

## NEWS AND COMMENTARY

### IL-1 $\beta$ /CD14 pathway induces IL-17 production

# Dendritic cells activated with IL-1 $\beta$ set Th17 cells on fire by CD14-mediated mechanisms

Jimena Tosello Boari and Eva V Acosta Rodriguez

*Immunology and Cell Biology* advance online publication, 11 October 2016; doi:10.1038/icb.2016.87

In 2005, the description of a new subset of effector CD4<sup>+</sup> T cells called Th17 broke the Th1/Th2 paradigm. Since then, Th17 cells and their eponymous cytokine interleukin (IL)-17 have emerged as central players underlying not only inflammatory and autoimmune processes but also host resistance to several infections. A selected group of pro-inflammatory cytokines including IL-1 $\beta$ , IL-6 and IL-23 has been associated with the development of Th17 cells.<sup>1</sup> IL-1 $\beta$ , in particular, was shown to promote IL-17 production by memory Th17 and  $\gamma\delta$  T cells, highlighting the tight link between IL-1 $\beta$  and IL-17 immunity. Indeed, mice with genetic ablation of IL-1 $\beta$  or its receptor IL-1R1 showed diminished Th17 development and phenotypes partially overlapping with those of IL-17-deficient mice (that is, reduced inflammation, increased susceptibility to some infections and resistance to autoimmune pathologies). So far, the IL-17-promoting activity of IL-1 $\beta$  has been ascribed to a direct effect on T cells.<sup>2</sup> However, the experimental approaches used did not exclude the possibility that IL-1 $\beta$  may modulate other cells to further trigger IL-17 secretion by T cells. On this issue, Ilarregui *et al.*<sup>3</sup> describe a novel mechanism by which IL-1 $\beta$  enhances IL-17 production by human memory T cells through indirectly instructing dendritic cells (DCs) to adopt a Th17-promoting program.

DCs are undoubtedly the immune cell subset best equipped to sense environmental clues and to induce the best tailored T-cell differentiation program. These cells, together with others of myeloid origin, are able to produce high amounts of IL-1 $\beta$  upon

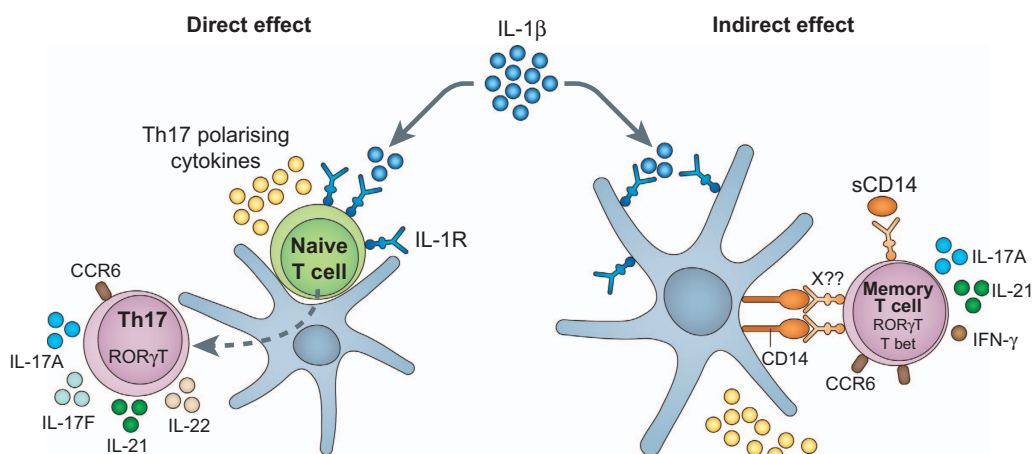
activation with different inflammatory mediators such as microbial ligands of toll-like receptors (TLR), activated complement and other cytokines such as TNF and IL-1 $\beta$  itself.<sup>2</sup> Therefore, the IL-1 $\beta$  putatively present at high concentrations in inflammatory environments could modulate the activation program of the responding DCs in autocrine/paracrine ways. On the basis of this premise, Ilarregui *et al.*<sup>3</sup> investigated whether IL-1 $\beta$  could instruct DCs to adopt a Th17-promoting profile. For comparison, these authors used DCs treated with peptidoglycan (PGN), a TLR2/NOD2 agonist well known to induce a Th17-promoting program in antigen presenting cells.<sup>4,5</sup> Conditioning of monocyte-derived DCs with IL-1 $\beta$  resulted in the acquisition of phenotypic and functional features very similar to that observed in PGN-treated DCs, including upregulation of CD14 and expression of high levels of Th17 inducing cytokines (that is, IL-1 $\beta$ , IL-23 and IL-6). Accordingly, IL-1 $\beta$ -treated DCs were almost as efficient as PGN-treated DCs in promotion of IL-17 production by co-cultured human memory T cells. Remarkably, Ilarregui *et al.*<sup>3</sup> found that while the Th17-promoting effect of PGN-stimulated DCs depended almost completely on soluble mediators like IL-1 $\beta$ , IL-6 and IL-23, the effect mediated by IL-1 $\beta$ -stimulated DCs required not only the secretion of cytokines but also DC T-cell contact. In addition, DCs treated with these two different conditioning stimuli also differed in their ability to induce interferon (IFN)- $\gamma$  production by memory T cells. Altogether, these data suggested that the T-cell modulatory program triggered in DCs by IL-1 $\beta$  has similarities but also peculiarities compared with that triggered by PGN.

