be efficient in its secretion of IL-1β compared with endothelial, smooth muscle cells, and fibroblasts. As much as 70% of the IL-1β is secreted by PBMC in 24 hours, whereas IL-1α remains cell-associated during the first 20 hours. Increasing the content of plasma proteases in the culture medium does not change the secretion of IL-1α. Unlike stimulation by LPS, IL-1β induction by IL-1α or IL-1β remains cell-associated.

It is still unclear how IL-1 is transported from the cytosol to the extracellular compartment and how it is cleaved to its mature peptides. Secretion of the 31-Kd IL-1 precursor and processing to its mature peptide appear to be linked events, although studies suggest that pro-IL-1β is secreted intact and then later cleaved by various enzymes present in inflammatory tissue. Mature IL-1β has an N-terminus at the alanine position 117 but other naturally occurring N-termini have been reported. Pro-IL-1β and a 22-Kd partially cleaved peptide are found in the supernates of monocytes, demonstrating that the pro-IL-1β is secreted before generation of the mature peptide. Some stimuli selectively increase secretion and processing (as originally proposed by Igal Gery), such as phagocytic stimuli and calcium ionophores.

Elastase, plasmin, cathepsin G, collagenase, and serine proteases as well as the surface enkephalinase have been implicated in the cleavage of pro-IL-1β into its 17.5-Kd mature carboxy terminal fragment. A monocyte-specific protease has been described that specifically cleaves IL-1β at...
the alanine position. This protease is not found in fibroblasts but rather in monocytes and monocyte cell lines. Blockade of specific pro-IL-1 processing enzymes has been proposed as a possible strategy for preventing the effects of IL-1 in disease. However, there appears to be more than a single protease that cleaves the precursor into active IL-1 peptides. Zidovudine decreases the amount of IL-1β secreted by human monocytes without affecting the total synthesis of IL-1.

A calcium-activated neutral protease (calpain, EC 3.4.22.17) has been described that processes IL-1α. Inhibitors of serine proteases prevent the appearance of mature and smaller molecular weight IL-1 peptides. The 17.5-Kd IL-1 mature peptide, as well as other subfragments detected by bioassay following gel-filtration, are routinely found in human plasma, urine, and peritoneal, pleural, and joint fluids. These fragments are likely cleaved via trypsin-sensitive sites. Human IL-1β contains several cleavage sites for serine proteases. In preparations of recombinant IL-1, which could represent the active C-terminal fragment.

**Membrane IL-1.** IL-1 activity has been described after fixation of macrophages and called “membrane-bound” IL-1. “Membrane-bound” IL-1 is active on lymphocyte and several nonlymphocytic cells. The existence of “membrane” IL-1 has been almost exclusively IL-1α in that histochemical and neutralizing antibodies to IL-1α, rather than IL-1β, have been effective. In addition to macrophages, membrane IL-1 has been detected on endothelial and dendritic cells and fibroblasts. A biochemical mechanism for pro-IL-1α anchoring to the cell membrane has been proposed via lectin-like binding because D-mannose dissociates the activity and immunoprecipitable IL-1.

Alternatively, IL-1α may be bound to its surface receptor, as has been shown for TNF. Recent controversy has focused on whether “membrane” IL-1 is a functioning integral membrane protein or whether the bioactivity of membrane IL-1 is caused by the leakage of IL-1 from inadequately fixed cells. Studies by Mizel and others have shown that 1% paraformaldehyde fixation for 15 minutes at room temperature results in IL-1 leakage. Other investigators have shown that following this standard fixation method, IL-1 (β and α) is secreted, although in decreasing amounts, for up to 96 hours. However, macrophages tested for biologic activity 144 hours after fixation continue to retain T-cell stimulating activity that is specifically neutralized by anti-IL-1α, suggesting that membrane IL-1 is still present. It is unclear how “membrane IL-1” is oriented on the surface of the cell so that its structural components are available for binding to IL-1 receptors.

**CELL SOURCES AND STIMULI OF IL-1**

**Cell sources of IL-1.** Several nucleated cells have been shown to synthesize IL-1. The sources of IL-1 include blood monocytes; tissue macrophages; blood neutrophils; central nervous system microglia; astrocytes; endothelial cells; smooth muscle cells; fibroblasts; synovial lining cells; dermal dendritic cells; keratinocytes; intestinal, gingival, and cervical epithelium; blood T lymphocytes; transformed and normal blood B lymphocytes; lymph node cells; natural killer cells; maternal placental cells; and newborn blood and dendritic cells. Leukemic cells also produce IL-1 (see below). Platelets contain IL-1 but it is not clear whether they synthesize IL-1. Contaminating monocytes or tissue macrophages must be ruled out in ascribing IL-1 production to any freshly obtained tissues.

**Stimuli for IL-1 production.** The most common stimulus used for IL-1 transcription is endotoxin (discussed below). The amounts of endotoxin that are capable of transcriptional and translation of IL-1 from human PBMC is approximately 5 molecules per monocyte. The role of the endotoxin receptor in the induction of IL-1 or endotoxin-stimulated second signals remains unclear. Other microbial products are also potent inducers of IL-1. Gram-positive organisms, particularly the staphylococci and streptococci, produce potent polypeptide exotoxins that stimulate IL-1 and TNF production. In fact, it is unclear whether the clinical symptoms and disease that develop after toxic shock syndrome-associated strains of *Staphylococcus aureus* produce disease because of the direct action of toxic shock toxin-1 or because the toxin induces IL-1 and TNF, which, in turn, results in toxic shock syndrome. Viral induction of IL-1 requires live agent. Synthetic adjuvants derived from bacterial wall structures are also inducers of IL-1. Naturally occurring substances such as complement components, thrombin, bile salts, androgen metabolites, and cytokines themselves can serve to initiate IL-1 transcription and translation.

**IL-1 RECEPTORS (IL-1Rs)**

**IL-1 Rs.** The initial studies on the binding of radiolabeled IL-1 were performed using a variety of cells in which there appeared to be a single class of intermediate affinity receptor (kd ranging from 200 pmol/L to 1 nmol/L) and relatively few receptors (200/cell). Although the IL-1R was specific in that it did not recognize other cytokines, the binding did not distinguish between IL-1α or IL-1β. Either IL-1α or IL-1β competed for binding of each other on T and fibroblast cell lines. In general, the binding correlated with the capacity of the cells to respond to IL-1, although this was not always the case. Subsequently, cell lines were found that expressed unusually high numbers of receptors (5 to 20,000) and relatively few receptors (200/cell). Although this was not always the case. Subsequently, cell lines were found that expressed unusually high numbers of receptors (5 to 20,000) and relatively few receptors (200/cell). However, in general, in nontransformed cells, there is strong evidence that the receptor is either too weak or too slow to effect the cell. Cross-linking of radiolabeled IL-1 showed that there were several proteins that specifically bound IL-1 at 30, 68, 80, 105, and 220 Kd. Of these, two molecular weight IL-1 binding proteins were prominent. On T cells and fibroblasts, an 80-Kd IL-1R was consistently observed whereas B-cell lines possessed a 68-Kd IL-1 binding protein. These two binding proteins have now been shown to be separate gene products, they are recognized as the two major
IL-1R molecules. The p80 IL-1R is called the IL-1RII and the p68 is the IL-1RIII. The other molecular weight IL-1 binding proteins (putative receptors) may be related to either the p80 or p68 receptor or represent other IL-1Rs or associated binding proteins as is the case with IL-2R. The 105-Kd IL-1 binding protein may represent a heavily glycosylated IL-1R, and the 220-Kd, observed by many investigators, may be a dimer of the IL-1RII with IL-1 as a cross-linking ligand, similar to the case for the TNF, fibroblast growth factor, and the platelet-derived growth factor receptors.

Compared with other cytokines such as the IFNs and CSFs, there is little species specificity of IL-1’s biologic effects on using a variety of mammoths and even reptiles and fish. However, there is evidence that species specificity can play a role in some biologic responses; Human IL-1β triggers ACTH release from rats, whereas human IL-1α does not.

However, when rat IL-1s are expressed and tested in the rat homologous system, rat IL-1α is 10 times more potent than human IL-1α. Biologic responses involving cells that express primarily the type II receptor appear to be more species-restricted than cells bearing the type I receptor.

**IL-1RII.** The IL-1RII has been cloned from mouse and human cells. It is found on T cells, fibroblasts, keratinocytes, endothelial cells, synovial lining cells, chondrocytes, and hepatocytes. Although a p80 IL-1R has been reported on purified human blood monocytes and has the characteristic ability to internalize IL-1, other studies suggest that murine macrophages do not express the type I receptor. The type I receptor belongs to the Ig super family. There is an extracellular segment that contains the three domains homologous to Igs. The extracellular segment has several sites for glycosylation; there is a single transmembrane portion of approximately 21 amino acids and a cytosolic region. This cytosolic region has no homology with any known protein kinase but the serine/threonine residues are phosphorylated soon after IL-1 binds to the extracellular domains. The possibility exists that the higher molecular weight IL-1 binding proteins represent glycosylated variants of the IL-1RII. Some T cells respond to subpicomolar concentrations of IL-1 without possessing demonstrable IL-1 binding. One explanation is that low receptor occupancy is sufficient to trigger intracellular events. This explanation is supported by the observation that less than 5% receptor occupancy triggers phosphorylation of the remaining IL-1RII. On the other hand, synovial sarcoma cell line with high-affinity type I receptors does not manifest a biologic response to IL-1, suggesting either tumor-related mutations in the IL-1RII or a dysfunction in signal transduction.

