Commentary

Regulatory Role of T Cells Producing both Interferon γ and Interleukin 10 in Persistent Infection

Giorgio Trinchieri

Laboratory for Immunological Research, Schering-Plough Research Institute, 69571 Dardilly, France

IL-10 was originally described as a cytokine produced by Th2 cells and mediating antiinflammatory effects, by acting primarily on phagocytic cells and on antigen-presenting cells (1). IL-10 inhibits, in these cells, transcription and production of proinflammatory cytokines, such as TNF and IL-12, expression of MHC class II, and costimulatory molecules, as well as the production of reactive oxygen and nitrogen intermediates (1). In part through inhibition of IL-12 production and of costimulatory molecule expression on antigen-presenting cells, IL-10 has an overall suppressive effect on the generation of Th1 responses. In addition, IL-10 profoundly affects the bactericidal activity of phagocytic cells, allowing intracellular survival of pathogens such as *Mycobacterium tuberculosis* (2) and *Leishmania major* (3). In addition to inhibit the intracellular bactericidal mechanisms, IL-10 was shown to prevent TNF-mediated apoptosis of *M. tuberculosis* infected macrophages thus possibly facilitating the maintenance of a chronic infection (4).

Many experimental and clinical studies have shown that the in vivo production of IL-10 during intracellular pathogen infections represents a regulatory mechanism to prevent pathogenic systemic inflammatory responses. Even in the presence of IL-10, the protective effect of a regulated Th1 response is largely preserved, although in some instances sterile cure in chronic infection by intracellular parasites may be prevented. Several studies also indicate that the principal source of IL-10 may be T cells that also produce IFN-γ, in addition or instead of Th2 cells or cells infected or exposed to parasite products, e.g., macrophages, which may be the predominant producer of IL-10 during the early acute phases of the infection.

IL-10 Is Essential to Protect Infected Animals from Severe Inflammatory Pathology. The central and necessary role of IL-10 in protecting against severe or systemic inflammatory pathology has been clearly shown in many models of experimental infection with intracellular pathogens using IL-10 genetically deficient (IL-$10^{-/-}$) mice. In these animals, the ability to resist infection to pathogens such as *L. major*, *M. tuberculosis*, *Listeria monocytogenes*, or *Toxoplasma gondii* is enhanced or unaffected (3, 5). However, severe pathogenic inflammatory responses upon infection are often observed in these animals. IL-$10^{-/-}$ mice exhibited lethal hyperinflammatory intracerebral immune response in *L. monocytogenes* meningoencephalitis, while, if infected intraperitoneally, they exhibited hepatic hyperinflammation (6). Female IL-$10^{-/-}$ mice infected with *Plasmodium chabaudi chabaudi* have an exacerbated pathology including hypoglycemia, hypothermia, and loss in body weight often resulting in death (7). IL-$10^{-/-}$ mice infected with *T. gondii*, although able to resist the infection, succumb within 1 or 2 wk to a systemic inflammatory response with enhanced production of IL-12, IFN-γ, and TNF (8).

In Experimental L. major Chronic Infection, IL-10 Produced by T Cells Prevents Sterile Cure. *L. major* infection in mice represents a powerful model to study the role of Th1 and Th2 responses in the resistance to intracellular pathogens. Whereas most mouse strains are able to mount a Th1 response to *L. major* and resist the infection, at least one strain, BALB/c, exhibits a Th2 response and it is unable to resist the infection that eventually becomes generalized and lethal. However, IL-$10^{-/-}$ BALB/c mice were relatively resistant to infection, indicating that endogenous IL-10 plays an important role in allowing disease progression in IL-10 sufficient mice (3). Interestingly, in this model, one of the mechanisms of IL-10 induction was the triggering of Fc receptor on macrophages by IgG antibody coated *L. major* amastigotes (9, 10). Although *L. major*–resistant mouse strains mount a protective Th1 response to the infection, sterile cure is not obtained even many weeks after infection and a small number of parasites persists at the site of infection and in the draining lymph node, possibly within dendritic cells (DCs) and fibroblasts, rather than in typical phagocytic cells (11–13). Immune pressure during this latency is mediated by Th1 cells, IL-12, IFN-γ, and inducible nitric oxide synthase (iNOS); blockage of these mechanisms induces parasite reactivation and reappearance of the lesions, reminding the clinical occurrence of latent infections and the severe forms of reactivation diseases in human leishmaniasis. In this issue, Belkaid et al. (14) show that IL-10 plays an essential role in *L. major* persistence in genetically resistant C57BL/6 mice after spontaneous healing of their dermal lesions. They demonstrate that sterile cure was achieved in IL-$10^{-/-}$ mice but not in IL-10 suffi-

