Cytokine & Growth Factor Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Mini review

The light and the dark sides of Interleukin-10 in immune-mediated diseases and cancer.

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ARTICLE INFO

Article history:
Received 28 January 2016
Accepted 18 February 2016
Available online xxx

Keywords:
Interleukin-10
T-cells
Colitis
Systemic lupus erythematosus
Cancer

ABSTRACT

Interleukin-10 (IL-10) is known to be a tolerogenic cytokine since it inhibits pro-inflammatory cytokine production and T cell stimulatory capacities of myeloid cells, such as macrophages and dendritic cells. In particular, it has a non-redundant tolerogenic role in intestinal immune homeostasis, since mice and patients with genetic defects in the IL-10/IL-10R pathway develop spontaneously colitis in the presence of a normal intestinal flora. However, IL-10 is also a growth and differentiation factor for B-cells, can promote autoantibody production and has consequently a pathogenic role in systemic lupus erythematosus. Moreover, IL-10 can promote cytotoxic T-cell (CTL) responses and this immunogenic activity might be relevant in type-1 diabetes and anti-tumor immune responses. This review summarizes these paradoxic effects of IL-10 on different types of immune responses, and proposes that different cellular sources of IL-10, in particular IL-10-secreting helper and regulatory T-cells, have different effects on B-cell and CTL responses. Based on this concept we discuss the rationales for targeting the IL-10 pathway in immune-mediated diseases and cancer.

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1. Introduction

IL-10 is generally considered a tolerogenic and anti-inflammatory cytokine, because it blocks the production of pro-inflammatory cytokines and the capacity of myeloid cells to efficiently activate T-cells [1,2]. Indeed, the production of IL-10 by T-cells is considered a hallmark of a subset of regulatory T-cells that inhibit or dampen immune responses [3,4]. However, as is the case for many other cytokines, the action of IL-10 is more complex and can have both stimulatory and inhibitory effects on different types of immune responses [5], depending on the cellular source of IL-10, the timing of its secretion and the type of immune cells that receives signals via the IL-10R. In particular, IL-10 has relevant positive effects on cytotoxic T-cell and B cell responses, in spite of the fact that these responses critically depend on help by $CD4^+$ T-cells, which are a major target of the tolerogenic effects of IL-10. In this mini-review we will summarize the current knowledge on these paradoxic effects of IL-10 on different types of immune responses and discuss how these effects impact on immune-mediated diseases and cancer.

2. The tolerogenic and anti-inflammatory role of T-cell-derived IL-10 in intestinal homeostasis

The major defect of IL-10-deficient mice is the spontaneous development of colitis [6], indicating that the principal non-redundant role of IL-10 is to maintain intestinal immune homeostasis. IL-10-deficient mice that are kept under germ-free conditions do not develop colitis [7], indicating that an intact intestinal microflora is required, and suggesting that IL-10 maintains tolerance to commensals. Moreover, patients with genetic defects in the IL-10/IL-10R pathway develop severe early-onset colitis that can be healed by transplanting IL-10/10R-sufficient stem cells that regenerate a new immune system, indicating that IL-10 is required to maintain intestinal tolerance also in humans

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http://dx.doi.org/10.1016/j.cytogfr.2016.02.003
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[8]. It was recently shown that macrophages are a relevant target population of the tolerogenic effects of IL-10 in mice, since selective IL-10R deficiency of CX3CR1$^+$ cells was sufficient to induce colitis [9,10]. Nevertheless, IL-10 can also directly act on CD4$^+$ T-cells and in particular Th17 cells express high levels of IL-10R, expand in the absence of IL-10R signaling and become pathogenic [11,12]. Indeed, CD4$^+$ T-cells specific for bacterial antigens can induce colitis [13]. Furthermore, intestinal Th17 cells are specific for commensal bacteria [14] and are controlled in the small intestine [15]. In addition, IL-10R signaling in Tregs is required for their suppressive functions [16]. Importantly, mice that lack IL-10 production selectively in T-cells also develop colitis, suggesting that T-cells are the relevant source of IL-10 to maintain intestinal immune homeostasis [17]. One important IL-10 producing subset among CD4$^+$ T-cells are Foxp3$^+$ regulatory T-cells (Tregs) [2,18], and indeed it was shown that IL-10-derived from Tregs is important at barrier surfaces, including the gut [19,20]. However, several T-cell subsets besides Foxp3$^+$ Tregs can produce IL-10 [2], and in particular also Foxp3-negative IL-10-producing "type-1 regulatory T(Tr1)-cells" can inhibit transfer colitis in an IL-10-dependent manner [3,11,21]. In humans, the contribution of different regulatory T-cell subsets is more difficult to address, but we found recently that IL-10 production by IFN-γ-secreting Tr1 cells [4,22] is selectively reduced in IBD patients. Interestingly, pro-inflammatory cytokines that are typically enhanced in IBD down-regulated IL-10 production selectively by IFN-γ-producing Tr1 cells, but did not affect IL-10 production by Foxp3$^+$ Tregs (Alfen&Larghi, manuscript in submission), suggesting that these peculiar Tr1-cells are highly plastic [22,23] and a critical source of IL-10 in the human gut. Consistently, Tr1-cells can be generated in response to probiotic bacteria *in vivo* [24] and the transfer of Ovalbumin-specific Tr1-cells had a transient beneficial effect in Crohn's disease patients [25].