The extracellular segment of the type I receptor has been expressed in HeLa cells as a separate molecule and binds IL-1 with the same affinity as the complete receptor on cell surface membranes. Using this soluble receptor, one IL-1α molecule binds to one truncated receptor. Transfection of cells with different deletion mutants of the receptor shows that the outer two domains are involved with ligand binding. Using antibodies to various synthetic peptides that represent 4 hydrophilic amino acid segments distributed throughout the extracellular domains, only antibodies to a 17-amino acid segment in the outermost Ig domain blocks the binding of IL-1. Glycosylation also contributes to IL-1 binding to the type I receptor and different patterns and types of sugar linkages differ on cells.

Using various T- and fibroblast cell lines of human or murine cell origin, there is still no consensus whether the IL-1R on these cells express a single binding affinity or two classes of binding affinity. Some reports clearly indicate two classes of receptor binding, but this finding is inconsistent. The multiple glycosylation sites on the IL-1RI may have a role in receptor expression, affinities, and specificities. Lectins block the binding of IL-1 on T cells; however, cells of separate lineage are affected by different lectins with different sugar specificities. The evidence suggests that N- and O-glycosylation patterns on cells differ, and this may affect the binding of IL-1α or β.

After binding, IL-1 is internalized, but internalization of IL-1 bound to truncated mutants of the type I extracellular domains can occur without a full signal transduction taking place. Internalized IL-1 bound to the type I receptor is not degraded and is found in the nuclear compartment after several hours. Although this translocation implies a nuclear site for IL-1 biologic activity, biologic responses such as rapid changes in arachidonic acid metabolism take place within a few minutes and are distinct from the growth and gene expression properties of IL-1.

**IL-1RIII.** The initial observation of the IL-1RIII was on Epstein-Barr virus (EBV)-transformed B cells. It was then shown that the IL-1R on various B-cell lines, including the Raji human B-cell lymphoma line, has a distinctly different molecular weight (68-Kd) and differed in many respects from the IL-1RI on T cells and fibroblasts. The type II receptor is also a member of the Ig super family with three Ig-like domains in the extracellular segment; there is 28% amino acid homology between the extracellular portions of the type I and II receptors. There is a highly homologous transmembrane segment. However, one major difference between the type I and II receptor is the truncated cytoplasmic portion of the type II receptor. This shortened cytoplasmic domain accounts for the lower molecular weight of the type II receptor and may explain the differences in signal transduction reported for IL-1 on B cells. Figure 1 illustrates the structural differences between the two IL-1 receptors.

At present, the IL-1RIII is found on B-cell lineages, neutrophils, and bone marrow cells. Besides being a different gene product, the type II receptor differs from the type I receptor in binding affinities, on and off rates, regulation of its surface expression, and the type of signal transduced. For example, at 37°C, 60% to 70% of the IL-1RIII is internalized within 5 minutes by an azide-sensitive mechanism and remains inside the cell for 12 hours, whereas IL-1 bound to the type II receptor remains in the surface for as long as 60 minutes and is poorly internalized. IL-1 bound to the IL-1RII is internalized and only a small amount is degraded, whereas that bound to the type II receptor is found in extracellular fluid in a
The molecules. The areas marked ~~~~'~'~'~'~~
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INTERLEUKIN-1 AND INTERLEUKIN-1 ANTAGONISM

Fig 1. Schematic representation of the two IL-1 receptors. The numbers in and above the bars represent the number of amino acids in each portion of the molecules. The areas marked extracellular, transmembrane, and cytosolic are approximations.1633

degraded form. These results suggest that there are different vesicles and acidification mechanisms for the two receptors. In general, the cells (transformed T cells, fibroblasts) that have high numbers of IL-1Rt1 are not producers of IL-1, but B cells and neutrophils readily produce IL-1.

The half-life of the type II receptor on B cells is faster (2 hours) than for the type I receptor on T cells (5 to 12 hours).145 B cells exhibit a heterogeneous population of IL-1R and some lines express both 80 and 86 receptors.150 Some EBV B-cell lines bind IL-1a with greater affinity than IL-1b.150 The Raji cell IL-1Rt11 has more binding sites for IL-1b than a (2,000 v 400).146 The type II receptor on Raji cells transduces a signal that results in IL-2R, c-Ha-ras, and c-myc gene expression145 but the type I receptor on neutrophils151 "primes" cells for other neutrophil agonists. IL-1 binding to neutrophils results in increased arachidonic acid metabolism with 60 minutes of exposure.152,153 This rapid effect on neutrophil arachidonic acid metabolism may be the "priming" effect of IL-1 on neutrophils. The activity of IL-1 on neutrophils is not caused by changes in cytosolic calcium.154

Distinct binding of IL-1b and IL-1a to IL-1 receptors. Although it is generally accepted that the IL-1Rt1 recognizes either a or b forms of IL-1 equally, in fact, there is ample evidence that, depending on the cell type or animal species, the two forms of IL-1 likely have distinctly different binding sites on the IL-1R. Studies demonstrate marked differences in the biologic response to either form of IL-1. For example, although human and murine IL-1a bind to human endothelial cells with an equal affinity, there is an unequal induction of biologic responses.155 Recombinant murine IL-1b was found to be 250- to 1,250-fold less active than recombinant human IL-1a in inducing endothelial cell adherence of human lymphocytes. Although both forms of IL-1 are equipotent for murine thymocytes, IL-1b is 30 times more potent than the a form in downregulating the luteinizing hormone receptor.156 Furthermore, the concentration of porcine IL-1b required to elicit half-maximal IL-2 production was 100-fold greater than that for porcine IL-1a, but both forms of IL-1 were equally active on 3T3 fibroblasts.157 These differences have been observed when evaluating the activity of the two forms of IL-1 in vivo. In fact, in a model of adjuvant activity in mice, IL-1b is active whereas IL-1a is not; moreover, the a form acts as a competitive inhibitor of the adjuvant properties of IL-1b.158 Because both a and b forms are active in the induction of amyloid protein from hepatocytes (a type I receptor cell), these data suggest that IL-1b triggers B cells in vivo whereas IL-1a does not.159 This finding is consistent with the greater affinity and receptor numbers for IL-1b than a on B cells.160 It is also consistent with lower molecular weight IL-1b binding protein in rat brain being type II receptors.159

In general, IL-1a binds best to the type I receptor and IL-1b to the type II receptor. Antibodies to the 17 amino acid segment on the extracellular domain of IL-1Rt19 preferentially block the binding of IL-1b to type-I receptors rather than IL-1a and this difference is most marked when murine IL-1 is used as a binding agent for murine cells.160 These results suggest that the binding domains of the IL-1Rt1 for the two species of IL-1 are distinct.

Regulation of surface and gene expression of the IL-1 receptors. Using radiolabeled IL-1, increased binding of IL-1 to human blood T cells has been observed after stimulation with mitogens,161 but decreased binding on murine Th2 cells has also been observed after overnight incubation with IL-1 itself.160 This downregulation of IL-1 binding after exposure of cells to IL-1 is not a function of receptor occupancy because downregulation is observed at concentrations of IL-1 that occupy less than 10% of the receptors.156 Downregulation by IL-1 of IL-1 receptors has been reported by other investigators.160 IL-1 also downregulates the surface expression of the TNF receptor162 and the luteinizing hormone receptor on granulosa cells.156

Regulation of the surface and gene expression for the type I receptors has been studied using specific cDNA probes and antibodies. With occupancy of 10% to 15% of the binding sites, IL-1 reduces surface expression by 60% to 80% over 24 hours and this effect persists for 72 hours.163 Occupancy of less than 5% of the binding sites also reduces surface expression. The mechanism for this downregulation is a decrease in the half-life of the mRNA from 6 to 8 hours to 1 hour by increased mRNA degradation. IL-2 increases transcription and surface expression as does phorbol esters.163 On fibroblasts, platelet-derived growth factor increases gene expression for the IL-1Rt1 and using binding methods, prostaglandins were shown to be responsible for upregulation of the IL-1R binding sites without chang-
Prostaglandins had no effect on the gene or surface expression of the type I receptor in T cells. Transforming growth factor β downregulates the binding of labeled IL-1 to T cells and bone marrow cells.

Expression of the type II receptor on neutrophils, B cells, and bone marrow cells is under different control than that of the type I receptor. In mice or humans administered IL-1, the binding of IL-1 to the neutrophils or bone marrow cells is enhanced. This finding is consistent with the effect of IL-1 in vivo to increase corticosteroids via ACTH release. In fact, glucocorticoids increase the binding sites of IL-1 to peripheral blood B lymphocytes.

**SIGNAL TRANSDUCTION**

In studying signal transduction events following the binding of IL-1 to either one of its cell surface receptors, no clear picture has emerged. This subject has been recently reviewed by Rosoff and a debate on whether cAMP is part of the IL-1 signal transduction cascade has been published. The only consistent observation concerning signal transduction pathways for IL-1 has been the inability to detect increases in cytosolic calcium in cells responding to IL-1.

