CMNSG Guest Lecture

Interleukin-1, interleukin-1 receptor, and interleukin-1 receptor antagonist

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Interleukin (IL)-1 is a pleitrophic cytokine that induces the acute response to injury; it is an endogenous pyrogen and promotes the synthesis of other pro-inflammatory cytokines. The IL-1 family, IL-1, the IL-1 cell-membrane receptor and endogenous IL-1 receptor antagonist (IL-1ra), are the focus of the present report.

Historically the biological activities of IL-1 have been well documented. IL-1 is not a new protein, since as early as the 1940s this material was known as 'endogenous pyrogen' for its ability to produce fever (Dinarello, 1988). The purified form of that material revealed a co-substance that was later called 'leukocytic endogenous mediator' which induced hepatic acute-phase-protein synthesis, decreased plasma Fe and Zn levels and produced a neutrophilia (Dinarello *et al.* 1986*b*). At present, the term IL-1 incorporates the activities and effects of the original endogenous pyrogen, leukocytic endogenous mediator, lymphocyte-activating factor, mononuclear cell factor, osteoclast-activating factor, catabolin, and haemopoetin 1.

INTERLEUKIN-1

Modern protein-purification and cDNA-cloning techniques have revealed that there are in fact two separate but distantly related polypeptides, IL-1α and IL-1β, which possess the biological activities previously ascribed to a single polypeptide. These two bio-logically-distinct but structurally-related molecules have been cloned and studied. They are known to have 26% amino acid sequence homology in the human, and each is thought to be coded and produced by separate genes both located on chromosome 2. Receptors for IL-1 equally recognize the β and α forms, and both possess the same spectrum of biological activity (Last-Barnet *et al.* 1988).

The IL-1β form predominates in the circulation. It is known to exist as a cytosolic protein and is released as a consequence of macrophage activation. When released, IL-1β is an inactive 31kd pro-form which requires serine protease-mediated cleavage for activation (Dinarello *et al.* 1986*a*).

The IL-1α form is a transmembrane constitutively bound protein that is active in its pro-form, and is not generally released. Because IL-1α lacks systemic capabilities its functions are paracrine and it is responsible for immunostimulatory effects seen on local tissues such as lymph nodes, joints and skin (Gubler *et al.* 1986).

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INTERLEUKIN-1 RECEPTORS

There are two distinct IL-1 receptors, type I and II, these differ in structure and are the products of separate genes. Ligand activation of the receptors is presumed to occur by one of two mechanisms; one in which ligand binding induces receptor aggregation, and the second postulates a ligand-induced conformational change transmitted through a membrane spanning region into the cytoplasmic domain (Chizzonite *et al.* 1989). The distribution of type I and type II receptors on various tissue types varies greatly. Type I receptors are found on most cell types, including T-lymphocytes, endothelial cells and hepatocytes. Type II receptors are limited to blood neutrophils, monocytes, bone-marrow progenitor cells and B-lymphocytes. The intracellular portion of the type II receptor is truncated and it is unclear whether binding to this receptor results in signal transduction. The extracellular domain of the type II receptor, but not the type I, is shed during inflammation and is capable of binding circulating IL-1α and β forms, which prevents their interaction with cellular receptors (Sims *et al.* 1990; Dower *et al.* 1992).

The anorexia, weight loss and the induction of hepatic acute-phase synthesis are functions of IL-1 binding to its type I receptor. Receptor blockade of the type I receptor attenuates the previously described responses, whereas type II receptor blockade exacerbates acute-phase response. This indicates that type II receptor blockade magnifies the inflammatory response by redirecting endogenously produced IL-1 to the type I receptor. Previous investigations have suggested that type II receptors do not lead to classic IL-1 agonist effects, and that perhaps IL-1 binding to the type II receptor may have anti-inflammatory capabilities (Sims *et al.* 1990).