IPEX patients that lack Foxp3-expressing Tregs [26], and non-IPEX autoimmune enteropathy patients that have only a partial deficit in Foxp3$^+$ Tregs also have severe chronic intestinal inflammation ([27],Paroni et al., under revision). In these patients IL-10-producing Tr1 cells are not affected ([28] Paroniet al., under revision), suggesting that Tregs are required in addition to Tr1-cells to maintain intestinal immune homeostasis in humans. Besides IL-10 and Tregs, also TGF-β has an important role in peripheral tolerance [29], in particular in the gut. Thus, Tregs fail to control

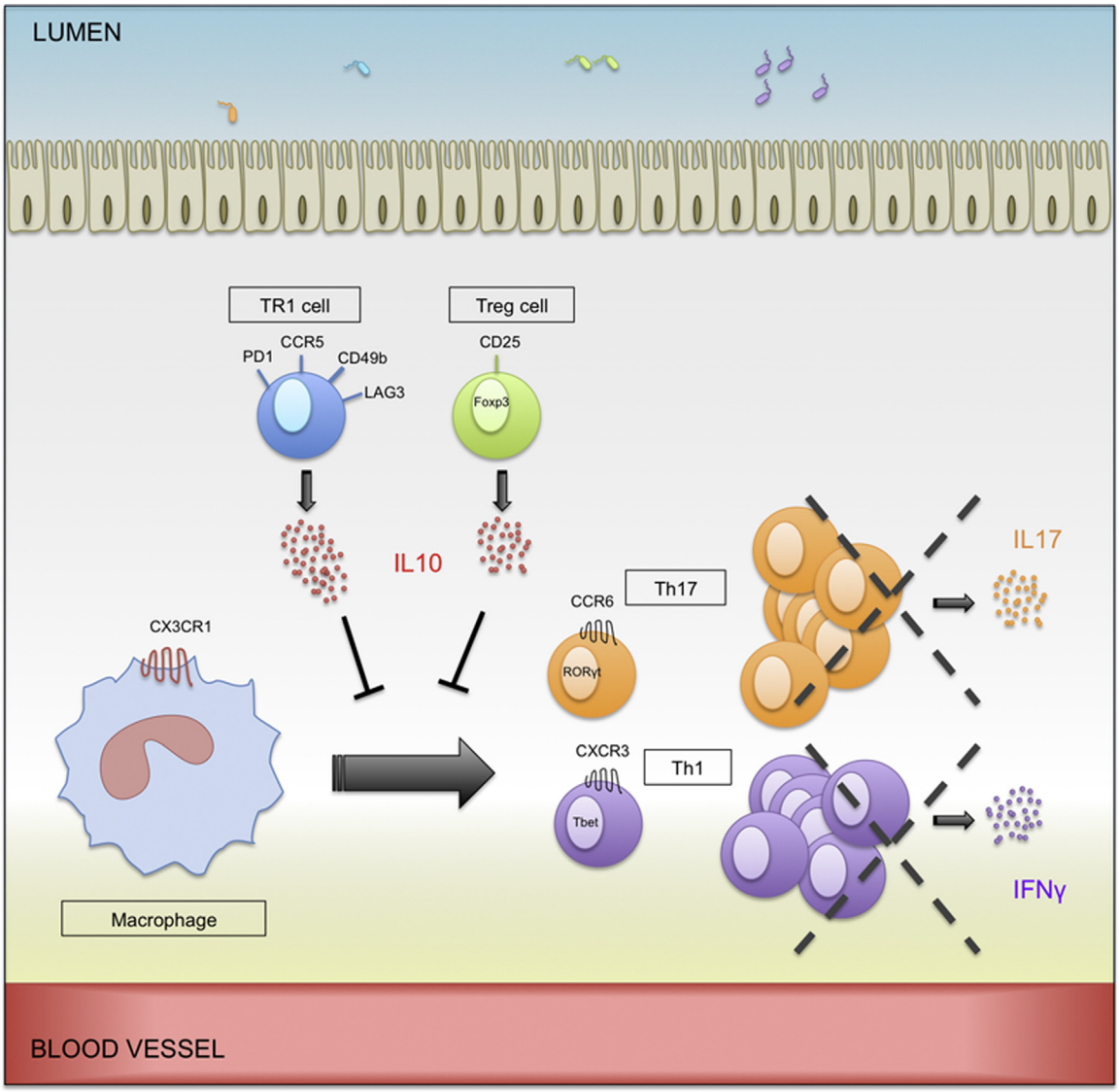

Fig. 1. IL-10 from intestinal Tregs and/or Tr1-cells acts on macrophages to inhibit Th1/17 expansion and colitis.
Intestinal Tregs and Tr1-cells produce IL-10, which inhibits cytokine production by CXCR3$^+$ resident macrophages that in turn fail to activate colitogenic Th1 and/or Th17 cells.

Please cite this article in press as: J. Geginat, et al., The light and the dark sides of Interleukin-10 in immune-mediated diseases and cancer., Cytokine Growth Factor Rev (2016), http://dx.doi.org/10.1016/j.cytogfr.2016.02.003

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