There is experimental evidence that IL-1 leads to increases in cAMP via G-protein activation of adenylate cyclase. Using data from various cell lines and primary cultures, Mizel has formulated a series of events that follow the triggering of IL-1 to either surface receptor. Those events are IL-1 binding, activation of GTP-binding protein, increased GTPase activity, activation of adenylate cyclase, synthesis of cAMP, protein kinase A (PKA) activation, and binding of transcriptional factors to NF-κB. The argument against such a mechanism is that increases in cAMP result in suppression of gene expression in lymphocytes rather than an increase. In lymphocytes, IL-1 treatment increases the genes for IL-2, IL-2R, and several other lymphokine genes. The concept that the IL-1R is coupled to a G-protein that activates adenylate cyclase is also inconsistent with a single transmembrane segment of the IL-1R because adenylate cyclase-coupled receptors have seven transmembrane segments. However, a short burst of cAMP induced by IL-1 may increase lymphocyte gene expression rather than sustained elevations of cAMP, which are suppressive. Within 15 seconds, IL-1 increases GTP hydrolysis, which is inhibited by pertussis toxin. This finding is inconsistent with the observation that pertussis toxin-sensitive G-proteins inhibit GTPase activity. Furthermore, direct evidence that IL-1 increases PKA is lacking.

Others studies show that, although IL-1 triggers G-protein activation, there is no increase in cAMP. In the experimental designs, the actions of IL-1 are also sensitive to pertussis toxin. With occupancy of less than 5% of the receptors, IL-1 induces phosphorylation of its own receptor at serine and threonine residues; IL-1 causes phosphorylation of the epidermal growth factor receptor. IL-1 also phosphorylates the p27 heat shock protein. IL-1-induced activation of kinases is not associated with activation of PKC, and activation of protein kinase A does not lead to the types of phosphorylations observed following exposure to IL-1. Hence, novel protein kinases may be part of the signal transduction event. Another postreceptor event that has been described for IL-1 is the ion flux of both Na+/H+ across the plasma membrane of a murine pre-B-cell line.

The activation of the IL-1 receptors appears to be rapid and consistent with G-protein coupling and activation of a phospholipase. IL-1 on T-cell membranes triggers the binding of the GTP analogue (GTPyS) within 1 minute and there is an associated increase in GTPase activity. One working hypothesis is that IL-1/IL-1R is coupled to a G-protein that activates a phospholipase C that, in turn, hydrolyzes phospholipids liberating diacylglycerol (DAG). The DAG then triggers protein kinases. However, the evidence does not support the concept that the IL-1-induced increase in DAG results in stimulation of PKC or PKA. There is evidence that IL-1 induces a rapid hydrolysis of phospholipids and that the DAG can be further cleaved by diacylglycerol lipase at the number 2 position to liberate arachidonic acid. Arachidonic acid is metabolized into prostaglandins, which would explain the brief but rapid (5 minute) increase in PGE₂ that has been observed. This rapid increase in PGE₂ would also be consistent with the ability of IL-1 to rapidly (5 minutes) increase body temperature by a cyclooxygenase-sensitive mechanism.

The increase in PGE₂ can also explain the transient increase in cAMP because PGE₂ is a stimulator of adenylate cyclase. However, indomethacin did not block the activation of adenylate cyclase. Stimulation of adenylate cyclase would be consistent with activation of PKA. The difficulty with the generation of DAG from PC turnover is the incomplete ability to alter IL-1 signals with inhibitors of PKC; there is only partial evidence that PKC is part of the IL-1 signal transduction mechanism.

Rosoff reported that IL-1 amplification of anti-CD3-stimulated IL-2 production is associated with increased DAG in Jurkat cells. The increase in DAG is not associated with hydrolysis of phosphatidylinositol 4,5-bisphosphate into inositol trisphosphate, suggesting a non-phosphatidylinositol phospholipid phospholipid turnover. Despite this activation, IL-1 does not increase cytosolic calcium in these cells, in neutrophils, or in any other cell that responds to IL-1. Using 3H-choline labeled cells, exposure to IL-1 caused phosphorylcholine to increase within 5 seconds, suggesting hydrolysis of phosphatidylcholine (PC). IL-1 induced PC turnover at a concentration of 30 fmol/L, reaching a maximum effect at 100 fmol/L, the concentration of IL-1 that stimulates biologic effects in vitro. The effective concentration of IL-1 that induces PC turnover becomes an important issue in these studies; for example, IL-1-activated Na+/H+ antiport requires three orders of magnitude greater concentrations of IL-1 than that required for proliferation in the same cells; furthermore, femtomolar concentrations of IL-1 inhibit adenylate cyclase in pituitary cells. TNF, which shares nearly all of IL-1’s pro-inflammatory properties, also triggers PC turnover with an associated increase in DAG.

Others have demonstrated that IL-1 increases phospholipid hydrolysis; in addition to PC turnover in T cells, increased mesangial phosphatidylethanolamine and T-cell phosphatidylerine turnover have been reported. The mechanism by which IL-1 triggers the activation of a PC-specific
phospholipase C (PLC) remains unclear, but recent studies suggest that proteins anchored by a glycosyl-phosphatidylinositol membrane linkage may be involved.187

**THE BIOLOGIC EFFECTS OF IL-1**

IL-1α and IL-1β have been administered to humans in Phase I trials during cancer therapy or bone marrow transplantation. Although the data have not yet been fully reported as of this writing, systemic administration of intravenous IL-1 from 10 to 100 ng/kg has produced fever, sleepiness, anorexia, generalized myalgias, arthralgias, headache, and some gastrointestinal disturbances; at higher doses, hypotension has been observed.15,16 The subcutaneous route is associated with less side effects. Laboratory data confirm the neutrophilia-inducing property of IL-1, but increased circulating platelets have been observed.18 In general, the early experience in humans are consistent with previous observations in the rabbit and other animals. In the following section, the multiple biologic activities of IL-1 are based on animal and in vitro studies. Table 1 summarizes some of the biologic activities of IL-1.

**IL-1 effects on receptors for other molecules.** IL-1 modulation of physiologic or pathologic processes can be through upregulation or downregulation of other receptors. IL-1 increases the binding of opiates to the opiate peptide receptor on brain slices and also increases the surface expression of transforming growth factor-β receptor. On the other hand, IL-1 downregulates the surface expression of its own type I receptor,163 decreases the number of TNF receptor(s),162 inhibits the binding of antibody to the CD4 antigen, reduces the affinity of epidermal growth factor receptor,177 downregulates mRNA for the IL-6 receptor, and inhibits the formation of the luteinizing hormone receptor.182

**Expression of various genes in cells exposed to IL-1.** IL-1 induces a wide variety of genes, some by inducing new transcripts such as SAA183 or IL-1 itself,184 whereas others represent stabilization and prolongation of mRNA half-life, eg, GM-CSF.184,185 IL-1 also suppresses the expression of other genes (eg, albumin, cytochrome P450, and aromatase) by reducing new transcription. IL-1 reduces the surface expression of its own type I receptor by accelerated mRNA degradation.186 In thyroid stimulating hormone (TSH)-stimulated thyrocytes, IL-1 inhibits gene expression for thyroglobulin and thyroid peroxidase. In isolated rat adrenal glomerulosa cells stimulated with angiotensin-II, aldosterone biosynthesis is reduced by femtomolar concentrations of IL-1, probably by reduced mRNA transcripts. In human marrow stromal cells, IL-1 selectively increases the c-abl protooncogene 6 kb but not the 5-kb transcript. The JE and KC genes, which are platelet-derived growth factor-inducible genes, are also induced by femtomolar levels of IL-1. In general, IL-1 stimulates new transcripts for several protooncogenes.187

The mechanism of IL-1–induced genes may involve the activation of nuclear factors. Two nuclear factors have been shown to be IL-1 inducible: NFκB188 and AP-1.189 An IL-1–responsive element was described in the IL-2 promoter gene, which shares homology with phorbol ester-inducible sequences and is recognized by the nuclear factor AP-1. The signal transduction mechanism for nuclear factors may be different in cells or various origins. Table 2 summarizes the effect of IL-1 on gene expression. It should be pointed out that the expression of some lymphokine

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### Table 1. Biologic Effects of IL-1

<table>
<thead>
<tr>
<th>Immunosuppressive Properties</th>
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<tbody>
<tr>
<td>T-cell activation; synergy with IL-6 for IL-2 synthesis</td>
<td>Increased IL-2R expression</td>
<td>Natural killer activity; synergy with IL-2 and IFN</td>
</tr>
<tr>
<td>Increased IL-2R expression</td>
<td>B-cell activation via induction of IL-6; synergy with IL-4</td>
<td>Lymphokine gene expression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pro-Inflammatory Properties</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Fever, sleep, anorexia, neuropeptide release</td>
<td>Gene expression for complement; suppression of P450 synthesis</td>
<td>Endothelial cell activation</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>Increased adhesion molecule expression</td>
<td>Neutrophil priming, eosinophil degranulation</td>
</tr>
<tr>
<td>Increased adhesion molecule expression</td>
<td>Hypotension, myocardial suppression, shock, death</td>
<td>Neutrophil tissue infiltration (via IL-8)</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>Beta islet cell cytotoxicity</td>
<td>Amino acid turnover; hyperlipidemia</td>
</tr>
<tr>
<td>Increased adhesion molecule expression</td>
<td>Cyclooxygenase and lipoxygenase gene expression</td>
<td>Synthesis of collagenases and collagens; osteoblast activation</td>
</tr>
<tr>
<td>Protective Effects</td>
<td>Suppression of</td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>INF regulatory factor</td>
<td>Adhesion molecules</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>Complement; C2; factor B</td>
<td>Oncogenes (c-fos; c-myc; c-jun)</td>
</tr>
<tr>
<td>Lethal radiation</td>
<td>Manganese superoxide dismutase</td>
<td>G-protein α-1-2-subunit</td>
</tr>
<tr>
<td>Early stem cell</td>
<td>Cyclooxygenase, phospholipase A2</td>
<td>INF regulatory factor</td>
</tr>
<tr>
<td>Hyperoxia</td>
<td>Platelet-derived growth factor (AA)</td>
<td>Prepro-endothelin</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Adhesion molecules</td>
<td>Corticotropin-releasing factor and pro-opio-melanocorticotropin</td>
</tr>
<tr>
<td>Histamine release</td>
<td>IL-1R</td>
<td>Amyloid A and amyloid beta proteins</td>
</tr>
</tbody>
</table>

