NOVEL PATHWAYS FOR NEGATIVE REGULATION OF INFLAMMATORY CYTOKINES

Alberto Mantovani

Instituto di Ricerche Farmacologiche "Mario Negri", Via Eritrea 62-20157 Milan, Italy and Dept. of Biotechnology, Section of General Pathology, University of Brescia, Italy.

Introduction

Inflammatory cytokines act in cascades. One can schematically recognize primary inflammatory cytokines, the prototype of which is IL-1, and secondary effector molecules, among which chemokines play an important role in recruitment. Pro and anti-inflammatory signals regulate the production of primary and secondary inflammatory cytokines, sometimes in unexpected ways (1). The possibility that microenvironmental signals may regulate the action of proinflammtory cytokines by acting at the receptor level has been less extensively studied. Here we will review recent results on the action of pro and anti-inflammatory signals on receptors for IL-1, which in fact is a complex system and for the chemokine monocyte chemotactic protein-1 (MCP-1), a prototypic inflammatory cytokine.

Given the existence of two distinct IL-1R, a number of studies have investigated the actual role played by each of them in IL-1 signaling. As summarized briefly hereafter, all available evidences indicate the IL-1-induced activities are mediated exclusively via the IL-1RI, whereas IL- 1RII has no signaling activity and inhibits IL-1 activities by acting as a decoy for IL-1 (1).

MCP-1 is a prototypic C-C chemokine active on mononuclear phagocytes, basophils, T cells and NK cells (2-4). Other CC chemokines, including the recently identified mocrophage derived chemokine (MDC), are also active on dendritic cells. We examined the effect of LPS on chemokine receptor expression and we found that LPS causes a drastic and rapid downregulation of the expression of CCR2, a receptor for MCP-1 and -3. The ED_{50} of LPS was $\cong$ 1 ng/mL and half maximal effect was reached with an optimal dose in $\cong$ 45 min. Inhibition of MCP-1 receptor expression was functionally relevant since LPS-treated monocytes showed a reduced capacity to bind and to respond to MCP-1 chemotactically. The action of LPS on C-C chemokine receptors was specific in that CXCR2 was unaffected. In neutrophils, LPS and TNF-α were reported to inhibit the expression of IL-8 receptors, while G-CSF increased it. IL-2 was shown to induce CCR2 in T lymphocytes and NK cells, and observation confirmed here for monocytes. Interestingly, CCR2 induction in T cells was a slow process, requiring four days of exposure to cytokine. The results reported here show a dramatic, rapid and differential downregulation of chemokine receptors by LPS in monocytes.

LPS did not inhibit the rate of nuclear transcription of CCR2, but did reduce the mRNA half life from 1.5 h to 45 min. regulation of CCR chemokine receptor expression, in addition to agonist production, is likely a crucial point for regulation of the chemokine system. We speculate that the divergent effect of certain proinflammatory signals on agonist versus receptor expression may serve to retain mononuclear phagocytes at sites of inflammation, to prevent their reverse transmigration, and, possibly, to limit excessive recruitment.

Primary and secondary inflammatory cytokines are highly regulated by diverse signals. Emphasis has largely been on how pro- and anti-inflammatory molecules affect cytokine production. The results summarized here obtained with IL-1 receptors and with the MCP-1 receptor indicate that receptor expression may represent a crucial regulatory element for the tuning of the action of primary and secondary inflammatory cytokines.

1. Colotta F, Dower SK, Sims JE, Mantovani A. The type II 'decoy' receptor: novel regulatory pathway for interleukin-1. Immunol Today 1994;15:562-566.

2. Mantovani A, Sozzani S, Proost P, Van Damme J. The monocyte chemoattractant protein family. In: Chemoattractant Ligands and Their Receptors, Horuk R ed., CRC Press, Inc. Boca Raton 1996;pp.169-192.

3. Godiska R, Chantry D, Raport CJ, Sozzani S, Allavena P, Leviten D, Mantovani A, Gray PW. Human macrophage derived chemokine (MDC) a novel chemoattractant for monocytes, monocyte derived dendritic cells, and natural killer cells. J Exp Med 1997;185:1595-1604.

4. Sica A, Saccani A, Borsatti A, Power CA, Wells TNC, Luini W, Polentarutti N, Sozzani S, Mantovani A. Bacterial lipopolysaccharide rapidly inhibits expression of C-C chemokine receptors in human monocytes. J Exp Med 1997; 185:969-974.

Trabajos selecionados del
Congreso Biotecnología Habana'97
diciembre 1-6, 1997

Selected papers from Congreso
Biotecnología Habana'97
December 1-6, 1997