INTERLEUKIN-1 RECEPTOR ANTAGONIST

Studies have elucidated the existence of an IL-1ra, with IL-1 regulatory capacity. Initial results from Arend *et al.* (1990) on a murine recombinant IL-1ra revealed a dose-dependent response-inhibition on the effects of IL-1. It is important to note that a 5–100-fold greater amount of IL-1ra is necessary to achieve a 50% inhibition of IL-1α/IL-1β stimulation of murine thymocytes, human synovial cells, or rabbit articular chondrocytes. This applies despite the fact that the receptor antagonist protein binds to the IL-1 receptors on all three cell types with equal affinity as IL-1α/β. It is probable that this occurs because maximal biological IL-1 response can be observed with <5% of total receptors being occupied. IL-1ra has been shown to impede IL-1-induced prostaglandin E2 (PGE2) synthesis by human foreskin fibroblasts, and yet exhibit no agonist effects. IL-1ra has not been found to have IL-1 agonist biological activity but shares receptor binding affinity similar to the agonists, IL-1α, and IL-1β (Dinarello, 1991; Thompson *et al.* 1992).

Moldawer *et al.* have shown that baboons produce a natural IL-1ra in response to lipopolysaccharide (LPS) or *Escherichia coli* challenge. This implies that IL-1ra is a naturally-occurring anti-inflammatory agent; however, the amount produced, while greater than the circulating IL-1, is far short of the 100–1000-fold levels needed for full efficacy (Arend *et al.* 1990; Moldawer, 1992).

IL-1ra does not interfere with cytotoxic T-cell response or mixed lymphocyte reaction. The possible mechanism for its function is, therefore, a selective suppression of immune components in the inflammatory response. Furthermore, it inhibits the recruitment of

neutrophils to the site of inflammation and the activation of local cells to make proteases and inflammatory lipid mediators (Birkhahn *et al.* 1980; Gershenwald *et al.* 1990).

SYSTEMIC EFFECTS OF INTERLEUKIN-1

Metabolic consequences

IL-1 is known to induce peripheral proteolysis, negative N balance, loss of lean body mass, hepatic protein synthesis, and increased basal metabolic expenditure in response to the inflammatory stimuli. The nutritional depletion and whole-organ catabolism seen with IL-1 is additive and synergistic with the effects of tumour necrosis factor (TNF), and as a syndrome is termed cachexia (Moldawer *et al.* 1987; Fong *et al.* 1989; Castell *et al.* 1990).

Hepatic effects

Most notably, besides its own specific effects, IL-1 induces production and release of IL-6. IL-6 has been shown to be a key mediator in the hepatic acute-phase response. The hepatic response to IL-1-mediated IL-6 production is selective protein synthesis of amyloid A, complement protein C3, α-1-antichymotrypsin, α-1 acid glycoprotein, inter-α-1-trypsin inhibitor and other acute-phase proteins (Geiger *et al.* 1988).

In addition, IL-1 inhibits lipoprotein lipase (*EC* 3.1.1.34) synthesis, thus severely limiting host capability to use stored lipids as a source of metabolic fuel. Furthermore, incorporation of triacylglycerols (TAG) into adipocytes is inhibited and high levels of blood TAG and deposition of lipid within the liver occur (Fong *et al.* 1990; Mule & Rosenberg, 1992).

The capacity of the liver to metabolize drugs is altered as there is an IL-1-induced depression in the activity of the P-450 cytochrome oxidase (*EC* 1.14.15.6) system.

Inflammatory response

Increased IL-1 levels result in the synthesis and release of TNF, IL-2, IL-6, the interferons, and other bone-marrow-stimulating factors (Moldawer, 1991). The cellular inflammatory response is modulated through increased production of arachidonic acid metabolites which lead to increased synthesis and release of prostaglandins and thromboxane. As an overall process, bone marrow is stimulated to produce increased numbers of granulocytes which are subsequently recruited to the area of injury. The granulocytic chemoattractant capacity and their subsequent trans-endothelial diapodesis are enhanced by a state of physiological hyperdynamics, compounded with vascular endothelial leak. Aggregation of granulocytes with subsequent degranulation lead to elevated local IL-1 levels and the resultant effects on the end organ.

Hypothalamic effects

IL-1 acts on the hypothalamus to alter the thermoregulatory centre temperature set-point, initiating fever. Furthermore, it induces the synthesis of PGE2 from the hypothalamic vascular organs. This release of PGE2 promotes pituitary release of

endorphins, and adrenocorticotrophic hormone (ACTH) (Endres *et al.* 1987; Goldberg *et al.* 1988).