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### Table 2. IL-1–Induced Gene Expression or Gene Suppression

<table>
<thead>
<tr>
<th>Increased Gene Expression</th>
<th>Suppression of Gene Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8</td>
<td>Albumin</td>
</tr>
<tr>
<td>TNFα, TNFβ, INFβ-1</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>GM-CSF, G-CSF, M-CSF</td>
<td>Lipoprotein lipase</td>
</tr>
<tr>
<td>IL-2R (Tac antigen)</td>
<td>Aromatase</td>
</tr>
<tr>
<td>Metallothionein; ceruloplasmin</td>
<td>Aldosterone</td>
</tr>
<tr>
<td>Complement; C2; factor B</td>
<td>Thromboglobulin</td>
</tr>
<tr>
<td>Manganese superoxide dismutase</td>
<td>Prepro-insulin</td>
</tr>
<tr>
<td>Cyclooxygenase, phospholipase A2</td>
<td>IL-1Rt</td>
</tr>
<tr>
<td>Platelet-derived growth factor (AA)</td>
<td></td>
</tr>
</tbody>
</table>

IL-1 does not affect the expression of all these genes in all cells.
genes by IL-1 requires the presence of another stimulant, particularly lectins or agents that increase cytosolic calcium.

**Central nervous system (CNS).** Compared with molecules of similar size, IL-1 does not cross the blood brain barrier and enter the substance of the CNS. In cats given large doses of endotoxin, third cerebroventricular levels of biologically active IL-1 are not detected. However, the rapid (5 minutes) induction of fever, sleep, and the release of a variety of neuropeptides suggest that IL-1 readily affects structures in the CNS. It is likely that IL-1 acts on the special endothelial cells of the periventricular organs where the blood barrier is interrupted; furthermore, arachidonic acid metabolites are released from these cells. IL-1 is found distributed throughout the brain, but glial and possible neuronal cells synthesize IL-1. This endogenously produced IL-1 may be acting as a co-factor in synaptic transmission. Femtomolar concentrations of IL-1 augment GABA receptor function.

**Hepatocytes.** IL-1 induces increases in normal hepatic proteins twofold to threefold, but the synthesis of pathologic proteins can increase 100-fold to 1,000-fold. One such protein, serum amyloid A (SAA) protein, contributes to the development of secondary amyloidosis. IL-1 induces hepatocytes to synthesize SAA, fibrinogen, complement components, factor B, metallothioneins, and various clotting factors. In isolated hepatocytes, IL-1 decreases the transcription of RNA coding for albumin, transferrin, lipoprotein lipase, and cytochromes. IL-1 stimulates fatty acid synthesis by increasing hepatic citrate levels. Some of IL-1’s effects on hepatocytes may be via the intermediate production of IL-6.

**Effects on synovial cells, bone, and cartilage.** Infusion of IL-1 into the joint space produces cellular and destructive changes indicative of arthritis. IL-1 induces PGE, collagenase production in synovial cells; in addition, IL-1 increases metalloproteinases and proteoglycanases from chondrocytes. IL-1 added to bone cultures in vitro induces proliferation, PGE, and plasminogen activator factor synthesis while antagonizing alkaline phosphatase induced by vitamin D. Systemically administered IL-1 stimulates bone resorption. IL-1 acts synergistically with either TNF or fibroblast growth factor in the induction of proteases from chondrocytes.

**Effects of IL-1 on fibroblasts and fibrosis.** IL-1 increases fibroblast proliferation, whereas IL-6 counters this proliferative response to IL-1 in fibroblasts. In vitro, however, IL-1-induced fibroblast and smooth muscle cell proliferation is often difficult to observe unless cyclooxygenase inhibitors are present. IL-1 directly increases the transcription of Type I and Type III collagen and Type IV (basement membrane) collagen. IL-1 produced by microglia and astrocytes in the brain is thought to result in local gliosis.

**Catabolic effects of IL-1.** Although early studies suggested that IL-1 played a role in the negative nitrogen balance often associated with chronic disease by inducing muscle proteolysis, subsequent studies have not confirmed that isolated muscle tissues incubated with IL-1 in vitro release amino acids. However, IL-1 likely contributes to the development of negative nitrogen balance because IL-1 induces reduced food intake in experimental animals. It should be pointed out that although animals administered daily injections of IL-1 lose weight initially, tachyphylaxis develops to the anorectic property of IL-1. IL-1 also induces hypoglycemia, and this effect may be due to the ability of IL-1 to increase the synthesis of glucose transporters and thus increase intracellular glucose levels. The mechanism of IL-1–induced anorexia is thought to be caused by a direct effect on the liver that subsequently affects the hypothalamic appetite center. This concept is supported by a study in which systemically administered antibodies to the IL-1RI block the weight loss associated with inflammation.

**Possible role of IL-1 in the pathogenesis of insulin-dependent Type I diabetes.** Prolonged incubation of islets of Langerhans with IL-1 results in specific loss of the insulin-producing beta cells. Isolated beta cells have similar responses and express an IL-1R. IL-1 action on the islets increases synthesis of the p70 heat shock and other proteins including oxygen scavengers, which may offer some protection from the cytotoxic effect of IL-1. However, some of the IL-1–induced new proteins in treated islets may contribute to programmed cell death. Depending on the glucose content of the medium, low concentrations of IL-1 stimulate mRNA for pre-proinsulin, whereas at higher concentrations, insulin production is suppressed. These in vitro effects can be demonstrated by local perfusion of the pancreas. A low dose of systemic IL-1 has a hypoglycemic effect.

**Effect of IL-1 on renal function.** Sodium excretion in rats is markedly enhanced by a systemic injection of IL-1, and this effect is independent of renal blood flow but sensitive to cyclooxygenase inhibitors. IL-1 also affects mesangial cells by inducing proliferation, arachidonic acid metabolism, and superoxide production. IL-1 has been proposed to play a role in the development of lupus nephritis and immune complex glomerulonephritis.

**Vascular effects of IL-1.** The systemic effects of high dose (> 1 μg/kg) IL-1 following an intravenous injection into animals include hypotension, decreased systemic vascular resistance, depressed myocardial function, lactic acidosis, leukopenia, thrombocytopenia, vascular leak, pulmonary congestion, and tissue neutrophil infiltration with necrosis. The hypotensive effects of intravenously administered IL-1 in humans have been observed at doses below 1 μg/kg and hypotension is the major clinical response for limiting the maximal dose tolerated at 300 ng/kg. The hypotensive effect of IL-1 may be via various mechanisms. The hypotension following IL-1 injection into rabbits is blocked by cyclooxygenase inhibitors. Arterial perfusion with IL-1 increases prostanooid synthesis, which lowers the pain threshold to branykinin. A single large dose of IL-1 (> 500 μg/kg) is not nearly as lethal as the same or lower doses divided into two separate injections. TNF potentiates these effects of IL-1, whereas pretreatment with cyclooxygenase inhibitors blocks the response to the combi-
nation of TNF and IL-1. IL-1 inhibits vascular smooth muscle contraction independent of prostaglandin synthesis. The inhibition of smooth muscle contraction by IL-1 appears to be due to an L-arginine–dependent increase in nitric oxide production leading to increased guanylate cyclase activity.

Cultured endothelial cells exposed to IL-1 increase the expression of adhesion molecules, which leads to the adherence of leukocytes to endothelial surfaces. These IL-1-treated endothelial cells also increase procoagulant activity, tissue factor, PGE₂, prostaglandin I₃ (PGI₂), platelet activating factor (PAF), plasminogen activator inhibitor production, enhancement of thrombin-induced von Willebrand factor, and the synthesis of other cytokines including IL-1 itself. IL-1 also increases smooth muscle cell synthesis of itself, other cytokines, and platelet-derived growth factor, and serves as an autocrine growth factor for smooth muscle cells. These effects of IL-1 are thought to play a role in the development of arteriosclerosis and neovascularization. On the other hand, the proinflammatory effect of IL-1 on endothelial cells plays a role in vasculitis and the inhibition of cell growth, perhaps by downregulation of receptors for fibroblast growth factor.

**Endocrinologic effects of IL-1.** IL-1 effects on insulin production are reviewed above. Low doses of IL-1 increase spermatogenesis, whereas high doses are suppressive. IL-1 inhibits human chorionic gonadotropin-induced testosterone synthesis. Other IL-1 effects have been reported on granulosa cell function. IL-1 inhibits the function of thyrocytes, and stimulates PGE formation; in addition, thyrocytes appear to synthesize an IL-1–like molecule. Although adrenal tissue shows evidence of IL-1 staining, perfusion of adrenal tissue with IL-1 increases steroid synthesis induced by ACTH.

Within 10 minutes of an intravenous injection of IL-1, several neuropeptides are released into the systemic circulation; increased corticotropin releasing factor, ACTH, vasopressin, and somatostatin are induced by IL-1, whereas IL-1 inhibits thyroid-releasing hormone-induced prolactin release. The effect of IL-1 on ACTH release is via a cyclooxygenase metabolite pathway, and IL-1 acts synergistically with IL-6 in the induction of ACTH (R. Neta, personal communication, 1990). It has been proposed that IL-1-induced corticosteroids (via direct and indirect ACTH action) represent a biologic negative feedback loop because corticosteroids inhibit cytokine gene expression. The IL-1–induced corticosteroids serve some protective effect because adrenalectomized mice are markedly sensitive to the IL-1–induced lethality.

