The role of interleukin-10 in the pathogenesis of bacterial infection

Clin Microbiol Infect 1997; 3: 605–607

Introduction

Infection is associated with enhanced production of cytokines, low-molecular-weight proteins important for the orchestration of inflammatory processes. Research on the role of cytokines in infection was boosted by a hallmark publication, now 10 years ago, by Tracey and coworkers, demonstrating that neutralization of the cytokine tumor necrosis factor-α (TNF) was protective against lethality in a model of severe Gram-negative bacteremia in baboons [1]. Since then, knowledge of the significance of cytokine production during infection has increased considerably. It is clear now that cytokines interact in a highly complex network, in which they influence each other's production and activity. TNF is an important pro-inflammatory cytokine. The production of these inflammation-facilitating cytokines can be inhibited by so-called anti-inflammatory cytokines. The most important member of this group of mediators is interleukin-10 (IL-10). In this article we will briefly discuss the relevance of IL-10 for current understanding of the host response to bacterial infection.

Production of IL-10

IL-10 is an 18-kDa polypeptide that can be synthesized by T-cells, B-cells, monocytes and macrophages [2]. Stimuli that can induce IL-10 production are diverse and include bacteria, bacterial products (e.g. endotoxin), parasites, fungi and viruses. In addition, several cytokines can enhance IL-10 synthesis, including TNF, IL-1, IL-6 and IL-12. Elevated plasma levels of IL-10 have been found in patients with sepsis [3–5]. During fulminant meningococcal septic shock, IL-10 could be detected in all patients on admission, while during non-meningococcal septic shock, serum IL-10 was detectable in 81–83% of patients. One study reporting sequential IL-10 measurements during the first 3 days after admission documented that plasma IL-10 remained high in non-surviving patients, while in survivors, plasma IL-10 significantly decreased, suggesting that plasma IL-10 may be a relatively stable indicator of the severity of the septic insult [5].

The production of IL-10 during infection can be influenced by several mechanisms. In humans and non-human primates injected with endotoxin the appearance of IL-10 in the circulation follows that of TNF, and the concentration peaks after 2–3 h [5,6]. Part of the endotoxin-induced IL-10 production may be regulated by TNF. Injection of recombinant TNF into healthy humans induced a modest rise in plasma IL-10 concentrations, and neutralization of TNF activity in endotoxin-treated chimpanzees by simultaneous infusion of an anti-TNF monoclonal antibody attenuated IL-10 secretion [6]. Further, in human whole blood, endotoxin-induced IL-10 production is in part TNF-dependent [7]. It should be noted, however, that in normal humans elimination of endogenous TNF by infusion of a recombinant dimeric TNF receptor did not reduce or only modestly reduced IL-10 release during endotoxemia [8,9]. Other endogenous factors that may control IL-10 synthesis include prostaglandins, cortisol, catecholamines, and, as mentioned above, other cytokines [7,10,11].

Effects of IL-10

IL-10 has many different biological activities (Table 1). The capacity of IL-10 to inhibit the stimulated production of a number of pro-inflammatory cytokines has received much attention. In vitro, IL-10 is a potent inhibitor of production of TNF, IL-1, IL-6, IL-8, IL-12 and other cytokines [12,13]. In addition, IL-10 is capable of attenuating the production of a number of other mediators of inflammation, including tissue factor, nitric oxide and arachidonic acid products [14–16]. Interestingly, IL-10 may also exert anti-inflammatory effects by enhancing the production of the IL-1 receptor antagonist, the main physiologic inhibitor of IL-1 [12].

Table 1 Biological effects of interleukin-10

Anti-inflammatory and immunosuppressive effects
Inhibition of cytokine production by macrophages, T-lymphocytes and granulocytes
Inhibition of production of reactive nitrogen oxides by macrophages
Inhibition of arachidonic acid metabolite production
Inhibition of killing of parasites and intracellular bacteria by macrophages
Suppression of procoagulant activity
Inhibition of class II MHC expression by monocytes
Inhibition of monocyte-dependent T helper cell proliferation
Immunostimulatory effects
Stimulation of B-cell functions (i.e. proliferation, immunoglobulin secretion, class II MHC expression)
Stimulation of development of cytotoxic T-cells
Stimulation of growth of thymocytes and mast cells
Enhancement of expression of type I FcR for IgG on monocytes

Several studies have demonstrated the anti-inflammatory potential of IL-10 in vivo. Administration of recombinant IL-10 directly before injection of a lethal dose of endotoxin to mice markedly suppressed TNF release, and prevented lethality [17]. In healthy humans, recombinant human IL-10, given as a single dose of 25 μg/kg immediately prior to endotoxin, reduced the rise in body temperature and in plasma TNF, IL-6 and IL-8 concentrations [18]. Endotoxin-induced granulocyte accumulation in lungs, as determined by dynamic granuloscintigrams, was prevented by IL-10 treatment, while granulocyte degranulation was blunted [18]. Further, IL-10 also inhibited the activation of the fibrinolytic system and the coagulation system [19]. Hence, exogenous IL-10 inhibits inflammation and reduces mortality in models of endotoxemia.