Adrenocortical axis

IL-1 induces hypothalamic-mediated release of ACTH. ACTH increases the level of circulating corticosterone, and directly augments adrenal steroid synthesis. Increased Na excretion is also noted in response to IL-1 infusion (Lumpkin, 1987).

Vascular effects

IL-1 results in the increased synthesis of PGE2 and PGE1, as well as production of platelet-activating factor (PAF), which are potent vasodilators. When administered intravenously IL-1 induces a prompt but reversible hypotension. More chronic and deleterious effects include vascular congestion, hypercoagulability with clot formation, and endothelial leak (Rossi *et al.* 1985; Nachman *et al.* 1986; Dejana *et al.* 1987).

Effects on T- and B-lymphocytes

Previously classified as 'lymphocyte-activating factor', IL-1 was defined as a soluble factor, produced by activated monocytes, that was required for T-cell immune response. IL-1 is required as a second signal for antigen-activated T-cells to synthesize and release IL-2. In addition IL-1 induces or enhances the expression of IL-2 receptors on T-cells and, thus, plays a key role in the IL-2-driven expansion of antigen-reactive T-cell populations. It also reduces the threshold for the antigen-induced T-lymphocyte proliferation (Dinarello *et al.* 1987; Bertoglio, 1988).

Also IL-1 has been shown to have direct and indirect effects in the stimulation of B-lymphocytes. Specifically, it promotes proliferation of activated B-lymphocytes by synergizing with the effects of B-cell growth factor, and enhances immunoglobulin synthesis (Mannel *et al.* 1980; Bertoglio, 1988).

MODULATION OF INTERLEUKIN-1

Pharmacologically, corticosteroids block the direct production of IL-1. Whether this mechanism is due to feedback inhibition or is dependent on ACTH is not known (Rossi *et al.* 1985). Cycloxygenase inhibitors, such as the non-steroidal anti-inflammatory agents, are useful in reducing IL-1-induced prostaglandin and thromboxane synthesis, thus diminishing the inflammatory response mediated by the substances, including pain, oedema, endothelial leak, and fever (Goldberg *et al.* 1988). Endogenous receptor antagonist in exaggerated concentration to IL-1, also, have been found to decrease the agonist effect of IL-1-mediated activities (Arend *et al.* 1990). Ultimately, it is the production of IL-1 and the duration of its effects that determine the net results of its release.

INTERLEUKIN-1-INDUCED DISEASE

There are several inflammatory diseases in which the pathological processes are believed to occur as a result of unregulated or unbalanced interaction between IL-1 and IL-1ra.

Diseases such as septic shock, rheumatoid arthritis, myeloblastic leukaemia, ulcerative colitis, tuberculosis, sarcoidosis, to name a few, have been shown to have elevated IL-1 as part of the physiological manifestation of the disease process (Dinarello & Endres, 1989).

Rheumatoid arthritis (RA)

RA is a systemic disease that can affect every organ of the body, including the cardiovascular, respiratory, nervous and musculoskeletal systems. Specifically, RA is characterized by congested and oedematous diarthroid joints, tendons, bursa and adjacent tissues (Duthie & Hoaglund, 1989). The articular cartilage is covered with inflammatory and reactive fibrin and collagen deposits, synovial tissues are infiltrated by mononuclear cells, proliferating fibroblasts and endothelial cells. Erosive changes with gross deformities of the joints are further hallmarks of this autoimmune disease (Arend *et al.* 1985). It is thought that the joint inflammation and subsequent evolution to joint destruction in RA result from the failure of the delicate balance between the production of pro-inflammatory cytokines and their inhibitors (Arend & Dayer, 1990). IL-1 is found in increased quantities in the joint fluid of individuals with RA, where it is thought to contribute to pain, leukocyte migration, and tissue remodelling. In addition to attracting leukocytes to the area, IL-1 also causes degranulation of basophils and eosinophils, stimulates thromboxane synthesis and potentiates the chemoattractant properties of migratory neutrophils (Harris, 1988; Carmichael *et al.* 1989). IL-1 is synonymous with osteoclast-activating factor and, furthermore, it is responsible for the improper deposition of abnormal proteins and thickening of scar tissue, which then lead to restrictions in joint movement (Esser *et al.* 1985).