**Effect of IL-1 on immunocompetent cells.** Recombinant IL-1 participates in the mechanism of T- and B-cell activation. This activation is a particularly important issue because IL-6, IL-4, IL-7, and GM-CSF also act as "lymphocyte-activating factors." IL-1 receptors are present on resting T and B lymphocytes, their numbers are small (200 to 600), but T- and B-cell–derived lines often have large numbers of receptors. Despite many studies, it is still unclear whether IL-1 is required for an immune response to a foreign antigen. This issue is clouded because T cells synthesize IL-1. Earlier studies using nonrecombinant preparations of IL-1 should be carefully evaluated because small amounts of contaminating IL-6 act synergistically with IL-1 during T-cell activation. In some T-cell studies in the absence of macrophages, IL-1 may be present on contaminating B cells.

The most often described T-cell activating property of IL-1 is its ability to act in a costimulator assay with suboptimal concentrations of antigens or mitogens. IL-1 amplifies T-cell activation by inducing IL-2 and IL-2R gene expression, particularly in conjunction with antigens, mitogens, calcium ionophores, or stimulators of PKC. This result is usually demonstrated in T-cell lines but also in freshly obtained thymocytes. The induction of IL-4 in Th2 or IL-2 in Th1 cells provides true T-cell growth factors. As T cells mature and acquire the T-cell receptor (TCR), an IL-1 requirement appears less likely; however, immature T cells in the thymus lacking the TCR cannot be stimulated to synthesize IL-2 without IL-1. It seems that part of the controversy of whether IL-1 is required for T-cell activation rests with the expression of different surface receptors or methods of triggering the TCR.

In various experimental conditions, the activation of mature T cells by IL-1 is dramatically increased by IL-6. The combination of IL-1 plus IL-6 acts synergistically in IL-2 production. IL-6, which is also B-cell growth factor-2, can act as a true T-cell growth factor, whereas IL-1 serves as an augmentation factor.

IL-1 increases thymic epithelial proliferation, is produced by the thymic epithelium, and contributes to T-cell growth in the thymus, where it augments TCR-mediated apoptosis. A monoclonal antibody (MoAb) directed against the thymocyte receptor L3T4 blocks the ability of IL-1 to act as a comitogen and it has been speculated that the L3T4 molecule is functionally involved with IL-1–induced thymocyte proliferation. Other data show that the Ly-1 antigen may serve as an IL-1 receptor. The Ly-1 antigen is a glycosyl phosphatidylinositol–anchored membrane protein.

The D10.G4.1 murine T-helper-2 cell line responds to IL-1 in the femtomolar range and is often used to study T-cell responses to IL-1. The effect of IL-1 on these cells is not through increased production of IL-2 but rather of IL-4. The IL-1 receptors for these cells can be in excess of 20,000/cell. It remains unclear whether these cells are inducing a secondary cytokine such as IL-4 or colony-stimulating factor. The greatest number of high-affinity receptors for IL-1 exist on T-cell lines. These include the EL-4 mouse thymoma cell line, the LBRM33 mouse thymoma cell line, the NOB-1 line (a subclone of the EL4 cell), and the D10S subclone of the murine T-helper cell line, D10.G4.1. IL-1 alone does not induce IL-2 but requires a second signal, usually one which increases cytosolic calcium.

**Effect of IL-1 on B-cell activation.** Many investigators have shown that B cells and other cells serve as accessory cells in antigen recognition, but have failed to demonstrate a role for IL-1 because IL-1 cannot be detected in B-cell supernatants. This issue may have been resolved by studies
that demonstrate that B cells produce IL-1 and that B cells express membrane-bound IL-1.\textsuperscript{20} In fact, nearly all cells that can act as accessory cells produce IL-1. These cells include astrocytes, mesangial cells, keratinocytes, and endothelial cells. Effects of IL-1 on B cells and Ig production are similar to those shown for T cells, i.e., IL-1 acts as a helper or cofactor during the activation process, particularly together with IL-4. Other studies demonstrated that IL-1 synergized with various B-cell growth and differentiation factors, leading to increased proliferation and antibody formation. Some of the biologic activity of the natural B-cell growth and differentiation factors may have been due to the presence of IL-6. The ability of IL-1 to synergize with IL-6 on T-cell activation extends to B-cell activation. The ability of IL-1 to induce other B-cell stimulation factors, including IL-6, IL-4, and IL-2, must also be considered because these substances activate B cells.

**Hematopoietic effects of IL-1.** There are various levels at which IL-1 affects hematopoiesis.\textsuperscript{28,25} IL-1 induces the production of GM-CSF, G-CSF, M-CSF, IL-3, and other cytokines; IL-1 acts synergistically with CSFs and other cytokines on hematopoiesis. IL-1 regulates the cell cycle of the hematopoietic progenitor cell and protects early progenitor cells from cytotoxic agents. Protection of the early progenitor cell may be due to cell cycle changes.\textsuperscript{22} IL-1 enhances CSF synthesis from a variety of cells, particularly bone marrow stromal cells.\textsuperscript{12,23} and increased production can be through new mRNA transcription or, as in the case of GM-CSF, through stabilization of mRNA.\textsuperscript{18,22} IL-1 acts synergistically with IL-3, IL-6, G-CSF, and GM-CSF in the induction of specific-lineage and multilineage colonies.\textsuperscript{11,12} IL-1 also increases the survival of progenitor cells in vitro. IL-1 by itself has no effect on stem cell proliferation or differentiation but requires CSFs such as IL-3 and GM-CSF. Stem cell factor by itself also has no effect but synergizes with CSFs,\textsuperscript{22} it is possible that IL-1's activity on stem cells is due to induction of stem cell factor.

The necessary co-factor for colony formation after bone marrow treatment with cytokotic drugs was originally described as "hematopoietin-1" (H-1); during molecular cloning, H-1 was identified as IL-1α. There are no differences between the two forms of IL-1 for H-1 activity. In vivo, the H-1 activity of IL-1 acts on the early progenitor stem cell's responsiveness to CSF as well as inducing the CSF. A single injection of IL-1 stimulates circulating CSF in normal mice, protects stem cells, and accelerates the return of granulocytes following cytotoxic drugs or irradiation.\textsuperscript{24,25} Following a single injection of IL-1 (<1 μg/kg) into animals there are increased circulating granulocytes\textsuperscript{29} and precursor forms,\textsuperscript{29} which seem to be a direct effect of IL-1 and not mediated by IL-6. The peak elevation in circulating neutrophils in animals has been 4 hours and similar kinetics have been reported in humans administered IL-1.\textsuperscript{25,26} Higher doses of IL-1 result in granulocytopenia caused by endothelial cell adherence. In patients receiving IL-1 (68 ng/kg), receptors (type II) for IL-1 on circulating neutrophils were initially reduced, but after 6 to 8 hours there was up to a sixfold increase in IL-1 binding sites.\textsuperscript{51} Similar data were obtained by adding IL-1 directly to neutrophils in vitro.

Recent studies in humans suggest that IL-1 directly stimulates platelet production.\textsuperscript{25} Although this effect may be due to a synergy between IL-1 and IL-3, no changes in plasma IL-3 levels were observed during IL-1 treatment. The effect of IL-1 on platelet counts was observed at relatively low IL-1 doses of 1 or 10 ng/kg. After five daily intravenous injections of IL-1 into patients with cancer, there were no significant increases in peripheral platelet counts, but on day 6 and for the next 5 days there was a rapid increase from approximately 250,000 to 350,000, which reached peak elevations on day 10 and then slowly decreased to baseline counts on day 28. There was no statistically significant difference between 1 and 10 ng/kg doses of IL-1β. These data support the concept that IL-1 is acting on an early and primitive stem cell and are supported by animal studies.\textsuperscript{26} In cynomologous primates, IL-1 is more effective in releasing hematopoietic stem cells into the peripheral circulation than IL-3 and GM-CSF.\textsuperscript{24}

The continued use of IL-1 in vivo is associated with the induction of TNF, which exerts a suppressive effect on hematopoiesis.\textsuperscript{25} In rabbits and humans PBMC, IL-1 induces TNF gene expression and circulating TNF.\textsuperscript{25} IL-1 can also be directly suppressive on erythropoiesis but this suppression can be overcome with erythropoietin.\textsuperscript{263}

**IL-1−induced nonspecific resistance to infection and injury.** Early studies on nonspecific resistance to infection by Israeli scientists used bacterial products. Because most of these products induce IL-1, IL-1 was tested in models of infection and was shown to afford protection. Thus, IL-1 could replace bacterial products in the induction of this resistance; like bacterial substances, the agent is most effective when administered 24 hours before the challenge. Pretreatment with IL-1 has been used in a variety of models: infection in normal and granulocytopenic mice, endotoxin in mice with severe liver failure, hyperoxia in rats, immune colitis in rabbits, anaphylaxis in guinea pigs, lethal radiation in mice, and malaria (see Table 1). The most consistent finding is the lack of effectiveness if the IL-1 is delayed beyond the onset of the pathologic process leading to death or inflammation.