Address correspondence to Giorgio Trinchieri, Schering-Plough Laboratory for Immunological Research, 27 chemin des Peupliers, B.P. 11, 69571 Dardilly, France. Phone: 33-4-72-17-27-40; Fax: 33-4-78-35-47-50; E-mail: Giorgio.Trinchieri@spcorp.com

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cient mice. This requirement for IL-10 in establishing latency was determined in mice infected either by intradermal injection of *L. major* metacyclic promastigotes and by the natural route by exposure of the skin to infected sand flies. Most importantly, IL-10 sufficient C57BL/6 mice treated transiently (2 wk) during the chronic phase with anti–IL-10 receptor antibodies achieved sterile cure, suggesting that IL-10 was actively involved in preventing complete parasite elimination even in the presence of a Th1 response (14). After 1 wk treatment with the anti–IL-10 receptor antibody, the number of $CD4^+$ and $CD8^+$ T cells recovered from the chronic phase lesions was dramatically reduced (14). This might be explained by the disappearance of the antigenic stimulus provided by the parasites or alternatively by the ability of IL-10 to prevent complete resolution of the infiltration by inhibiting production of TNF that induces T cell apoptosis or by directly protecting T cells from apoptosis (4, 15, 16). Thus, IL-10 produced in the lesion during the latent infection may control various parameters of the host parasite relationship, including the survival and persistence of the infiltrating T cells and their ability to induce bactericidal activity in the cells harboring the parasites.

The $CD4^+$ and, in part, the $CD8^+$ T cells infiltrating the dermal chronic lesion maintained high levels of IFN-γ production until the latent infection persisted (14). IL-10 also derived from T cells and prevalently from $CD4^+$ T cells: the majority of the $CD4^+$ T cell producing IL-10 (7% of total $CD4^+$ T cells) also produced IFN-γ: these double IL-10 and IFN-γ producing cells represented approximately one quarter of all the IFN-γ–producing cells. Thus, the IL-10 responsible of the immunoregulation of the anti-*Leishmania* response in this resistant strain of mice was produced primarily by a subset of IFN-γ producing CD4 cells, rather than by Th2 cells or by the infected phagocytic cells.

$CD4^+$ T Cells Producing both IFN-γ and IL-10 Are Present in Human Clinical Infections. The ability of $CD4^+$ T cell to produce both IFN-γ and IL-10 clearly shows that the production of IL-10 from T cells is not always associated with a Th2 response, but could be observed from T cells participating to a Th1–type response (17, 18). Before their identification in *L. major* infection (14), T cells producing both IFN-γ and IL-10 had not been directly shown in any experimental model of chronic infection, but in humans there are many examples of an immune regulatory balance between IFN-γ and IL-10 in persistent infection as well as direct evidence of simultaneous production of both cytokines from T cells.

It is of interest that all human $CD4^+$ T cell clones expanded in vitro in the presence of the Th1 inducing cytokine IL-12 produced high levels of both IFN-γ and IL-10 (19). If the clones were expanded in the presence of both IL-12 and IL-4, their ability to produce IL-10 was completely suppressed, whereas the production of IFN-γ was minimally affected (19). Thus, the ability of $CD4^+$ T cells to produce IL-10 is positively regulated by IL-12 and negatively by IL-4, suggesting that the balance between IL-12 and IL-4 during an infection may regulate not only the dichotomy between Th1 and Th2 responses, but also the type of Th1 responses and their association with the anti-inflammatory cytokine IL-10.

