Cytokines such as IL-1, TNFα, GM-CSF, and members of the chemokine α and β family (e.g., IL-8, MCP-1), have marked proinflammatory effects. These proinflammatory effects can be countered, in part, by other cytokines that have potent anti-inflammatory activities (e.g., TGF-β1, IL-10) or by the binding of proinflammatory cytokines to soluble cytokine receptors in the extracellular milieu. In the case of IL-1, an additional novel mechanism can downregulate its proinflammatory activity. This involves the production and secretion of a naturally occurring protein, termed IL-1 receptor antagonist (IL-1ra). IL-1ra is structurally related to IL-1 and binds to type I IL-1 receptors. Since IL-1ra has no intrinsic signaling activity through the IL-1 receptor, it, in effect, blocks this receptor. Administration of sufficient quantities of IL-1ra can decrease the inflammatory response in a number of model systems in which an important proinflammatory role of IL-1 has been documented (1). However, less is known regarding the importance of endogenously produced IL-1ra in downregulating the inflammatory response in vivo in acute inflammatory reactions in which IL-1 has a documented role.

In this issue of the *JCI,* Ferretti et al. (2) add to our knowledge in this area through studies using a model of acute colitis. This model involves the induction of an acute colitis in rabbits by intrarectal administration of formaldehyde followed by intravenous injection of immune complexes in antigen excess. The ensuing cellular infiltrate includes neutrophils and eosinophils, and is accompanied by crypt abscesses, epithelial cell degeneration, edema, and mucosal necrosis. In two of their prior studies, IL-1 production and colonic tissue levels of IL-1 in this model correlated with the degree of inflammation (3, 4). Moreover, administration of IL-1ra suppressed colonic inflammation and the colonic production of PGE2 and LTB4, mediators thought to be important in the pathogenesis of this inflammatory response.

The report in this issue of the *JCI* addresses two important issues which further validate the role endogenous IL-1 and IL-1ra may play in the induction and regulation of acute intestinal inflammation. The experiments first demonstrate that, temporally, the production of IL-1ra in the colon increases 48 h after the induction of colitis, a time which is delayed with respect to endogenous IL-1 production, but precedes the significant decrease in endogenous IL-1 production associated with the resolution of acute colitis. Second, in studies in which a neutralizing antibody against IL-1ra was administered in vivo, the investigators report a significant increase in the degree of colonic inflammation and in mortality compared with rabbits given control antibodies. Thus, together with their prior reports, the current results add substantial evidence to the notion that endogenous IL-1 and IL-1ra play a balancing role in the activation and regulation of acute mucosal inflammation in the colon.

A significant issue regarding intestinal inflammation is why, in some individuals the acute inflammatory response, rather than resolving, develops into chronic persistent inflammation that injures the intestinal mucosa and impairs its function. This question is particularly germane in diseases like ulcerative colitis. Acute inflammation in vivo is mostly initiated by environmental causes. We now know that colon epithelial cells, which represent a major interface between the host and the external milieu, play a major role in initiating an acute mucosal inflammatory response. For example after bacterial invasion, intestinal epithelial cells express a specific array of proinflammatory cytokines, including potent neutrophil (5, 6) and monocyte/macrophage chemoattractants and activators (Jung, H. C., L. Eckmann, S.-K. Yang, J. Fierer, E. Morzycka-Wroblewska, and M. F. Kagnoff, manuscript submitted for publication). These cytokines act as an early signaling system for the chemotaxis and activation of mucosal inflammatory cells. How is the acute inflammatory response that ensues subsequently downregulated and the normal "physiologic state" of low grade mucosal inflammation restored? The need to maintain an appropriate balance between the production of proinflammatory and anti-inflammatory cytokines, and the importance of the endogenous host microflora and its products in this balance is evident, from the development of marked chronic intestinal inflammation in two recently reported models of transgenic cytokine gene knockout mice. In these models, mice lacking either IL-10 or IL-2 developed striking chronic inflammation of the large and/or small intestine, the extent of which was highly dependent on the animals' intestinal microflora (7, 8). Although IL-10 has well described anti-inflammatory effects, the mechanism by which IL-2 is involved in balancing the "ups and downs" of mucosal inflammation is not known. The report by Ferretti et al. (2) in this issue of the *JCI* provides potential insight into the role of IL-1ra as an additional endogenous anti-inflammatory regulator of the acute mucosal inflammatory response. It will be important to determine whether abnormalities in host IL-1ra production during the course of acute inflammation can lead to chronic intestinal inflammation and ultimately disease in humans.

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