Although in models of infection in granulocytopenic mice there is the possibility of IL-1 accelerating bone marrow recovery, this is not the mechanism of protection and neither is protection related to a cyclooxygenase product.\textsuperscript{265} However, protection against colitis and hyperoxia are mediated, in part, by IL-1−stimulated prostaglandins.\textsuperscript{266,247} Explanations for how a single, low dose of IL-1 can be so effective in affording protection include IL-1's ability to downregulate the TNF and IL-1 receptors,\textsuperscript{163,248} induce oxygen scavenger molecules, or induce corticosteroids.

**COMPARISON OF IL-1, TNF, AND IL-6**

**IL-1 and TNF.** The biologic properties of TNF share remarkable similarities to those of IL-1, particularly the nonimmunologic effects of IL-1. Some lymphocyte-activating properties of IL-1 or IL-6 are shared with TNF, but these require considerably higher concentrations of TNF than of IL-1 or IL-6. Similar to IL-1, TNF induces fever by its direct ability to stimulate hypothalamic PGE\textsubscript{2} synthesis.\textsuperscript{65}
Levels of circulating TNF increase rapidly in human subjects injected with endotoxin. IL-1 and TNF both increase CSF in vitro and in vivo. On a weight basis in rabbits, TNF is more potent than IL-1 in producing a shock. Administration of anti-TNF antibodies to rabbits or baboons prevents the shock induced by endotoxin, but IL-1 levels are suppressed by anti-TNF therapy suggesting that IL-1 is under the control of TNF in some models.

**Synergism between IL-1 and TNF.** When the two cytokines are used together in experimental studies, the net effect often exceeds the additive effect of each cytokine. Potentiation or frank synergism between these two molecules has been demonstrated in studies on fibroblast production of PGE₂, the cytotoxic effect on certain tumor cells, and administration to tumor-bearing mice. IL-1 acts synergistically with TNF to protect rats exposed to lethal hyperoxia or radiation. IL-1 cytotoxic effects on the insulin-producing beta cells of the islets of Langerhans are dramatically augmented by TNF. Rats receiving intravenous infusions of IL-1 or TNF manifest metabolic changes reflected in plasma amino acid levels, but, when given together, negative nitrogen balance and muscle proteolysis can be demonstrated. Although high doses (10 to 20 μg/kg) of TNF produce a shock-like state with tissue damage, IL-1 and TNF act synergistically to produce hemodynamic shock and pulmonary hemorrhage at doses of only 1 μg/kg when given together. The synergism between these two cytokines seems to be caused by second message molecules rather than upregulation of cell receptors; in fact, IL-1 reduces TNF receptors.

**IL-1 and IL-6.** In some models, the production of IL-6 appears to be under the control of IL-1; for example, mice subjected to inflammatory event following intramuscular turpentine fail to produce IL-6 when pretreated with anti-IL-1 receptor antibodies. Like IL-1 and TNF, IL-6 is an endogenous pyrogen and an inducer of acute-phase responses. Because IL-1 and TNF induce IL-6, levels of IL-6 often correlate with the amount of fever and disease in patients. IL-6 levels have also been reported elevated in patients undergoing renal resection and in the cerebrospinal fluid of patients with CNS infections. IL-6 suppresses endotoxin- and TNF-induced IL-1 production. In general, IL-6 appears to be a weak inflammatory peptide. Of considerable importance is the observation that IL-1 and IL-6 both act as hematopoietin-1 on bone marrow cultures. In addition, IL-6 protects granulocytic mice against lethal Gram-negative infection similar to the protection afforded by IL-1; however, unlike IL-1 and TNF, IL-6 is radiosensitizing. Table 3 summarizes the comparison of the three cytokines.

**IL-1 in Human Disease**

**Circulating IL-1 in various disease states.** Before specific radio- or enzyme-linked immunoassays, it was necessary to chromatographically separate IL-1 from binding or inhibitory substances that interfered with bioassays. Using this method, small levels of biologically active IL-1 were detected in the circulation of healthy individuals. Elevated IL-1 circulating levels have been reported following strenuous exercise and in women following ovulation. With specific immunorecognition assays, the levels of IL-1β in health have been, with a few exceptions, under 60 pg/mL; however, this is dependent on whether serum or plasma is taken and the presence of acute phase reactants. Plasma in the presence of protease inhibitors results in better recovery than serum.

**Extraction methods are needed before IL-1β can be accurately detected by radio- or enzyme-linked immunoassays.** Putative IL-1 binding proteins have been α2-macroglobulin and the third component of complement. Extraction of plasma is particularly important in samples from patients with ongoing disease, once extracted, patients with acute exacerbations of rheumatoid arthritis had elevated plasma IL-1β levels that correlated with disease activity. Elevated circulating IL-1 has been reported in patients with renal allograft rejection, acute attacks of rheumatoid arthritis, and alcoholic hepatitis. IL-1 is elevated in burns and in sepsis due to a variety of different organisms. In some clinical settings it has been possible to induce IL-1, eg, following experimental endotoxin injection in volunteers; in patients after ultraviolet radiation for treatment of psoriasis, after high-dose IL-2 therapy, following cardiopulmonary bypass, and after OKT3 therapy for organ rejection. In each case, IL-1β (not IL-1α) reaches peak elevation 3 to 4 hours following treatment, whereas in these same studies, TNF peak levels occur at 60 to 90 minutes and return to the pretreatment level by the time IL-1β levels are maximal. In patients undergoing routine hemodialysis, several studies have shown elevations in plasma IL-1 levels 3 to 4 hours following the initiation of the procedure. IL-6 levels are also elevated in the same clinical settings and reach peak elevation with or after IL-1.

**IL-1 in human body fluids.** IL-1 has been detected in human joint fluids from patients with rheumatoid arthritis, osteo-arthritis, traumatic arthritis, and psoriatic arthritis. It is common to find IL-6 and TNF in the same fluids. In addition, IL-1 has been demonstrated in the CSF of patients with closed head trauma and meningitis. IL-1 in peritoneal, gingival, middle ear, ocular, and nasal fluids.
have been reported in different disease conditions compared with control fluid from healthy individuals who are undergoing a diagnostic procedure. Amniotic fluid contains IL-1, but in preterm delivery associated with infection these levels are elevated and thought to be a poor prognostic indicator.

Production of IL-1 ex vivo in cells from human disease states. The amount of IL-1 produced in PBMC from patients with various diseases compared with healthy control subjects has been examined. Two methods are used: spontaneous production ex vivo and inducible production in vitro. In healthy subjects, PBMC prepared in the strict absence of endotoxins or other contaminants do not contain mRNA for IL-1β (by Northern or polymerase chain reaction analysis) nor do they synthesize more than 40 pg/5.0 × 10⁶/24 h. Therefore, “spontaneous” production above these under endotoxin-free culture conditions suggests that the PBMC have been activated in vivo presumably because of the disease process. Another method is to stimulate the cells with small amounts of endotoxin and compare the production with that from the PBMC of healthy subjects. In those situations where increased production occurs, the assumption is that the PBMC were “primed” by the disease state in vivo; in those situations where induced production is lower than that of the healthy cohort, it is proposed that the disease state has suppressed normal responses to endotoxin or resulted in an intrinsic production defect.

The production of IL-1 from PBMC in different disease states should be interpreted with caution. Bioassays are vulnerable to inhibitory molecules and the synergistic effect of more than one cytokine on the bioassay target cells. Specific immunoreactive reactive assays for IL-1β and IL-1α are preferred. Cytokine synthesis from PBMC varies depending on (1) the time of day, (2) dietary fat content and type of fatty acid of the subject,25 and (3) consumption of cyclooxygenase inhibitors,26 antihistamines, H2 receptor blockers,27 antimalarials, corticosteroids, calcium channel blockers, and angiotensin-converting enzyme inhibitors. Separating monocytes from the other cell types in PBMC by adherence, surface antigens, or elutriation selects different populations of monocytes with different sensitivity to endotoxin or production levels of IL-1. The presence of non-monocytic cells in the PBMC contributes to the production of IL-1 depending on the type of stimulus used.

IL-1 production from patients with inflammatory or autoimmune diseases. There are several studies that suggest that PBMC or monocytes from patients with active rheumatoid arthritis produce more IL-1 than do cells from normal individuals. Patients with ankylosing spondylitis produce the same amount of IL-1 as that produced by monocytes from healthy control subjects, whereas decreased IL-1 production has been consistently demonstrated from monocytes of patients with scleroderma or systemic lupus erythematosus. Tonsillar mononuclear cells from patients with rheumatic heart disease produce less IL-1 than controls.28 Other disease states such as alcoholic hepatitis, sarcoidosis, and AIDS have been reported. Table 4 lists the disease processes where spontaneous or endotoxin-inducible IL-1 has been reported.