Eisenberg *et al.* (1990) have demonstrated *in vitro* that the use of IL-1ra at a concentration 10-fold greater than IL-1 prevents bovine cartilage breakdown.

In contrast to RA, in patients with osteoarthritis, a non-inflammatory degenerative disease of the joints, the synovial tissues have fewer IL-1- and IL-1ra-positive macrophages. Thus, the production of IL-1 which is unbalanced by insufficient IL-1ra may contribute to the joint destruction found in the inflammatory joint diseases, such as RA (Moissec, 1987; Harris, 1990).

Acute myeloblastic leukaemia (AML)

Myeloblastic leukaemia is a malignancy of the bone marrow in which immature myeloblasts are produced in greatly increased quantities and released into the circulation. Myeloblasts are the most primitive precursors of the granulocytic, haematopoetic cell series, and are not normally found in the peripheral blood. Their overabundance in the circulation correlates with a general failure of normal erythrocytes to achieve full and functional maturation (Young *et al.* 1987; Schwartz, 1989).

IL-1 has been demonstrated to be spontaneously produced in cultured cells of patients with AML cells. IL-1 also induces the synthesis of colony-stimulating factors (CSF) and sustains leukaemic growth (Cozzolino *et al.* 1990; Rodriguez-Cimadevilla *et al.* 1990). Recent studies have revealed that the use of IL-1ra on proliferate blast cells from the marrow of patients with AML inhibits their spontaneous proliferation in a dose-dependent fashion. These findings suggest that an imbalance between IL-1 production

and the endogenous receptor antagonist contributes to the unrestricted growth of AML cells. It is believed that in leukaemic cells the coordination between proliferation and differentiation is lost, mostly because of an uncontrolled supply of growth factors (Rambaldi *et al.* 1991). In particular, IL-1 and granulocyte-macrophage (GM)-CSF through autocrine and paracrine systems support leukaemic growth *in vivo*, and a possible effect of IL-1ra on AML cells is that there is decreased release of GM-CSF and IL-1 by IL-1ra-treated malignant cells as a result of receptor blockade (Young & Griffin, 1986; Lang & Burgess, 1990).

Ulcerative colitis

Ulcerative colitis is an inflammatory disease of the colon. Grossly, the bowel is foreshortened without evidence of transmural inflammation; the mucosa and submucosa, however, are granular, granulomatous, swollen and friable. Clinically these patients present with abdominal cramping, bloody, explosive diarrhoeic stools, fever and massive haemorrhage. There is a malignant potential in long-standing cases (Goldberg *et al.* 1989).

IL-1 has been implicated in the pathogenesis of ulcerative colitis, since it has been found in increased amounts in the diseased areas in the bowel. Animal models also show a correlation between high levels of IL-1 and local tissue inflammation. Cominelli *et al.* (1990) have shown that the tissue necrosis in the bowel can be reduced by the use of IL-1ra. A characteristic effect of the receptor antagonist is a diminished neutrophil presence at the site of inflammation, suggesting that a principal role of IL-1 in this inflammatory bowel disease may be to induce neutrophil extravastation and release of lytic products locally.

Regulation of interleukin family

The multiple and diverse roles of IL-1 have been established. However, the complexity of the IL-1 system and its regulation are only beginning to be understood. Because of the pleiotrophic effects of IL-1 on different target cells, and its capacity to alter normal physiology and mediate pathophysiology it was hypothesized that there was possibly a natural inhibitor of IL-1. This IL-1 receptor antagonist has been identified and purified. Currently it is believed that the mechanisms of IL-1-mediated tissue and metabolic pathophysiology, particularly in autoimmune diseases, are the result of failed regulation of the activity of IL-1. The use of the IL-1ra as a treatment modality continues to be in its early stages of study; however, it is expected that these studies will yield valuable information on how the overall system is balanced.

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