HHS Public Access

Author manuscript

J Invest Dermatol. Author manuscript; available in PMC 2015 March 01.

Published in final edited form as:

J Invest Dermatol. 2014 September ; 134(9): 2305–2307. doi:10.1038/jid.2014.216.

A new player on the psoriasis block: IL-17A- and IL-22-producing innate lymphoid cells

Nicole L. Ward and **Dale T. Umetsu**

Department of Dermatology, Case Western Reserve University, Cleveland, Ohio 44106; Genentech, San Francisco, CA 94080

Abstract

Innate lymphoid cells (ILCs) are a recently discovered family of innate immune cells belonging to the lymphoid lineage, yet lacking antigen-specific receptors. ILCs were first identified in the intestinal tract, where they contribute to epithelial barrier integrity and host responses to commensal microbes. Teunissen *et al.* in the current issue and Villanova *et al.* (JID, 134, 984-99) now suggest an important role for type 3 ILCs (ILC3s) in the skin, particularly in psoriasis. Both groups found an increased frequency of IL-22- and/or IL-17A-producing ILCs in psoriatic skin and blood. These cells are activated in response to IL-1β and IL-23, correlate with disease severity, and are decreased following anti-TNFα treatment. The presence of a novel ILC population in psoriatic skin, one that responds to biologic therapeutics, suggests that dysregulation of ILCs is a contributing factor to psoriasis pathogenesis.

Introduction

Innate lymphoid cells (ILCs) represent a family of multi-functional, lymphoid-lineage cells that lack B- and T-cell receptors and display innate immune effector functions. These cells often reside at mucosal interfaces where they rapidly produce cytokines in response to environmental challenges. At least three groups of ILCs have been identified, based upon unique transcription factor utilization, cytokine profiles, and effector functions. Groups 1 and 2 produce type 1 and 2 cytokines, respectively, while Group 3 has a unique capacity to produce IL-17A and IL-22. Dysregulation of ILCs has been implicated in autoimmune and inflammatory diseases, thus broadening our understanding of how innate immune cells contribute to disease pathogenesis.

However, less well understood until now is the potential role of ILCs in psoriasis. Two papers, both published in the Journal of Investigative Dermatology in 2014 (Teunissen *et al.*, 2014; Villanova *et al.*, 2014), provide compelling evidence for a pathogenic role of ILCs in psoriasis. Teunissen *et al.* show the upregulation of Group 3 ILCs (ILC3s) in nonlesional and lesional skin and blood of psoriasis patients, and show that these cells are novel cellular

Correspondence to either NLW nlw4@cwru.edu or DTU umetsud@gene.com.

Conflict of interest

The authors state no conflict of interest.

sources of IL-22 in the skin. Nestle and colleagues (Villanova *et al.*, 2014) demonstrate a close association between disease improvement and the number of IL-17A- and IL-22-producing ILC3s in the skin and circulation following anti-TNFα therapy, suggesting that ILC3s contribute to the pathogenesis of psoriasis.

ILCs

ILCs lack T cell receptors (TCRs) and B cell receptors (BCRs), and therefore are antigen non-specific; however, they respond rapidly to environmental challenges, such as tissue injury or infection, via cytokine secretion. Type 1 ILCs, or ILC1s, require the transcription factor T-bet, are induced in response to IL-12, produce type 1 cytokines such as IFNγ and have been observed in the intestines of patients with inflammatory bowel disease. Type 2 ILCs, or ILC2s, require the transcription factor RORα and GATA3, respond to the innate cytokines IL-33, IL-25 and TSLP, produce IL-5 and IL-13 but not IL-4, and have been found in the intestines in the context of helminth infection (Neill *et al.*, 2010), in the lungs in the context of asthma (Chang *et al.*, 2011), and in the skin in the context of atopic dermatitis (Salimi *et al.*, 2013). Type 3 ILCs, or ILC3s, require the transcription factor RORγt, respond to IL-23 and IL-1β, and produce IL-17A and/or IL-22. ILC3s producing IL-17A have been observed in the intestines of patients with Crohn's disease (Coccia *et al.*, 2012) and in the lungs of patients with non-allergic asthma (Kim *et al.*, 2014).

