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COMMENTARY

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Hierarchical governance of cytokine production by 6-sulfo LacNAc (slan) dendritic cells for the control of psoriasis pathogenesis

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The skin immune system comprises a heterogeneous network of local cellular immune mediators. Their complex interplay establishes an efficient first-line barrier defense against pathogens and other environmental assaults. It also assures immune homeostasis and tolerance of the commensal microbiota. In psoriasis, a chronic inflammatory skin disease, the skin immune homeostasis is dysregulated resulting in immune cell infiltration and hyperplasia of epidermal keratinocytes.

Th17 cells have been identified as major constituents of psoriasis pathogenesis and many other autoimmune diseases. For this reason, the analysis of their polarization conditions, effector functions and plasticity has culminated in intense research efforts over the past 10 years. Direct targeting of Th17 cell effector functions such as IL-17 production (secukinumab) or Th17 differentiation (ustekinumab) has translated into great therapeutic success. An antigen-presenting cell that is hard-wired for creating a microenvironment for optimal Th17 cell polarization and maintenance, has yet not been identified. Schäkel and colleagues have previously proposed human 6-sulfo LacNAc$^+$ (slan) dendritic cells (slan-DC) as a major dermal dendritic cell population in psoriasis with optimal functions for creating a Th17 cell permissive microenvironment by IL-23 and IL-1β production.[1] They now propose an additional layer of complexity with their identification of an autocrine cytokine hierarchy that primes slan-DC for high-level production of IL-23 (Fig. 1).[2]

Commentary to: "Autocrine TNF-α and IL-1β prime 6-sulfo LacNAc$^+$ dendritic cells for high level production of IL-23" by Kunze A., Förster U., Oehrl S., Schmitz M., Schäkel K.

IL-1β renders Th17 cells proinflammatory by simultaneous IL-10 suppression and IFN-γ upregulation (hybrid Th1/Th17 population).[3] This makes IL-1β a critical switch factor for imprinting a pro- versus anti-inflammatory Th17 cell identity and thus a potentially interesting therapeutic target. In fact, autoinflammatory syndromes that are characterized by recurrent fever attacks, skin rashes, joint pain and other variable symptoms are mediated by systemic IL-1β overproduction due to gain of function mutations in the NLRP3 inflammasome. This translates into a shift from anti- to proinflammatory Th17 cells, which can be reversed by systemic IL-1β depletion. This has recently been demonstrated in patients suffering from the Schnitzler syndrome, who were treated with canakinumab, a monoclonal antibody neutralizing IL-1β.[4] While targeting IL-1β might have dramatic effects on Th17 cell functionalities within settings of systemic IL-1β overproduction, its role in psoriasis seems less profound as judged by limited efficacy of therapeutic IL-1β blockade. IL-23, instead, has recently emerged as a very potent therapeutic target for psoriasis. Similar to IL-1β, its role in imprinting the pathogenicity of Th17 cells has been well established, particularly in mouse models.[5] Its cellular source, however, remains ill defined.

In their recent publication in this journal, Schäkel and colleagues have proposed slan-DC as potent producers of both IL-23 and IL-1β and major players in the pathogenesis of psoriasis through their ability to induce hybrid Th1/Th17 cell responses.[1,2] In psoriatic skin, the frequency of slan-DC, characterized as CD11c$^+$CD1c$^-$CD163$^-$ DCs, is twice as high as compared to healthy skin. Upon stimulation of

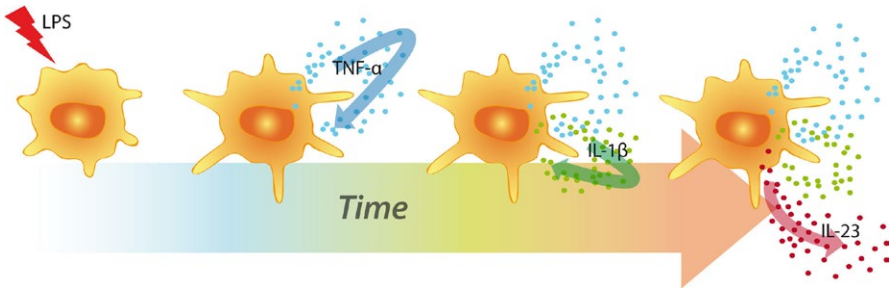

FIGURE 1 An autocrine cytokine hierarchy in slan-DCs controls IL-23 production.

