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Jimena Tosello Boari and Eva V Acosta Rodriguez

In 2005, the description of a new subset of effector CD4+ 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-1β, IL-6 and IL-23 has been associated with the development of Th17 cells. IL-1β, in particular, was shown to promote IL-17 production by memory Th17 and γδ T cells, highlighting the tight link between IL-1β and IL-17 immunity. Indeed, mice with genetic ablation of IL-1β 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-1β has been ascribed to a direct effect on T cells. However, the experimental approaches used did not exclude the possibility that IL-1β may modulate other cells to further trigger IL-17 secretion by T cells. On this issue, Ilarregui et al. described a novel mechanism by which IL-1β 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-1β 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-1β itself. Therefore, the IL-1β 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. investigated whether IL-1β 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. Conditioning of monocyte-derived DCs with IL-1β 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-1β, IL-23 and IL-6). Accordingly, IL-1β-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. found that while the Th17-promoting effect of PGN-stimulated DCs depended almost completely on soluble mediators like IL-1β, IL-6 and IL-23, the effect mediated by IL-1β-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)-γ production by memory T cells. Altogether, these data suggested that the T-cell modulatory program triggered in DCs by IL-1β has similarities but also peculiarities compared with that triggered by PGN.

Given that the upregulation of CD14 was a prominent feature of IL-1β-treated DCs and that CD14 has been reported to have lipopolysaccharide-independent effects on human T cells, 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-1β and to a much lesser extent, by PGN. Furthermore, Ilarregui et al. 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-1β 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-1β-conditioned DCs and the combination of sCD14+ plus Th17-polarizing cytokines were also able to increase the frequency of IL-17+IFNγ+ effector T cells and to promote IFNγ production. As IL-17+IFNγ+ Th17 cells have been linked to immunity against pathogens but also to pathogenicity during autoimmune disease, 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

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NEWS AND COMMENTARY

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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 IFNγ 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, Ilarregui et al.3 validated their findings in a more physiological human skin explant model. The injection of IL-1β (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-1β 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-1β 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+ 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 CD14.9 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.4

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-1β, present at high concentrations in many inflammatory settings, may be one of the critical environmental cues that instructs infiltrating monocytes to acquire the developmental program of ‘Th17-promoting’ inflammatory DCs.

Collectively, the results of Ilarregui et al.3 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-1β 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.

References