ILCs and skin inflammation

A role for ILC3s in human skin until now has remained unexplained. In murine studies, psoriasiform skin inflammation was still observed in Aldara-treated $Rag2^{-/-}$ mice, despite the lack of lymphocytes and NKT cells (Hedrick *et al.*, 2009; Pantelyushin *et al.*, 2012). Sustained expression of IL-17A and IL-22 in the skin of these mice suggested an alternative innate cellular source for these psoriasis-critical cytokines. Indeed, Pantelyushin and colleagues demonstrated the presence of IL-22-producing ILC3s in Aldara-induced skin inflammation (Pantelyushin *et al.*, 2012) that mediated the inflammatory response to Aldara, because backcrossing the $Rag2^{-/-}$ mice with $IL2r\gamma c^{-/-}$ mice, which lack ILCs, eliminated the response to Aldara. The work of Teunissen *et al.* in the current issue, along with that recently published by Villanova and colleagues translates these findings into human skin disease and provides new insights into the roles of ILC3s in psoriasis.

Clinical context of ILCs in psoriasis

In healthy skin and blood, ILC2 and ILC3s are present at low levels and express the cutaneous lymphocyte-associated antigen (CLA), thus having the capacity to localize in skin. Although few ILC3s are found in normal healthy skin, when grown *ex vivo* as cultured dermal explants, they express IL-22. Of particular translational importance were the findings by both Teunissen *et al.* and Villanova *et al.* showing increases in the ILC3 (and not the ILC1 or ILC2) population in involved- and uninvolved-psoriasis skin and peripheral blood that produced IL-22 and possibly IL-17A, two cytokines known to be especially pathogenic in human psoriasis. Moreover, ILC3s cultured *ex vivo* responded to IL-1β and IL-23, cytokines known to be elevated in psoriasis, and this converted them to the activated natural cytotoxicity receptor positive (NCR^{+}) form of ILC3 that produce IL-22. Although

Teunnissen *et al.* did not directly demonstrate ILC3-derived IL-17A in human psoriasis skin; Villanova *et al.* reported the ability of ILC3s in psoriasis skin and blood to produce both IL-17A and IL-22. These results may reflect methodological differences in how cells were isolated, the purity of the cell populations and/or differences among the patients from whom the cells were taken. Interestingly, work done in our laboratories using fresh psoriasis patient skin, both involved and uninvolved, has validated the increased presence (~4-fold) of IL-22-producing ILC3s (S. Yu, data not shown). However, we have not yet examined whether these cells produce IL-17A. All of these observations, taken together, suggest that ILC3s serve as an innate counterpart to skin-resident memory T cells, are a significant source of pathogenic cytokines in psoriatic skin, and perhaps serve as a first line defense in the skin, one that initiates the development of psoriasis.

Another observation specifically relevant to psoriasis may be found in a recent report by one of the same groups (Hergen Spits and Jenny Mjosberg), who identified tonsil-resident ILC3s that also respond to IL-1β and IL-23, with the production of IL-22 and IL-17A (Bernink *et al.*, 2013). Considering recent evidence that psoriasis patients' tonsils have a higher frequency of skin-homing lymphocytes (Sigurdardottir *et al.*, 2013) and that psoriasis patients often report onset or worsening of their skin disease after Streptococcal infection (Gudjonsson *et al.*, 2003), it will be interesting to determine whether tonsil-resident ILC3s in psoriasis patients upregulate CLA following Steptococcal infection. Such a relationship would support a role for ILC3s in psoriasis initiation and pathogenesis.

Both the Teunisson and Villanova groups demonstrated a correlation between ILC3 frequency and severity of psoriasis, as measured using the psoriasis area severity index (PASI) scoring system, and the Villanova group has also demonstrated ILC3s to decrease by 75% following TNFα inhibition (using adalimumab) in one patient. These results extend the work of Powell *et al.* (Powell *et al.*, 2012), showing that IL-23 and TNFα can drive ILC3 differentiation, and of Zaba and Krueger (Zaba *et al.*, 2009), demonstrating that IL-17/TNFα signature transcriptome probe sets predict disease remission in patients treated with etanercept (soluble TNFα receptor). Thus, it is likely that ILC3s and their elaborted cytokines are suppressed following TNFα inhibition in patients who are responsive to TNFα inhibition. Similarly, it is likely that IL-12/23 inhibitors also target ILC3s, based upon the capacity of IL-23 to drive differentiation and secretion of IL-17A/IL-22 from ILC3s.

