

NEWS & VIEWS

Groundbreaking Discoveries in Clinical & Basic Science

IL-13: An essential cDC2s partner to maintain skin homeostasis

Interleukin (IL)-13 and IL-4 are potent cytokines critical for the development of T-cell-mediated humoral responses due to their capacity to recruit and activate IgE-producing B cells, enhancing the allergic response. Moreover, these cytokines can modulate the immune response of both innate and adaptive cells.¹ Dendritic cells (DCs) have a pivotal role in the recognition, processing, and presenting antigens to naïve T cells, with the main goal of maintaining the homeostasis or initiating both the adaptive and innate immune responses. This is crucial in the skin, the most important organ for protection against environmental threats.² Skin-located DCs develop multiple functions, from regulatory activity to being responsible for directing inflammatory responses. The inflammatory subset of DCs plays an important role in the initiation and maintenance of skin diseases such as psoriasis, atopic dermatitis, and eczema throughout cytokine production.³ For example, in eczema and atopic dermatitis, the skin barrier impairment produces a release of thymic stromal lymphopoietin (TSLP) from the epidermal keratinocytes, activating the DCs that trigger the attraction of T helper type 2 (Th2) cells into the skin, and priming naïve T cells into Th2 cells.⁴ Moreover, despite DCs being reported to express both IL-13 and IL-4 receptors,¹ the role of these cytokines in DCs remains unknown, mainly because of the high heterogeneity, activation stages, and environments in which DCs are present.⁵

Conventional DCs (cDCs) can be classified into two major types based on its phenotypical, transcriptomic, and functionality features: cDC1 and cDC2. Developmentally, cDC1 is dependent on the transcription factors IRF8 and BATF3, while cDC2s express IRF4. As for functionality, cDC1s are implicated in the antigen presentation of CD8⁺ T cells and T helper (Th)1 development, whereas cDC2s are involved in Th2, Th9, Th17, and Treg responses. cDC2s, present in mouse skin, have been sorted based on their different levels of CD11b.⁵

The study developed by Mayer et al.⁶ addressed the recognition of diverse cDCs populations, focusing on how mature CD11b^{lo} cDC2s exert a specific role in allergic or homeostatic responses, to establish the knowledge basis on the potential participation of these cells in pathological and homeostatic skin conditions. Principal component analysis revealed that CD11b^{lo} belongs to a unique cluster of cells enriched in STAT6, a transcription factor with no described role in cDC2 at steady state, although it seems to control genes of maturation and differentiation in these cells.⁶ These results could confirm the inflammatory role of STAT6, similarly to other inflammatory and

allergic diseases such as asthma. Pre-DCs from bone marrow and skin show high levels of CD11b; however, downregulation of this marker is associated with maturation of cDC2 in the skin. Different assays in STAT6 knockout mice demonstrate that maturation of CD11b^{lo} cells in the skin only occurs under the control of multiple downstream genes of STAT6, which enhances the fact that this transcription factor might be a potential new drug target. This fact could be related to IL-4/IL-13 signaling, which mediates the activation of STAT6, and therefore, triggers cDC2 differentiation. However, Mayer and collaborators demonstrated that only IL-13 is implicated in dermal cDC2 CD11b^{lo} maturation process, independently of IL-4. Interestingly, this phenomenon occurs only in the skin but not in other tissues such as the lung or small intestine. Nevertheless, the concrete mechanism explaining the specific activation of STAT-6 by IL-13, but not by IL-4, remains poorly understood.

The main source of IL-13 in the skin is associated with dermal ICOS⁺ innate lymphoid cells (ILCs), which are most abundant in female than in male mice.⁶ However, it must be taken into account that the percentage of ILC2 in the skin could be low and, in addition, the induction of IL-13 release by these ILC2 is dependent on the activation of other cytokines, such as IL-25, IL-33, and TSLP, released in case of dermal barrier impairment. Moreover, other cells such as T cells and B cells can release IL-13, which could be playing an important role. IL-13 produced by ILCs is essential in the formation of CD11b^{lo} cDC2 by enhancing the expression of KLF4, a transcription factor downstream of STAT6.⁷ Moreover, the IL-13/STAT6 axis is essential in the homeostatic maintenance of cDC2 levels in healthy subjects, although under conditions of immune system activation, cDC2 induces Th2 more than Th17 responses (Figure 1). A similar mechanism could be proposed in human skin diseases such as psoriasis or atopic dermatitis, where polymorphism associated with IL-13 promotes Th2 dysregulation and Th17 responses. This study is only based on an animal model, by using wild-type or knockout mice; therefore, the extrapolation of the results to humans is very difficult. In fact, this is even more complicated when specific skin diseases with immunological mechanisms involved such as eczema, urticaria, psoriasis, or atopic dermatitis are studied, due to the high number of different cell populations and the heterogeneous mechanisms involved.

Collectively, the study proposed by Mayer et al.⁶ identifies a unique cDC2 subset whose maturation depends on IL-13, mainly produced by ILCs, although other IL-13-producing cells such as

Abbreviations: cDCs, conventional DCs; DCs, dendritic cells; IL, interleukin; ILCs, innate lymphoid cells; Th, T helper; TSLP, thymic stromal lymphopoietin.