In human tuberculosis, increased expression of both IFN-γ and IL-10, but not of typical Th2 cytokines (e.g., IL-4) was observed in lymph nodes and at the sites of infection, although the production of IL-10 from T cells was not directly demonstrated (20). However, within $CD4^+$ clones derived from bronchoalveolar lavage (BAL) of active pulmonary tuberculosis patients, clones producing high levels of both IFN-γ and IL-10 predominated and represented approximately half of the clones, whereas their proportion was significantly lower in clones derived from BAL of healthy controls (19). This pattern was not observed in $CD4^+$ clones derived from peripheral blood in which IL-10 production was observed predominantly in typical Th2 clones producing also IL-4 (19). The simultaneous production of IFN-γ and IL-10 was observed both in *M. tuberculosis* specific and nonantigen specific clones. This observation suggests that the IFN-γ and IL-10 producing clones may be preferentially enriched at the site of infection and/or specific anatomical localization such as the lungs. Because these clones were isolated from patients with active pulmonary tuberculosis, it is possible that the production of IL-10 was responsible for the inability of the patients to clear the infection, or that IL-10 had a protective role in preventing a more severe inflammatory pathology in the patients' infected tissues. The possible role of IL-10 producing T cells in suppressing the immune response of pulmonary tuberculosis patients was suggested by the observation that T cells from anergic patients that lacked dermal reaction to tuberculin produced IL-10 but not IFN-γ both constitutively and upon stimulation, were defective in T cell receptor–induced signal transduction, and inhibited allogeneic mixed leukocyte reactions (21).

Production of high levels of both IFN-γ and IL-10 was observed in a high proportion of *Borrelia burgdorferi*–specific T cell lines isolated from patients with Lyme disease, but not in tetanus toxoid positive lines from patients or in *B. burgdorferi*–reactive lines from healthy controls (22). Neutralization of IL-12 inhibited the generation of the double producing T cell lines, indicating the role of IL-12 in inducing IFN-γ and IL-10 producing T cells (22). In mice, early production of IFN-γ and IL-10 upon infection with *B. burgdorferi* was observed. However, in strains susceptible to Lyme disease, IFN-γ production was higher and less controlled by IL-10 than in resistant strains, suggesting that IL-10 production and sensitivity to the regulation by IL-10 of IFN-γ production during *B. burgdorferi* infection may determine the susceptibility to Lyme arthritis (23).

In malaria there is a complex relationship between the roles played by both innate and adaptive inflammatory responses in the protection against parasite proliferation and in the induction of the most acute and life threatening manifestations of the disease (24). In particular, both TGF-β and IL-10 have been shown to mediate important antiinflammatory mechanisms in malaria, with TGF-β being able to induce IL-10 production without decreasing IFN-γ

production (25). High IL-10 to TNF ratios were observed in *P. falciparum* infected patients from endemic areas with uncomplicated malaria or hyperparasitemia, whereas low IL-10 to TNF ratios were associated with anemia and cerebral malaria complications (26, 27). In patients with acute uncomplicated *P. falciparum* malaria, a significant number of peripheral blood $CD4^+$ T cells producing both IFN-γ and IL-10 was indeed observed and their number increased during drug-induced clearance of parasitemia (28).

The IFN-γ/IL-10 Double-producing $CD4^+$ T Cells in Infection May Correspond to T Regulatory Cell Subsets. The stimuli by which IL-10 and IFN-γ double-producing T cells are induced and the exact mechanism by which they regulate the anti-parasite response while preventing hyperinflammation remain largely unknown. However, some leads for the understanding of the regulation and activity of these cells have been provided by the recent flow of information regarding T regulatory cells in autoimmunity, transplantation, and cancer. Particularly relevant are the Tr1 cells that are generated by stimulation in the presence of IL-10 and produce high level of IL-10 associated with intermediate level of IFN-γ as well as the $CD4^+CD25^+$ Tr cells recently characterized both in mouse and in humans (29, 30). Although IL-10 production and often TGF-β production were reported to be general characteristics of T regulatory cells, the ability of these cells to suppress immune responses in vivo or in vitro has been shown to be mediated at least in part by IL-10 in some experimental system but not in others (29–31). In particular, the human $CD4^+CD25^+$ peripheral blood T cell subset identified recently in several studies was shown to produce IL-10 but to exert immunosuppressive activity via a cell contact-dependent IL-10–independent mechanism (31).

