Interleukin-1 Receptor Antagonist: A "Novel" Acute Phase Protein with Antiinflammatory Activities

Editorial

The interleukin-1 receptor antagonist (IL-1ra) is an antiinflammatory cytokine which specifically binds to IL-1 receptors without inducing signal transduction, thus blocking the biological activities of IL-1 (for review see reference 1). It is unique in that it is the only described naturally occurring cytokine receptor antagonist with no known agonist function. Two isoforms were originally characterized, a secreted (s) and predominantly glycosylated form, and an intracellular (ic) variant, which are the products of alternative splicing from a single gene. Recently, the initial characterization of additional icIL-1ra isoforms with unknown function(s) has been reported.

After its cloning in 1990 (2) and subsequent production of large amounts of recombinant protein, a great deal of interest was generated by the pharmaceutical industry for possible applications of recombinant IL-1ra as a novel antiinflammatory drug. In fact, IL-1ra was shown to reduce the severity of disease in a variety of preclinical animal models of inflammation and tissue injury (3), thus initiating the impetus for its therapeutic value in treating human diseases. In particular, a phase II clinical trial in patients with septic shock showed a markedly reduced mortality in the IL-1ra–treated group compared to placebo, and generated premature excitement regarding the discovery of a novel disease-modifying drug (4). However, a subsequent phase III clinical trial did not confirm preliminary results of the previous study, and as is so often the case, dampened enthusiasm for this unique anticytokine resulted.

In recent years, investigators have refocused on examining the biological functions and basic science of endogenous IL-1ra as well as the pathophysiological significance of the balance between IL-1 and its natural antagonist, IL-1ra, as a mechanism of disease. In fact, the role of endogenous IL-1ra as a regulating mediator of the inflammatory response was clearly demonstrated by antibody knockout studies in animal models of colitis (5) and pulmonary granulomatous disease (6). The importance of IL-1ra's homeostatic function has been further supported by studies done in mutant mice lacking the IL-1ra gene in which increased susceptibility to the lethal effects of experimental endotoxemia was demonstrated (7).

In this issue of the *Journal*, Gabay et al. (8) add to our knowledge of the biological functions of IL-1ra by investigating the expression of IL-1ra in hepatocytes stimulated by IL-1, TNF, and IL-6. These experiments clearly demonstrate that the secreted form of IL-1ra is produced by both primary hepatocytes as well as HepG2 cells in response to IL-1β and IL-6 stimulation, resembling characteristics of an acute phase protein (APP). In addition, in elegant transfection and mutation studies, this group showed that both NF-κB and C/EBP family members are involved in transcription of the sIL-1ra similar to that found in other classically described APPs. APPs are released during an early and immediate set of reactions known as the acute phase response, which occurs after host tissue injury, trauma, or infection (9). Although it is speculated that APPs are synthesized by the liver in an effort to prevent ongoing tissue damage and initiate repair processes, the specific function(s) of classical APPs, such as C-reactive protein and serum amyloid A, has not yet been fully elucidated. The report in this issue of the *Journal* adds the IL-1ra, the antiinflammatory effects of which are well-characterized, to the list of APPs produced during an acute phase response, and suggests a "novel" biological function for IL-1ra (8). Further in vivo studies are necessary to confirm that hepatocytes are the major source of circulating IL-1ra during an acute phase response, therefore verifying the physiological role of IL-1ra as an APP. The studies by Gabay et al. in this issue of the *Journal*, however, provide additional insight into the concept that the balance between IL-1 and IL-1ra is an important regulating mechanism needed to maintain homeostasis of host immune functions and that dysregulation of this balance may lead to disease states (8). Whether manipulation of the IL-1ra/IL-1 balance, by inhibition of IL-1 or stimulation of endogenous IL-1ra, may ameliorate the natural course of a variety of inflammatory diseases remains to be seen.

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