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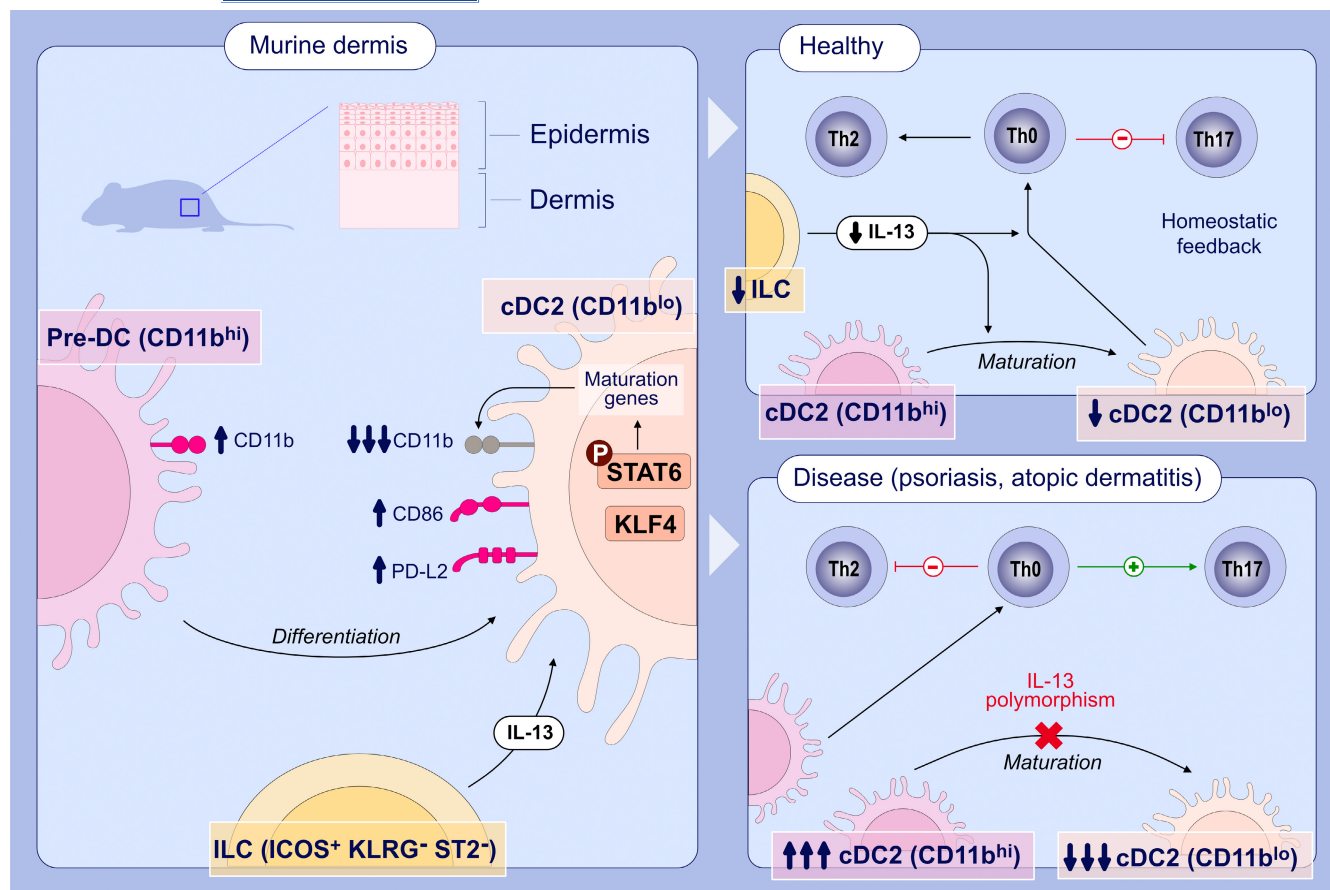


FIGURE 1 IL-13 controls cDC2 promotion and maintenance in murine skin. Maturation and differentiation of pre-DCs CD11b^{hi} towards cDC2 CD11b^{lo} is STAT6-dependent and occurs in the skin. Secretion of IL-13 from ILCs can control cDC2 maturation in murine skin by activating STAT6/KLF4 transcription factors, promoting the differentiation of cDC2 towards CD11b^{lo} phenotype. Moreover, IL-13 production is independent of alarmins and bacterial signals. After immune activation in the skin, cDC2 enhance Th2 responses by inhibiting Th17 immunity. In homeostatic conditions, a subset of ILCs secretes IL-13, which maintains normal levels of cDCs in healthy skin. Due to the low number of ILCs under healthy conditions, no aberrant immune responses are promoted. However, under pathological conditions characterized by an increased IL-13 production, Th2/Th17 imbalance towards Th17 responses occurs in atopic dermatitis and psoriasis

CD4⁺ T cells, B cells, or myeloid cells might also be relevant. They hypothesized that these cells in the skin may be responsible for triggering a Th2 response in pathologic state, and essential for maintaining the homeostasis in healthy status. Although the key role of IL-13 in skin diseases, such as atopic dermatitis, has already been described,⁸ it is still not fully understood. This cytokine contributes to skin barrier dysfunction, alteration of immune response, and induces the symptoms like itch. Thus, IL-13 could constitute a promising therapeutic target, and currently, some drugs that target and block IL-13 are being developed for the treatment of atopic skin diseases such as lebrikizumab and tralokinumab. This study opens up a world of possibilities, due to this phenomenon could be occurring in other tissues, where IL-13-producing ILCs cells have been also described.⁹ Nevertheless, because CD11b^{lo} cDC2 cells are only found in skin, as it has been shown in this study, the involvement of this DCs subset maintaining the homeostasis in healthy donors is not clear. This DC absence in other organs such as lungs or intestine may suggest the involvement of other cell populations and immunological mechanisms. Because of

all of this, more research is needed to elucidate the concrete role of CD11b^{lo} cDC2 cells maturation in humans and specific pathological processes.

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KEYWORDS

CD11b, conventional dendritic cells, IL-13, skin

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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