Both in the mouse and in humans IL-10 and TGF-β have been shown to be important for activation/differentiation of Tr cells (28–30). These two cytokines, produced early in the infection by phagocytes or other cells infected or exposed to parasite products, could activate T cell subsets producing them (e.g., the IL-10 and IFN-γ producing T cells). These T cells could then persist at the site of infection modulating the inflammatory response. Studies in patients with Lyme disease, as mentioned above, suggests that also IL-12 may be an important cytokine responsible for the differentiation of the IL-10 and IFN-γ producing T cells in human chronic intracellular infections (22).

In the mouse, $CD4^+CD25^+$ Tr cells have been shown to be generated in the thymus after high affinity TCR interaction with self-peptide through a process distinct from positive selection and deletion (32). However, whether they can also derive in the periphery from naive T cells or are simply expanded or activated from thymus-derived cells already primed for regulatory functions remains an open question (29). Although both autoimmunity and transplantation studies suggest the possibility that Tr may differentiate from naive T cells (29), the fact that in infectious diseases IFN-γ and IL-10 producing T cells are often observed in both parasite-specific and nonspecific T cell clones may argue in favor of activation of nonspecific bystander T cells or of T cells cross-reactive with self-antigens. These T cells may regulate the specific immune and inflammatory responses in a nonantigen specific way by producing antiinflammatory cytokines such as IL-10 and TGF-β or by other mechanisms. An example of possible activation by pathogens of Tr cells cross-reactive with self-antigens is provided by the induction of immunosuppressive IL-10–producing T cells by a mycobacterial hsp70 sequence cross-reacting with the mammalian hsp-70 homologue (33). Stimulation of *P. falciparum* specific clones by the specific peptide in the presence of certain naturally occurring altered peptide ligands was also shown to alter the functional characteristics of established antigen-specific clones from effector Th1 type cells producing high levels of IFN-γ to immunosuppressive cells producing IL-10 and lower level of IFN-γ (34). It was proposed that this mechanism could be responsible for the low level of T cell responses observed in endemic malaria areas in which coinfection with several *P. falciparum* variants is frequent (34).

Chronic exposure to superantigen in mice, possibly mimicking what happens in persistent infection, induces regulatory T cell with IL-10 mediated suppressive activity (35). Both in vivo and in vitro it has been shown that immature DCs may induce the differentiation of Tr (30) suggesting that intracellular pathogens such as *L. major* could induce Tr cells because of their ability to infect DCs and to modulate the activation and cytokine production of antigen presenting cells (13, 36). Alternatively, it is possible that different subsets of DCs might be responsible for differentiation of functional subsets of T cells (30). The IFN-α producing human plasmacytoid DCs, when infected by viruses, have been shown to induce the differentiation of T cells producing both IL-10 and IFN-γ (37, 38). This effect was mediated by IFN-α and probably IL-12. IFN-α in cooperation with IL-10 has indeed been shown to induce human Tr cells that produce both IFN-γ and IL-10 (39). The production of IFN-α/β and the possible role of plasmacytoid DCs in intracellular infections by pathogens other than viruses has been poorly investigated. However, IFN-α/β was shown to be induced early after infection of mice with *L. major* and to be required for iNOS activation (40) and virulence of a *M. tuberculosis* clinical isolated was demonstrated to be associated with its ability to induce IFN-α/β production (41).

Conclusions. From the many experimental and clinical studies discussed above a clear picture is emerging that IL-10 is involved in limiting inflammation although often also in preventing sterile cure in chronic infection by intracellular parasites. The principal source of IL-10 in persistent infection may be T cells that also produce IFN-γ, in addition or instead of Th2 cells or cells infected or exposed to parasite products, e.g., macrophages. However, the observation in various clinical studies of the presence of T cells producing both IFN-γ and IL-10 was almost anedoctical and of unclear physiological significance. The demonstration by Belkaid et al. (14) in this issue of the presence of these cells in *L. major* infected mice and of their role in preventing a sterile cure of the infected animals indicates that these cells

play an important role in modulating the immune response against intracellular parasites and provides an experimental model for their study. The understanding of the specificity of these cells, their mechanisms of activation and persistence as well as the cytokines and the antigen presenting cells involved in their generation and function will undoubtedly teach us much about the regulation of the host-parasite relationship, especially in chronic persistent infection.

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