Role of endogenous IL-10 during endotoxemia and infection

Administration of endotoxin to different species, including humans, induces a transient rise in the plasma levels of IL-10 [5–9,11]. Neutralization of this endogenously produced IL-10 in endotoxemic mice resulted in an increased production of several pro-inflammatory cytokines, including TNF, and an enhanced mortality [20,21]. Similarly, IL-10 gene-deficient mice demonstrated enhanced mortality after endotoxin injection, which was associated with elevated levels of TNF, IL-1, IL-6, IL-12, interferon-γ and nitrate [22]. Interestingly, a number of cytokines may contribute to the increased endotoxin-induced lethality in the absence of endogenous IL-10, since it can be prevented in part by antibodies directed against TNF, interferon-γ or macrophage inflammatory protein-2 [21,22]. Thus, in models of endotoxemia endogenous IL-10 represents an important autoregulatory mechanism controlling the production of pro-inflammatory cytokines and endotoxin toxicity in vivo. Further, in patients with meningococcal septic shock, IL-10 accounted for most of the monocyte-deactivating properties in the circulation, confirming the anti-inflammatory role of IL-10 during clinical infection [23].

Acute models of extensive immune activation do not provide insight into the potential beneficial effects of pro-inflammatory cytokines at the site of an infection, and should therefore be interpreted with caution. Indeed, neutralization of IL-10 has been found to augment mouse resistance to pneumonia caused by *Klebsiella pneumoniae* or *Streptococcus pneumoniae* [24,25]. It therefore seems likely that IL-10 produced during at least some active infections hampers an adequate pro-inflammatory response crucial for effective clearance of an infectious agent. The anti-inflammatory properties of IL-10 may also explain why containment of pneumonia was compromized further by administration of recombinant IL-10 [25]. It should be noted, however, that IL-10 does not impair host defense during bacterial peritonitis induced by cecal ligation and puncture. Cecal ligation and puncture results in spillage of bacteria from the gut into the peritoneal cavity, leading to polymicrobial peritonitis, and systemic infection. Inhibition of IL-10 in this model was associated with enhanced lethality, while administration of recombinant IL-10 improved survival [26,27].

Conclusion

The effects of IL-10 during bacterial infections seem complex, and are likely to be determined by the source of the infection and the functional balance between pro-inflammatory and anti-inflammatory forces within the cytokine network. During overwhelming immune activation, such as after administration of endotoxin or during meningococcal septic shock, the anti-inflammatory effects of IL-10 can be beneficial. In such models, high levels of pro-inflammatory cytokines appear in the circulation, and inhibition of their systemic effects confers protection against tissue injury and lethality. During localized infections, however, such as pneumonia, endogenously produced IL-10 hampers an appropriate host response to invading microorganisms. Inhibition of inflammation in patients with bacterial infection with recombinant IL-10 may therefore be hazardous to some and beneficial to others.

Tom van der Poll[1,2]
Arnaud Marchant[3]
Sander J.H. van Deventer[1]
[1]Academic Medical Center,
University of Amsterdam,
Laboratory of Experimental Internal Medicine,
Amsterdam,
The Netherlands;
[2]Department of Infectious Diseases,
AIDS and Tropical Medicine,
University of Amsterdam,
Amsterdam,
The Netherlands;
[3]Hôpital Erasme,
Université Libre de Bruxelles,
Department of Immunology,
Brussels, Belgium