While IL-17/IL-23 inhibitors are showing considerable efficacy in clinical trials for psoriasis, IL-22 inhibitors have thus far failed clinically for psoriasis. IL-22 appears to play a critical role in driving keratinocyte hyperproliferation, a major feature of psoriasis. However, targeting it directly may be insufficient. Targeting IL-23 or IL-17 (produced by T cells (αβ and γδ), neutrophils and ILC3s) inhibits IL-17A directly, and it also likely targets T cell- and ILC3-derived IL-22. It is possible that the combined targeting of both IL-17A and IL-22 leads to a better clinical resolution. Future work exploring relative cell-specific contributions to IL-17-mediated inflammatory responses may provide additional insight into key cellular players in psoriasis pathogenesis.

Acknowledgments

The authors thank Dr. Wendy Goodman for helpful feedback during the preparation of this commentary and Dr. Sanhong Yu for her work examining ILC3s in psoriasis skin. NLW is supported by grants from the National Institutes of Health (P30AR39750, RO1AR063437, RO1AR062546 and R21AR063852 NLW) and the National Psoriasis Foundation (NLW). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIAMS or NIH.

DTU is a full-time employee of Genentech. NLW has received grants from Allergan, and is or has been a consultant or paid speaker for Amgen, Novartis, Eli Lilly, Allergan and Galapagos.

References

Bernink JH, Peters CP, Munneke M, et al. Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. Nat Immunol. 2013; 14:221–9. [PubMed: 23334791]

Chang Y-J, Kim H, Albacker L, et al. Innate lymphoid cells mediate influenza-induced airway hyperreactivity independent of adaptive immunity. Nature Immunol. 2011; 12:631–8. [PubMed: 21623379]

Coccia M, Harrison OJ, Schiering C, et al. IL-1beta mediates chronic intestinal inflammation by promoting the accumulation of IL-17A secreting innate lymphoid cells and CD4(+) Th17 cells. The Journal of experimental medicine. 2012; 209:1595–609. [PubMed: 22891275]

Gudjonsson JE, Thorarinsson AM, Sigurgeirsson B, et al. Streptococcal throat infections and exacerbation of chronic plaque psoriasis: a prospective study. The British journal of dermatology. 2003; 149:530–4. [PubMed: 14510985]

Hedrick MN, Lonsdorf AS, Shirakawa AK, et al. CCR6 is required for IL-23-induced psoriasis-like inflammation in mice. J Clin Invest. 2009; 119:2317–29. [PubMed: 19662682]

Kim H, Lee H, Chang Y-J, et al. IL-17 producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. Nature Medicine. 2014; 20:54–61.

Neill DR, Wong SH, Bellosi A, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. Nature. 2010; 464:1367–70. [PubMed: 20200518]

Pantelyushin S, Haak S, Ingold B, et al. Rorgammat+ innate lymphocytes and gammadelta T cells initiate psoriasiform plaque formation in mice. J Clin Invest. 2012; 122:2252–6. [PubMed: 22546855]

Powell N, Walker AW, Stolarczyk E, et al. The transcription factor T-bet regulates intestinal inflammation mediated by interleukin-7 receptor+ innate lymphoid cells. Immunity. 2012; 37:674–84. [PubMed: 23063332]

Salimi M, Barlow JL, Saunders SP, et al. A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. The Journal of experimental medicine. 2013; 210:2939–50. [PubMed: 24323357]

Sigurdardottir SL, Thorleifsdottir RH, Valdimarsson H, et al. The association of sore throat and psoriasis might be explained by histologically distinctive tonsils and increased expression of skin-homing molecules by tonsil T cells. Clin Exp Immunol. 2013; 174:139–51. [PubMed: 23750651]

Teunissen M, Munneke M, Bernink J, et al. Enrichment of NCR+ ILC3 in lesional skin and blood of psoriasis patients. Journal of Investigative Dermatology. 2014

Villanova F, Flutter B, Tosi I, et al. Characterization of Innate Lymphoid Cells in Human Skin and Blood Demonstrates Increase of NKp44+ ILC3 in Psoriasis. J Invest Dermatol. 2014; 134:984–91. [PubMed: 24352038]

Zaba LC, Suarez-Farinas M, Fuentes-Duculan J, et al. Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. The Journal of allergy and clinical immunology. 2009; 124:1022–10. e1–395. [PubMed: 19895991]