<table>
<thead>
<tr>
<th>Disease States</th>
<th>Elevated Production</th>
<th>Depressed</th>
<th>“Normal”</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA (synovial lining cells)</td>
<td>Schistosoma infection</td>
<td>Lungs cancer</td>
<td>RA</td>
</tr>
<tr>
<td>HIV infection and AIDS</td>
<td>Systemic lupus erythematosus</td>
<td>Lung Cancer (AM)</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>Respiratory distress syndrome (AM)</td>
<td>Smokers</td>
<td>Lipoid nephrosis</td>
</tr>
<tr>
<td>Respiratory distress syndrome (AM)</td>
<td>Alcoholic cirrhosis</td>
<td>Respiratory viral infection</td>
<td>Rheumatic fever (tonsillar cells)</td>
</tr>
<tr>
<td>Smokers (AM)</td>
<td>Cuprophane hemodialysis</td>
<td>Cardiopulmonary bypass</td>
<td>Scleroderma</td>
</tr>
<tr>
<td>Coal miner pneumoconiosis (AM)</td>
<td>Chronic hepatitis B</td>
<td>Cardiopulmonary bypass</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Alcoholics</td>
<td>Thermal injury (burn)</td>
<td>Rheumatic fever</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Cancer</td>
<td>Reticulohistiocytosis</td>
<td>Sarcoidosis; tuberculosis</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Obstructive jaundice</td>
<td>Hodgkin’s disease</td>
<td>Obstructive jaundice</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Pagets’s disease and osteomalacia</td>
<td>IDDM (newly diagnosed)</td>
<td>Pagets’s disease and osteomalacia</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Pagets’s disease and osteomalacia</td>
<td>Kawasaki’s disease</td>
<td>Pagets’s disease and osteomalacia</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Pagets’s disease and osteomalacia</td>
<td>Inflammatory bowel disease (mucosal mononuclear cells)</td>
<td>Pagets’s disease and osteomalacia</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Pagets’s disease and osteomalacia</td>
<td>Rutile phase; strenuous exercise</td>
<td>Pagets’s disease and osteomalacia</td>
<td>Metastatic cancer</td>
</tr>
</tbody>
</table>

Data are derived from studies using either bioassays or immunoreactive assays.

Abbreviations: RA, rheumatoid arthritis; AM, alveolar macrophages; IDDM, insulin dependent diabetes mellitus.

IL-1 production from neoplastic and leukemic cells. The first studies demonstrating spontaneous IL-1 production from malignant cells described the spontaneous production of endogenous pyrogen from PBMC of patients with monocytic leukemia, lymph node cells from patients with Hodgkin’s, and renal cell carcinoma tissue.29 Using specific mRNA probes and immunosassays, spontaneous IL-1 production has been observed in B cells of chronic lymphocytic leukemia,25 adult T-cell leukemia associated with infection by the human T-lymphotropic virus type 1,26,32 Reed-Sternberg cells,29 myeloma cells,20,39 acute myelogenous leukemia blasts,27,29 and chronic granulocytic leukemia of the juvenile type.27,28 Using a mouse acute myeloid leukemia model induced by radiation, a translocation of the IL-1β gene on chromosome 2 was observed resulting in deregulation of IL-1β gene expression.30

IL-1 ANTAGONISM

Naturally occurring inhibitors of IL-1 activity. Lipoproteins, lipids, and α-2 macroglobulin are examples of naturally occurring substances that inhibit IL-1 activity; but these molecules also inhibit other cytokines, such as IL-6 and IL-2. However, there are polypeptides which specifically inhibit IL-1; these have been detected in the serum of human volunteers injected with bacterial endotoxin,30 urine of febrile patients,32 plasma following hemodialysis,33 supernatants of human monocytes adhering to IgG-coated sur-
faces, and urine of patients with monocytic leukemia. An IL-1-specific inhibitory molecule of 52 to 66 Kd secreted from a human myelomonocytic cell line, and the mouse macrophage cell line, P388D, have also been reported. Another inhibitory material isolated from the urine of pregnant women had been identified as uromodulin, which is a glycosylated form of the Tamm-Horsfall protein. The carbohydrate portion of uromodulin binds IL-1 as well as TNF and other cytokines and is thus nonspecific. IL-1 inhibitory activities have also been reported from virus-infected monocytes, blood neutrophils, UV-exposed keratinocytes, Epstein-Barr infected B-cell lines, and from normal submandibular glands.

The IL-1ra. The IL-1ra was originally called the “IL-1 inhibitor”; it was a 23- to 25-Kd protein purified from the urine of patients with monocytic leukemia. Natural IL-1 inhibitor blocked the ability of IL-1 to stimulate synovial cell PGE2 production and thymocyte proliferation, and decreased insulin release from isolated pancreatic islets. It is unclear whether similar IL-1-specific inhibitory activities found in the serum during endotoxemia in the urine of patients with fever or secreted from myelomonocytic cell lines share identity with the IL-1ra. However, in each case, the IL-1 inhibitory activity was shown to prevent IL-1 but not IL-2 or mitogen-induced T-cell proliferation. The “IL-1 inhibitor” blocked the binding of IL-1 to receptors on T cells and fibroblasts but did not affect the binding of TNF or IL-2 to their receptors. The IL-1 inhibitor also did not bind to IL-1 itself, unlike the TNF inhibitors, which were also isolated from the urine, and which have been recently shown to be the soluble forms of the two TNF receptors. Thus, the IL-1 inhibitor was a competitive inhibitor of IL-1/IL-1R interaction.

Using the IL-1 inhibitor purified from adherent monocytes, N-terminal sequence was obtained and the molecule was cloned. The cDNA sequence codes for a polypeptide of approximately 17 Kd, whereas the 25-Kd molecular weight is due to glycosylation. The amino acid sequence deduced from the cDNA showed a 26% amino acid homology to IL-1β and a 19% homology to IL-1α. Conserved amino acids as defined by Dayhoff et al. showed a 41% homology of the IL-1ra to IL-1β and 30% to IL-1α. The IL-1ra was also cloned from U937 cells and reported as the IL-1 receptor antagonist protein (IRAP). Figure 2 illustrates the sequence alignments of the three proteins. The alignment of IL-1ra amino acids is distributed throughout both IL-1 forms. Mutations in the IL-1β or α amino acids are marked with asterisks (see section on Structural Analysis of IL-1). The arginine in position 120 of IL-1β has been mutated to glutamic acid with loss of biologic activity; in the IL-1ra and IL-1α, there is a lysine (conserved) residue, suggesting a role for these basic amino acids in biologic and receptor-binding activity. The arginine at position 127, when mutated to a glycine, still binds to cells expressing the IL-1RI but without bioologic activity and at this position there is a tryptophan in the IL-1ra. There has also been a mutation of IL-1β at position 125 (threonine to glycine) with an associated loss of 99.6% of bioologic activity, but little change in receptor-binding affinity. Mutations of the histidine in the IL-1β position 146 (150 in IL-1α) results in loss of both biologic activity and binding capacity; in the IL-1ra, this position is occupied by a tyrosine, although the adjacent amino acids are homologous with the IL-1ra for both IL-1β and α. The other asterisks depict amino acid mutations for IL-1 at which sites the IL-1ra has either conserved or perfect homology with IL-1β. The two cysteines in IL-1β have been shown to provide structural stability in the reduced form; the IL-1ra is homologous with the cysteine in carboxyl end of IL-1β, but not the N-terminal cysteine at 124. However, the IL-1ra is homologous with the phenylalanine in IL-1α in N-terminus. The lysine of IL-1β in the carboxyl end had been changed to a cysteine without affecting bioologic activity or binding.

Similar to the purified naturally occurring IL-1 urinary inhibitor, the recombinant IL-1 inhibitor competes with...
the binding of IL-1 to its cell surface receptors. Because of its sequence homology and mode of activity, the IL-1 inhibitor was renamed the IL-1 receptor antagonist (IL-1ra). Recombinant human IL-1ra expressed by *Escherichia coli* is not glycosylated but blocks binding of IL-1 equally well as the glycosylated natural form.

The IL-1ra blocks IL-1 activity in vitro and in vivo. In vitro, the IL-1ra appears to occupy the IL-1R11 on T cells and fibroblasts with nearly the same affinity as that for bone fide IL-1 but without demonstrable agonist activity.292 On the other hand, in murine pre-B cell lines that express only the p68 IL-1R (IL-1R11) there was no blockade of IL-1 binding by the IL-1ra.292,295,296 However, this finding appears to be caused by species differences of the human receptor antagonist for murine cells because human IL-1ra blocks the binding of IL-1 to human cells bearing the IL-1R11 such as neutrophils and B cells299 as well as human peripheral myelomonocytic leukemia cells.300 Using murine T cells (IL-1R11), the human IL-1ra blocks the binding of IL-1 at nearly equimolar concentration; however, a 10-fold to 50-fold molar excess of the IL-1ra is required to block the binding of human IL-1 to human type II receptor-bearing cells.296

It is not surprising that recombinant IL-1ra will block the activity of IL-1 in various animal models of disease. Rabbits301 or baboons (L. Moldawer, personal communication, 1991) injected with IL-1 develop hypotension, which is reversed by prior administration of the IL-1ra. However, a larger question remains: during acute or chronic disease several cytokines are produced but what is the effect of specific blockade of IL-1? For example, when baboons subjected to *E. coli* sepsis are pretreated with an MoAb to TNF, attenuation of severity of the hemodynamic parameters is observed.251 Although this result would suggest an essential role for TNF in the pathogenesis of septic shock, baboons pretreated with anti-TNF had markedly diminished levels of circulating IL-1.251 Because hypotension and death to *E. coli* can be prevented by the IL-1ra (see below), the role for TNF in the pathogenesis of hypotension appears to include the induction of IL-1.

**Effect of IL-1ra on septic shock.** The administration of IL-1ra prevents death in rabbits due to LPS.300 The intravenous injection of *E. coli* suspensions to rabbits produces several parameters of the septic shock syndrome, namely, hypotension, decreased systemic vascular resistance, leukopenia, thrombocytopenia, and tissue damage. When rabbits were pretreated with the IL-1ra, only a transient and mild hypotensive episode was observed, whereas severe and sustained hypotension with a 50% mortality was observed in control rabbits.302 There was also reduced numbers of tissue infiltrating neutrophils. In these studies the circulating levels of TNF and IL-18 (as determined by specific radioimmunoassay) were unchanged. The interpretation of these results suggests that TNF may be responsible for the initial fall in blood pressure but that IL-1 is playing an essential role in the progression of the shock state. The human IL-1ra also prevents lethal *Klebsiella pneumoniae* sepsis in newborn rats303 and *E. coli* induced hypotension in baboons (Moldawer, personal communication, 1991).