References

1. Tracey KJ, Fong Y, Hesse DG, et al. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. Nature 1987; 330: 662–4.

2. Moore KW, O'Garra A, de Waal Malefyt R, Vieira P, Mosmann TR. Interleukin 10. Ann Rev Immunol 1993; 11: 165–90.
3. Marchant A, Deviere J, Byl B, de Groote D, Vincent JL, Goldman M. Interleukin-10 production during septicaemia. Lancet 1994; 343: 707–8.
4. Derkx B, Marchant A, Goldman M, Bijlmer R, van Deventer S. High levels of interleukin-10 during the initial phase of fulminant meningococcal septic shock. J Infect Dis 1995; 171: 229–32.
5. Van der Poll T, de Waal Malefyt R, Coyle SM, Lowry SF. Antiinflammatory cytokine responses during clinical sepsis and experimental endotoxemia: sequential measurements of plasma soluble interleukin (IL)-1 receptor type II, IL-10 and IL-13 concentrations. J Infect Dis 1997; 175: 118–22.
6. Van der Poll T, Jansen J, Levi M, ten Cate H, ten Cate JW, van Deventer SJH. Regulation of interleukin 10 release by tumor necrosis factor in humans and chimpanzees. J Exp Med 1994; 180: 1985–8.
7. Van der Poll T, Coyle SM, Barbosa K, Braxton CC, Lowry SF. Epinephrine inhibits tumor necrosis factor α and potentiates interleukin 10 release during human endotoxemia. J Clin Invest 1996; 97: 713–19.
8. Suffredini AF, Reda D, Banks SM, Tropea M, Agosti JM, Miller R. Effects of recombinant dimeric TNF receptor on human inflammatory responses following intravenous endotoxin administration. J Immunol 1995; 155: 5038–45.
9. Van der Poll T, Coyle SM, Levi M, et al. Effect of a recombinant dimeric tumor necrosis factor receptor on inflammatory responses to intravenous endotoxin in normal humans. Blood 1997; 89: 3727–34.
10. Van der Pouw-Kraan TCTM, Boeije LCM, Smeenk RJT, Wijdenes J, Aarden LA. Prostaglandin-E_2 is a potent inhibitor of human interleukin 12 production. J Exp Med 1995; 181: 775–9.
11. Van der Poll T, Barber AE, Coyle SM, Lowry SF. Hypercortisolemia increases plasma interleukin 10 concentrations during human endotoxemia. J Clin Endocrinol Metab 1996; 81: 3604–6.
12. De Waal Malefyt R, Abrams J, Bennett B, Figdor C, de Vries JE. IL-10 inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. J Exp Med 1991; 174: 1209–20.
13. D'Andrea A, Aste-Amezaga M, Valiante NM, Ma X, Kubin M, Trinchieri G. Interleukin 10 (IL-10) inhibits human lymphocyte interferon-γ production by suppressing natural killer cell stimulatory factor/IL-12 synthesis in accessory cells. J Exp Med 1993; 178: 1041–8.
14. Pradier O, Gérard C, Delvaux A, et al. Interleukin-10 inhibits the induction of monocyte procoagulant activity by bacterial lipopolysaccharide. Eur J Immunol 1993; 23: 2700–3.
15. Gazzinelli RT, Oswald IP, James SL, Sher A. IL-10 inhibits parasite killing and nitrogen oxide production by IFN-γ activated macrophages. J Immunol 1992; 148: 1792–6.
16. Endo T, Ogushi F, Sone S. LPS-dependent cyclooxygenase-2 induction in human monocytes is down-regulated by IL-13, but not by IFN-γ. J Immunol 1996; 156: 2240–6.
17. Gérard C, Bruyns C, Marchant A, et al. Interleukin 10 reduces the release of tumor necrosis factor and prevents lethality in experimental endotoxemia. J Exp Med 1993; 177: 547–50.
18. Pajkrt D, Camoglio L, Tiel-van Buul MCM, et al. Attenuation of proinflammatory response by recombinant human IL-10 in human endotoxemia: the effect of timing of rhIL-10 administration. J Immunol 1997; 158: 3971–7.
19. Pajkrt D, van der Poll T, Levi M, et al. Interleukin 10 inhibits activation of coagulation and fibrinolysis during human endotoxemia. Blood 1997; 89: 2701–5.
20. Marchant A, Bruyns C, Vandenabeele P, et al. IL-10 controls IFN-γ and TNF production during experimental endotoxemia. Eur J Immunol 1994; 24: 1167–71.
21. Standiford TJ, Strieter RM, Lukacs NW, Kunkel SL. Neutralization of IL-10 increases lethality in endotoxemia. Cooperative effects of macrophage inflammatory protein-2 and tumor necrosis factor. J Immunol 1995; 155: 2222–9.
22. Berg DJ, Kühn R, Rajewsky K, et al. Interleukin-10 is a central regulator of the response to LPS in murine models of endotoxic shock and the Shwartzman reaction but not endotoxin tolerance. J Clin Invest 1995; 96: 2339–47.
23. Brandtzaeg P, Osnes L, Ovstebo R, Joo GB, Westvik AB, Kierulf P. Net inflammatory capacity of human septic shock plasma evaluated by a monocyte-based target cell assay: identification of interleukin-10 as a major functional deactivator of human monocytes. J Exp Med 1996; 184: 51–60.
24. Greenberger MJ, Strieter RM, Kunkel SL, Danforth JM, Goodman RE, Standiford TJ. Neutralization of IL-10 increases survival in a murine model of *Klebsiella pneumonia*. J Immunol 1995; 155: 722–9.
25. Van der Poll T, Marchant A, Keogh CV, Goldman M, Lowry SF. Interleukin 10 impairs host defense in murine pneumococcal pneumonia. J Infect Dis 1996; 174: 994–1000.
26. Van der Poll T, Marchant A, Buurman WA, et al. Endogenous interleukin 10 protects mice from death during septic peritonitis. J Immunol 1995; 155: 5397–401.
27. Kato T, Murata A, Toda H, et al. Interleukin 10 reduces mortality from severe peritonitis in mice. Antimicrob Agents Chemother 1995; 39: 1336–40.