toll-like receptors (TLRs), slan-DCs secrete high amounts of IL-23 as well as IL-12p70, which jointly promotes hybrid Th17/Th1 effector T-cell responses.[1] As the balance of Th1 and Th17 is reciprocally regulated by the ability of IL-12p17 to promote Th1 cell responses at the expense of Th17 cells,[6–8] it can be assumed that the balance of innate cytokine production by slan-DC needs to be tightly regulated to achieve coexistence of IFN-γ and IL-17 effector functions. Differential engagement of TLRs within the same dendritic cell is known to elicit different cytokine responses. In addition, a kinetic segregation of cytokine production by the antigen-presenting cells might also influence T-cell effector functions on the population level. In the recent publication by Kunze et al.[2], the kinetic timeline of cytokine production by slan-DC following lipopolysaccharide stimulation was also shown to follow a hierarchy of autocrine feed-forward amplification loops.

The authors demonstrated that IL-23 production by slan-DC occurred relatively late and followed autocrine TNF-α, IL-1β and IL-6 production. As the last member of this kinetic hierarchy, IL-23 production is potentially prone to qualitative modulation by its predecessors. Kunze et al.[2] demonstrated that autocrine TNF-α and IL-1β production indeed modulated IL-23 production levels since autocrine TNF-α and IL-1β inhibition using monoclonal antibodies strongly downregulated IL-23 secretion. IL-23 inhibition, however, did not influence production levels of any other slan-DC cytokines, corroborating its role as the last member in the cytokine hierarchy. Therefore, the great success of therapeutic IL-23 inhibition in psoriasis can be attributed to its direct effects on T cells, such as their polarization into pathogenic Th17 cells, but not its involvement in the modulation of innate cytokine networks in slan-DC. The top member of the cytokine hierarchy is TNF-α, as its expression levels could not be modulated by any other cytokine, while autocrine TNF-α itself displayed a feed-forward amplification effect on all downstream slan-DC cytokines.[2] Interestingly, autocrine IL-6, although identified as an early slan-DC cytokine, did not affect slan-DC cytokines significantly nor was its expression level significantly influenced by other slan-DC cytokines.[2] According to these data, the poor efficacy of IL-6 blocking therapies could be explained by their lack in perpetuating inhibition of other proinflammatory cytokine networks. However, the essential involvement of IL-6 in the generation of Th17 cells, the major effector cells in pathogenic tissue damage, still leaves the lack in efficacy of this treatment modality in most Th17-mediated diseases a poorly resolved issue.[9]

IL-12 production by slan-DC has not been investigated as part of the cytokine hierarchy in the recent study of Kunze et al.[2], although its high production has previously been reported to be a major feature of slan-DC.[1] Due to its role in Th1 polarization and Th17 cell suppression, its categorization within the hierarchy of slan-DC cytokines would be of great interest. This could provide information on whether IL-12 targeting could amplify or downregulate other innate slan-DC cytokine networks or whether targeting other members of the slan-DC cytokine hierarchy would also affect IL-12 and thus T helper cell polarization.

Understanding the cutaneous cytokine networks generated by heterogeneous DC subsets including slan-DC as abundant mediators of tissue inflammation will be of major importance in the future. This study has stressed that cutaneous cytokine networks have an additional layer of complexity based on kinetic segregation of cytokine secretion as well as on hierarchical governance of autocrine amplification loops. Further dissection of this complexity and its translation into downstream T-cell effector functions will be an important next step to harness these functions for therapeutic purposes in psoriasis as well as in other chronic inflammatory diseases.

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CONFLICT OF INTEREST

The authors have declared no conflicting interests.

REFERENCES

1. Hansel A, Gunther C, Ingwersen J, et al. *J Allergy Clin Immunol*. 2011;127:787–794 e781–789.
2. Kunze A, Forster U, Oehrl S, et al. *Exp Dermatol*. 2016;26:314.
3. Zielinski CE, Mele F, Aschenbrenner D, et al. *Nature*. 2012;484:514–518.
4. Noster R, de Koning HD, Maier E, et al. *J Allergy Clin Immunol*. 2016;138:1161.
5. Jain R, Chen Y, Kanno Y, et al. *Immunity*. 2016;44:131–142.
6. Zielinski CE. *Cell Cycle*. 2014;13:2489–2490.
7. Noster R, Riedel R, Mashreghi MF, et al. *Sci Transl Med*. 2014;6:241ra280.
8. Zielinski CE. *Exp Dermatol*. 2014;23:795–798.
9. Veldhoen M, Hocking RJ, Atkins CJ, et al. *Immunity*. 2006;24:179–189.