**The IL-1ra in immune complex-induced colitis.** A role for IL-1 has been proposed in the pathogenesis of inflammatory bowel disease. Three studies support this conclusion: (1) rabbit colonic tissue releases large amounts of PG_E, and LTB_ for several hours following a brief period of perfusion with IL-1;304 (2) there is a reduction in the severity of colonic inflammation in rabbits pretreated with a single low dose of IL-1 24 hours before the induction of colitis;305 and (3) the degree of inflammation, edema, and necrosis in colonic tissue correlate with the tissue levels of IL-1 in these tissues.306 Although IL-1 levels and tissue injury correlate, these data do not necessarily support an essential role for IL-1 in the pathogenesis of colitis in this model as other inflammatory cytokines may also be involved. However, when rabbits were pretreated with the IL-1ra, a marked decrease in tissue inflammatory cell infiltration, edema, and necrosis was observed.306 In addition, decreased PG_E was measured in the rectal lumen despite the fact that IL-1 tissue levels were unchanged.307 Together, these data demonstrate that blockade of IL-1 prevents the onset and development of the inflammatory lesion in this model of immune complex-induced colitis.

**Effect of IL-1ra on spontaneous CSF production by acute myelogenous leukemia cells.** IL-1 induces CSFs from fibroblasts, endothelial cells, lymphocytes, and blood monocytes.308,309,310,311 As discussed above, myeloma and Hodgkin’s cells as well as B, T, granulocytic, and acute myelogenous leukemic cells spontaneously produce IL-1. Transcripts for IL-1 beta have been detected in acute myelogenous leukemia cells and receptors for IL-1 exist on leukemic cells.309,310 An autocrine role for IL-1 has been proposed in which IL-1 production by leukemic blasts is uncontrolled and results in production of CSFs that, in turn, drive proliferation of the cells. Antibodies to human IL-1B reduce the spontaneous proliferation and colony-stimulating activity production of juvenile type chronic granulocytic and acute myelogenous leukemia cells.310 Therefore, it was hypothesized that growth factor production is under the control of IL-1 in these cells. Recent studies have shown that the IL-1ra blocks the spontaneous proliferation as well as spontaneous production of GM-CSF, IL-1, and IL-6 in peripheral blood or bone marrow-derived acute myelogenous leukemia cells from over 25 patients.300 The leukemic cell spontaneous proliferation was inhibited in each case; cells from some patients were inhibited by concentrations of 1 ng/mL, whereas cells from all patients were inhibited at 100 ng/mL. The IL-1ra reduced the spontaneous production of GM-CSF in each case. The IL-1ra was removed after 48 hours of exposure and the leukemic cells showed evidence of death during a subsequent 72 hours of incubation without the receptor antagonist. These studies suggest that IL-1 is controlling the production of GM-CSF in these cells and that treatment with the IL-1ra may be highly effective in reducing the proliferation of these leukemia cells.

**Other effects of the IL-1ra.** The recombinant IL-1ra blocks IL-1 augmentation of thymocyte proliferation to mitogens, IL-1-induced synovial cell PGE synthesis, and collagenase synthesis from chondrocytes.312 To inhibit 50%
of these IL-1-induced responses in vitro, 100-fold excess IL-1ra is required. The IL-1ra also blocks the production of IL-1-induced IL-1, TNF, and IL-6 from human PBMC as well as from purified monocytes. However, 50% inhibition is observed at equimolar ratios, whereas at 10-fold molar excess of IL-1ra to IL-1 a complete inhibition is observed. In a rabbit model of meningeal inflammation, the IL-1ra blocks cerebrospinal pleocytosis induced by cerebroventricular IL-1 and this requires 5,000-fold excess IL-1ra to block 90% of the IL-1-induced pleocytosis. A similar study has shown that intracerebroventricular injection of 100 µg of the IL-1ra (10,000-fold excess) blocks non-rapid eye movement sleep and fever induced by 10 ng of IL-1B administered by the same route. Systemic injection of the 100-fold molar excess of the IL-1ra blocks 95% of the fever caused by the intravenous injection of IL-1 in rabbits. Administration of the IL-1ra to rats with adjuvant arthritis has reduced the severity of the joint lesions.

**Antibodies to the IL-1R.** Antibodies have been produced to the IL-1R1 on murine cells. These antibodies have been shown to block IL-1 effects in vitro and in vivo. They have also been used in models of sepsis, inflammation, and radiation and show significant responses of animals to IL-1 or LPS are mediated by the IL-1R1. For example, mice administered intraperitoneal injections of IL-1 develop peritonitis with large numbers of neutrophils; however, prior treatment with anti-IL-1R1 prevents the influx of neutrophils, synthesis of serum amyloid A protein, and circulating IL-6 levels. Anti-IL-1R1 also blocks the neutrophil influx in response to endotoxin by 50%. Mice administered an intramuscular injection of turpentine manifest several acute phase changes typical of inflammation such as decreased food intake, weight loss (lean and fat loss), IL-6 production, hepatic synthesis of amyloid P component, and elevated corticosterone levels. When anti-IL-1R1 was administered before the inflammatory event, 80% to 90% of the intensity of the responses were reduced with the exception of elevated corticosterone levels. The protective effect of IL-1 on lethal radiation appears to be caused by the type I receptor because anti-type I receptor antibodies block this IL-1 response and also the protective response induced by LPS. These findings demonstrate that other cytokines induced by the turpentine manifest several acute phase changes typical of inflammation such as decreased food intake, weight loss (lean and fat loss), IL-6 production, hepatic synthesis of amyloid P component, and elevated corticosterone levels. When anti-IL-1R1 was administered before the inflammatory event, 80% to 90% of the intensity of the responses were reduced with the exception of elevated corticosterone levels. The protective effect of IL-1 on lethal radiation appears to be caused by the type I receptor because anti-type I receptor antibodies block this IL-1 response and also the protective response induced by LPS. These findings demonstrate that other cytokines induced by the turpentine manifestation or LPS are secondary to the production and activity of IL-1.

**Soluble IL-1R proteins.** The extracellular domain of the IL-1R1 has been expressed and shown to bind both forms of IL-1. Unlike soluble TNF, IL-6, and INFγ receptors, which occur naturally in the urine, soluble IL-1R have yet to be found naturally. When the recombinant soluble IL-1R1 was administered to mice undergoing heart transplantation, survival of the heterotopic allografts was increased. Lymphnodes directly injected with allogeneic cells have reduced hyperplasia with the use of the soluble IL-1R1. However, it is unclear from these experiments how much of the effects of the soluble type I receptor is due to decreased inflammation rather than decreased immunoresponsiveness. There are no data suggesting that the type I IL-1R is naturally shed; however, conditioned media from the IL-1R1-bearing Raji cells contain the soluble form (35 to 45 Kd) of the IL-1R1.

**TGFβ, IFNγ, retroviral envelope protein, α-melanocyte-stimulating factor (αMSH), and corticotropin-releasing factors.** These structurally unrelated proteins possess the ability to oppose the biologic action of IL-1 in vitro as well as in vivo. None of these substances antagonize the action of IL-1 by interfering with IL-1 binding to its surface receptors, although in the case TGFβ, IL-1R expression is reduced. TGFβ blocks bacterial shock in rats and IL-1-induced T-cell proliferation; however, these effects are not specific for IL-1 as TNF and IL-2 production are also inhibited. TGFβ and IFNγ both antagonize the ability of IL-1 to induce bone resorption and cartilage degradation independent of cyclooxygenase products. A 17-amino acid peptide derived from the envelope protein of T-lymphotropic retroviruses is immunosuppressive and appears to specifically block IL-1 effects, but not by interfering with receptor binding nor binding to IL-1 itself.

Several neuropeptides, such as somatostatin and thyroid-releasing factor, have been shown to block the fever-inducing property of IL-1 but this effect is not specific to IL-1. Corticotropin-releasing factor inhibits IL-1-induced PGE synthesis, sleep, and anorexia. However, all of the neuropeptides, αMSH is an effective inhibitor of many of IL-1’s effects such as fever, sleep, hyperalgesia, neutrophilia, neutrophil infiltration into tissues, suppression of contact hypersensitivity to antigens, mause paw edema, increases in hepatic acute phase proteins, induction of fibroblast PGE synthesis, thymocyte proliferation, and release of ACTH. These effects are observed when the neuropeptide is administered peripherally and there is no evidence of tolerance to its inhibiting effects. Fever following TNF injection is also inhibited by αMSH. The reduction in hepatic C-reactive protein induced by injection of IL-1 by pretreatment with αMSH may be via inhibition of IL-1-induced IL-6 synthesis; the inhibition of IL-1-induced neutrophil accumulation by αMSH may be via inhibition of IL-1-induced IL-8 synthesis. The effects of αMSH on IL-1 activities can also be shown for a carboxyl terminal tripeptide, lysine-proline-valine.

Pretreatment of rabbits with an analogue of muramyl dipeptide, methyl ester muramyl dipeptide, blocks the fever induced by IL-1 but has no effect on sleep. When administered at the same time as IL-1, the analogue enhances the febrile response. Methyl ester muramyl dipeptide, like αMSH, does not block the binding of IL-1 to its surface receptors and, hence, these agents cannot be classified as IL-1 receptor antagonists. They likely suppress IL-1 activity by altering IL-1 signal transduction. Nevertheless, they may be useful to block IL-1 activity in some limited clinical situations.

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