Given that the upregulation of CD14 was a prominent feature of IL-1 $\beta$ -treated DCs and that CD14 has been reported to have

lipopolysaccharide-independent effects on human T cells,<sup>6</sup> this membrane glycoprotein emerged as the candidate to underlie the phenomenon described. Neutralization experiments confirmed that CD14 signaling is an important mediator of the Th17-promoting program triggered in DCs by IL-1 $\beta$  and to a much lesser extent, by PGN. Furthermore, Ilarregui *et al.*<sup>3</sup> showed that addition of the soluble form of CD14 (sCD14) to cultures of activated T cells was sufficient to promote IL-17 production by memory but not by naive T cells. This effect correlated with greater binding of sCD14 to activated memory T cells versus activated naive T cells. Interestingly, sCD14 alone or in combination with Th17-polarizing cytokines was able to not only enhance IL-17 production but also induce the expression of genes associated with the Th17 program, such as *RORC*, *CCR6* and *IL-21*, and repress expression of the Th1-associated transcription factor *TBX21*. Altogether, these data indicate that IL-1 $\beta$  triggers distinct direct and indirect pathways that cooperatively enhance the Th17 program in memory T cells (Figure 1). It remains unclear whether these factors generate stable Th17 cells even in inflammatory conditions that promote Th1 responses. In this regard, it is striking that besides enhancing IL-17 production, IL-1 $\beta$ -conditioned DCs and the combination of sCD14+ plus Th17-polarizing cytokines were also able to increase the frequency of IL-17+IFN $\gamma$ + effector T cells and to promote IFN $\gamma$  production. As IL-17+IFN $\gamma$ + Th17 cells have been linked to immunity against pathogens<sup>7</sup> but also to pathogenicity during autoimmune disease,<sup>8</sup> it would be very relevant to dissect the precise mechanisms operating in these conditions. Which memory T cell subset is binding

to and being modulated by CD14? What molecule is acting as a CD14 ligand? Does

J Tosello Boari and EV Acosta Rodriguez are at Centro de Investigaciones en Bioquímica Clínica e Inmunología (CIBICI-CONICET), Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina  
E-mail: eacosta@fcq.unc.edu.ar



**Figure 1** IL-1 $\beta$ -mediated enhancement of Th17 immunity. The pro-inflammatory cytokine IL-1 $\beta$  promotes Th17 responses and function by direct and indirect mechanisms. On one side, IL-1 $\beta$  in combination with transforming growth factor- $\beta$ , IL-6 and IL-23 is able to commit naïve T cells to the Th17 differentiation pathway. On the other hand, as described in this issue by Ibarregui *et al.*,<sup>3</sup> IL-1 $\beta$  is able to act in an autocrine/paracrine way to instruct DCs to adopt a Th17-promoting program. This program that enhances IL-17 (and to a lesser extent IFN $\gamma$ ) production by memory CD4<sup>+</sup> T cells, is characterized by the secretion of Th17-polarizing cytokines (IL-1 $\beta$ , IL-6 and IL-23) and also the upregulation of CD14. Besides modulation of IL-17 and IFN $\gamma$  production, sCD14 alone or in combination with Th17-polarizing cytokines is able to upregulate many genes associated with the Th17 signature such as *Ccr6*, *Rorc* and *Ii21* and downregulate others associated with Th1 cells such as *Tbx21*.

CD14 only bind to memory Th17 cells to promote IL-17 secretion, or is CD14 signaling alone or in combination with Th17 polarizing cytokines able to induce plasticity and IL-17 and IFN $\gamma$  secretion by Th17, Th1 or Th2 cells? The answers to these questions could be important to many inflammatory processes where IL-17-mediated immunity is involved.

