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Pillars of Immunology

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Interleukin-10 was first discovered in 1989 as cytokine synthesis inhibitory factor produced by $CD4^+$ Th2 clones in response to the lectin Con A or Ag stimulation (1). At this time, increasing evidence suggested that Th1 and Th2 subsets possessed reciprocal inhibitory functions (i.e., IFN-γ from Th1 clones inhibited Th2 proliferation); however, the Th2 cytokine responsible for inhibiting Th1 proliferation was unknown. Fiorentino et al. (1) were the first to show that cytokine synthesis inhibitory factor, now known as IL-10, inhibited Th1 effector function by blocking cytokine synthesis at the transcriptional level.

Fiorentino and colleagues (2, 3) later published two seminal articles in 1991 detailing key functions of IL-10, followed by a 1997 article from Steinbrink et al. (4), all originally published in *The Journal of Immunology* and reprinted here as *Pillars of Immunology*. Together, these studies established the foundational knowledge of IL-10 function.

Fiorentino et al. (2) showed that IL-10 inhibited Th1 release of IFN-γ by regulating macrophage accessory cell function. Preincubation of splenic APCs with IL-10 drastically reduced IFN-γ production by Th1 clones, suggesting that IL-10 acted directly on APCs. This was independent of Ag processing, because IL-10 was able to suppress Th1 responses to staphylococcal enterotoxin B, which does not require Ag processing. Fixation of the APCs used in Th1 stimulation negated the effects of IL-10, implying that metabolically active macrophages were required for IL-10 function. Moreover, IL-10 did not affect class II MHC expression on APCs, suggesting that IL-10 acted independently of the MHC-TCR complex.

Later that year, Fiorentino et al. (3) published a follow-up article that extended the insights of the aforementioned studies to sepsis and inflammation. These data showed that IL-10 inhibited LPS-induced release of IL-1, IL-6, and TNF-α by macrophages. This inhibition occurred at the mRNA level and was accompanied by changes in macrophage morphology. In line with the hypothesis that IL-10 and IFN-γ exerted opposing effects, IFN-γ induced macrophage production of these proinflammatory cytokines while inhibiting endogenous production of IL-10. These studies suggested that, in addition to modulating T cell responses, IL-10 was a key regulator of acute inflammatory responses. This regulation was mediated through the IL-10R, which was subsequently cloned and described in mice and humans by Tan et al. (5) and Liu et al. (6), respectively.

In 1997, Steinbrink et al. (4) described the role of IL-10 in modulating dendritic cell (DC) function and, consequently, Th1 priming/function. By adding IL-10 at different doses and stages of blood-derived DC development, they showed that IL-10 inhibited DC maturation in a dose-dependent fashion. In these studies, IL-10 downregulated the surface expression of class II MHC and costimulatory molecules CD58 and CD86. Furthermore, coculture assays with allogeneic donor APCs showed that IL-10 was capable of inducing a state of alloantigen-specific anergy in $CD4^+$ T cells. Studies using HA1.7 T cell clones that recognize influenza hemagglutinin suggested that peptide-specific anergy could be induced as well (4). This work, combined with that of Fiorentino and colleagues, initially established how IL-10 inhibited Th1 effector function through macrophages and DCs.

Subsequent work on IL-10 revealed that it is produced by a number of cells beyond Th2 cells, including Tr1 cells and macrophages. IL-10 was not only produced by Tr1 cells, but also promoted their differentiation (7). Recently, it also was shown that *Staphylococcus aureus* priming of naive human T cells generated IL-10–producing Th17 cells (regulatory Th17 cells), potentially as an intrinsic mechanism to suppress excessive inflammation in response to infection (8, 9). Studies using in vivo infection with *Toxoplasma gondii* and *Leishmania major* revealed that $Tbet^+$ Th1 cells also secreted IL-10 (10, 11). Whereas IL-10 produced by $Foxp3^-$ T cells was required to control the healing response in *L. major* infection, IL-10 from regulatory T cells was responsible for host resistance against this protozoan parasite (11). This suggested that the cellular source of IL-10 dictated its in vivo function.

It became evident that IL-10 could be protective or detrimental, depending on the disease condition. $Il10^{-/-}$ mice developed spontaneous colitis, suggesting a protective role in intestinal homeostasis (12). In contrast, increased IL-10 was associated with enhanced susceptibility to *Listeria monocytogenes*, *Streptococcus pneumoniae*, and *Trypanosoma cruzi* in mice, implying a detrimental role in these infection models (13–15). In humans, increased IL-10 secretion by $CD4^+$ T cells and macrophages was associated with systemic lupus erythematosus and non-small cell lung cancer,

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Abbreviation used in this article: DC, dendritic cell.

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respectively (16–18), whereas decreased serum IL-10 was observed in psoriatic patients (19). Together, these data suggest that enhancing or blocking IL-10 function may be promising therapeutic strategies, particularly for autoimmune diseases, such as inflammatory bowel disease.

As such, multiple clinical trials involving immunomodulation of IL-10 have been conducted. rIL-10 supplementation in psoriasis and IL-10 blockade in systemic lupus erythematosus exhibited therapeutic effects in clinical trials (20, 21). In contrast, despite favorable results in mouse models and encouraging phase I clinical trials, human rIL-10 failed to improve inflammatory bowel disease or rheumatoid arthritis (22–25). Apart from the natural complications that arise when transitioning from preclinical mouse studies to human clinical trials, investigators have speculated that these negative results may be due to variation in host genetics, and multiple endophenotypes in complex diseases such as Crohn's disease (26). It is also possible that the tested doses of IL-10 supplementation were not sufficient to suppress the excessive inflammatory environment, particularly in severe disease states (26). There are ongoing studies modifying IL-10 to increase its potency. For example, Dekavil is a fusion protein in which IL-10 is fused with F8, an Ab specific for the alternatively spliced EDA domain of fibronectin (27). Now in phase II clinical trials, this fusion protein is hypothesized to result in targeted delivery of IL-10 to arthritic lesions (27, 28). Therefore, although IL-10 continues to be a promising therapeutic target, it is clear that its involvement in complex immunologic networks partnered with phenotypic heterogeneity within diseases poses a challenge that needs to be addressed to successfully use this cytokine as an immunomodulatory therapeutic. However, as we celebrate the first 100 years of *The Journal of Immunology*, it is worth noting the important role of the studies by Fiorentino et al. and Steinbrink et al. in laying much of the groundwork for our understanding of the complex functions of this cytokine, a foundation on which many future studies will no doubt rely.

Disclosures

The authors have no financial conflicts of interest.

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