The IL-1 family: The role of IL-1 and IL-18 in inflammation

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Introduction

IL-1 and its related family member IL-18 are primarily proinflammatory cytokines by their ability to stimulate the expression of genes associated with inflammation and autoimmune diseases. The most salient and relevant properties of IL-1 in inflammation are the initiation of cyclooxygenase type 2 (COX-2), type 2 phospholipase A and inducible nitric oxide synthase (iNOS). This accounts for the large amount of prostaglandin-E$_2$ (PGE$_2$), platelet activating factor, leukotrienes and nitric oxide (NO) produced by cells exposed to IL-1 or in animals or humans injected with IL-1. Another important proinflammatory property of IL-1 is its ability to increase the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) on mesenchymal cells and vascular-cell adhesion molecule-1 (VCAM-1) on endothelial cells. This latter property promotes the infiltration of inflammatory and immunocompetent cells into the extravascular space. IL-1 is also an angiogenic factor and plays a role in tumor metastasis and blood vessel supply [1]. Mice lacking IL-1 receptors fail to develop proliferative lesions of vascular smooth muscle cells in mechanically injured arteries. In humans with rheumatoid arthritis (RA), the inflammation and joint destructive nature of the disease is reduced with systemic injections of the IL-1 receptor antagonist (IL-1Ra), a member of the IL-1 family that prevents IL-1 activity. However, in addition to these and other proinflammatory properties, IL-1 is also an adjuvant during antibody production and acts on bone marrow stem cells for differentiation in the myeloid series. In fact, unlike TNF, IL-1 is a bone marrow stimulant and was used to treat patients with bone marrow suppression in order to reduce the nadir of thrombocytopenia [2].

In terms of the role of IL-1 in human disease, specific blockade of the IL-1 receptor type I (the ligand binding chain of the heterodimeric IL-1 receptor signaling complex) with the naturally occurring IL-1Ra in patients with RA has resulted in reduced disease activity and reduced joint destruction [3–6]. IL-1Ra has been approved for use in the United States, Canada and Europe for the treatment of RA and over 50,000 patients receive daily treatment; the results support the essential inflammatory and tissue remodeling functions of IL-1.
Processing and secretion of the IL-1 family members: a unique evolution for cytokines

IL-1α, IL-1β, IL-1Ra and IL-18 are unique in the cytokine families. IL-1Ra, the only naturally occurring cytokine receptor antagonist, is readily secreted from macrophagic cells. Evolving from a common gene, IL-1β is found diffusely in the cells whereas IL-1Ra possesses a clear signal peptide and is secreted via the Golgi apparatus in a typical fashion similar to most secreted proteins. Secretion of IL-1Ra provides a mechanism to reduce IL-1 activity in health and disease. Indeed, mice deficient in IL-1Ra develop spontaneous disease [7, 8]. On the other hand, the agonist members of the IL-1 family are not readily secreted and require a series of intracellular steps before being biologically active cytokines.

IL-1α, IL-1β and IL-18 are each initially synthesized as precursor molecules without a signal peptide. In the case of IL-1α, the precursor form (31 kDa) is biologically active when inserted into the cell membrane as a surface protein [9, 10] as well as an intracellular cytokine [11, 12]. Evidence also supports the concept that the intracellular IL-1α can bind to nucleic acid and act as a transcription factor. This is due to the nuclear localization site in the N-terminus of the IL-1α precursor. IL-1α can also be cleaved from its membrane inserted form by calcium activated calpain [13]. The role of cell-associated IL-1α in disease is unclear, but mice deficient in IL-1α are protected in some models of inflammation and tumor growth [1, 14]. IL-1Ra blocks the activity of extracellular IL-1β and membrane IL-1α.

The IL-1β converting enzyme

After removal of N-terminal amino acids of IL-1β and IL-18 by a specific intracellular protease, the resulting active peptides are called “mature” or active forms of the cytokines. The precursor forms of IL-1β (31 kDa) and IL-18 (24 kDa) are biologically inactive and require cleavage by the intracellular cysteine protease, termed IL-1β converting enzyme (ICE). ICE is also termed caspase-1 [15], the first member of a large family of intracellular cysteine proteases with important roles in programmed cell death. However, there is little evidence that ICE (caspase-1) participates in programmed cell death [16]. Rather, ICE seems to be primarily used by the cell to cleave the IL-1β and IL-18 precursors. ICE cleaves both the IL-1β as well as the IL-18 precursors immediately following the aspartic acid in the P1 position. As a result of cleavage, a mature form of IL-1β of 17.5 kDa and 18 kDa for IL-18 are generated. Specific inhibitors of ICE effectively reduce the secretion of IL-1β as well as IL-18 and as a result, reduce the biological activities of either cytokine [17]. Oral inhibitors of ICE are in clinical trials in patients with RA. Although ICE is primarily responsible for cleavage of the IL-1β precursor intracellularly, other proteases such as proteinase-3 can process the IL-1β precursor extracellularly into an active