Most of the results of this study were obtained using *in vitro* generated monocyte-derived DCs that, although widely employed, have the drawback of not having equivalents *in vivo*. To get over this, Ibarregui *et al.*<sup>3</sup> validated their findings in a more physiological human skin explant model. The injection of IL-1 $\beta$  (or PGN) in these explants triggered the migration of DCs with high expression of CD14 and IL-23. In contrast, DCs that migrated after the injection of another TLR-ligand (Poly I:C) showed low expression of these molecules. In agreement, only the skin DCs that migrated upon IL-1 $\beta$  or PGN treatment were able to enhance IL-17 secretion by memory T cells via a CD14-dependent mechanism. These results indicate that the effects observed *in vitro* also operate in tissues. It is still unclear whether IL-1 $\beta$  triggers CD14 upregulation and a Th17-promoting program in all DCs of any tissue, or activates/induces migration of one particular DC subset seeded in that tissue (that is, dermal CD14<sup>+</sup> DCs). Interestingly, an inflammation-associated subset of human DCs exists with a unique phenotype characterized by the expression

of several distinct markers not present in conventional DCs, including CD14.<sup>9</sup> Of note, these inflammatory DCs are potent stimulators of Th17 cells and show a gene signature that suggests a monocyte origin. These findings are in agreement with many previous reports showing that monocytes are much better inducers of Th17 responses than conventional DCs.<sup>4</sup> Hence, in addition to the ability to produce Th17-polarizing cytokines, the expression of CD14 seems to be a common feature to all the cell subsets able to enhance IL-17 production. Integrating these results, it could be hypothesized that IL-1 $\beta$ , present at high concentrations in many inflammatory settings, may be one of the critical environmental clues that instructs infiltrating monocytes to acquire the developmental program of 'Th17-promoting' inflammatory DCs.

Collectively, the results of Ibarregui *et al.*<sup>3</sup> provide novel and relevant information about the mechanisms that operate locally at inflammatory environments to regulate IL-17-mediated immunity. Although the mechanisms underlying the phenomenon described remain to be precisely elucidated, the description of the role of IL-1 $\beta$  in instructing DCs to acquire a Th17-promoting program mediated by CD14 opens new possibilities for the local manipulation of Th17 responses, which may be of relevance in several pathological conditions.

## CONFLICT OF INTEREST

The author declares no conflict of interest.

- Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. *Nat Rev Immunol* 2014; **14**: 585–600.
- Garlanda C, Dinarello CA, Mantovani A. The interleukin-1 family: back to the future. *Immunity* 2013; **39**: 1003–1018.
- Ibarregui JM, van Beelen AJ, Fehres CM, Bruijns SCM, Garcia-Vallejo JJ, van Kooyk Y. New roles for CD14 and IL-1 $\beta$  linking inflammatory dendritic cells to IL-17 production in memory CD4<sup>+</sup> T cells. *Immunol Cell Biol* (e-pub ahead of print 23 August 2016; doi:10.1038/icb.2016.66).
- Acosta-Rodriguez EV, Napolitani G, Lanzavecchia A, Sallusto F. Interleukins 1 $\beta$  and 6 but not transforming growth factor- $\beta$  are essential for the differentiation of interleukin 17-producing human T helper cells. *Nat Immunol* 2007; **8**: 942–949.
- van Beelen AJ, Zelinkova Z, Taanman-Kueter EW, Muller FJ, Hommes DW, Zaat SA *et al.* Stimulation of the intracellular bacterial sensor NOD2 programs dendritic cells to promote interleukin-17 production in human memory T cells. *Immunity* 2007; **27**: 660–669.
- Rey Nores JE, Bensussan A, Vita N, Stelter F, Arias MA, Jones M *et al.* Soluble CD14 acts as a negative regulator of human T cell activation and function. *Eur J Immunol* 1999; **29**: 265–276.
- Zielinski CE, Mele F, Aschenbrenner D, Jarrossay D, Ronchi F, Gattorno M *et al.* Pathogen-induced human TH17 cells produce IFN- $\gamma$  or IL-10 and are regulated by IL-1 $\beta$ . *Nature* 2012; **484**: 514–518.
- Lee Y, Awasthi A, Yosef N, Quintana FJ, Xiao S, Peters A *et al.* Induction and molecular signature of pathogenic TH17 cells. *Nat Immunol* 2012; **13**: 991–999.
- Segura E, Touzot M, Bohineust A, Cappuccio A, Chiochia G, Hosmalin A *et al.* Human inflammatory dendritic cells induce Th17 cell differentiation. *Immunity* 2013; **38**: 336–348.