

Psoriasis Pathogenesis: Keratinocytes Are Back in the Spotlight

Natalie Garzorz-Stark¹ and Kilian Eyerich¹



Psoriasis is a T helper type 17–mediated immune disease. Initial triggers that lead to T helper type 17 production and inflammatory cell recruitment into skin are being delineated. Autoantigens that stimulate T helper type 17 cells are also being identified. A new and important piece of the puzzle indicates that keratinocytes not only amplify inflammation, but that they are essential for a full-blown IL-17–mediated psoriatic phenotype in mice.

Journal of Investigative Dermatology (2019) **139**, 995–996. doi:10.1016/j.jid.2019.01.026

Chronic inflammatory skin diseases are thought to result from the interaction of immune and/or inflammatory cells and resident epithelial cells. Distinct T-cell subsets that migrate into skin and release specific cytokines can induce one of six major response patterns in keratinocytes (Eyerich and Eyerich, 2018). One recently characterized example is lichenoid inflammation, characteristic of lichen planus and cutaneous lupus, where type 1 cytokines such as IFN- γ and TNF- α induce necroptosis and apoptosis in keratinocytes, resulting in interface dermatitis (Lauffer et al., 2018). One of the best described types of T cell-mediated inflammation leading to a chronic inflammatory skin disease is type 17 immune-driven induction of psoriasis. Moos and colleagues (2019) now provide convincing evidence that this inflammatory cascade is critically dependent on keratinocytes (Moos et al., 2019).

Moos and colleagues (2019) investigated several murine models in which the IL-17 receptor component IL-17RA was deleted in distinct cell types, including T cells, neutrophils, macrophages, or keratinocytes, to determine which cell types were critical IL-17 responders in skin. Topical imiquimod was used to induce psoriasis-like

inflammation in the genetically manipulated and control mice. While the imiquimod mouse model does not recapitulate all aspects of human psoriasis, it is widely used (Hawkes et al., 2017). In addition, toll-like receptor 7/8 agonists, such as imiquimod, do stimulate plasmacytoid dendritic cells to produce type 1 IFNs and initiate type 17 immune responses in humans (Garzorz-Stark et al., 2018). Interestingly, Moos and coworkers (2019) observed that elimination of IL-17RA signaling in T cells, neutrophils, or macrophages did not significantly alter psoriasis-like inflammation in imiquimod-treated mice. In contrast, mice with a specific deletion of IL-17RA in keratinocytes were largely protected from the inflammatory response. Thus, keratinocytes are critical for developing the full-blown psoriasisform phenotype in this model.

Incorporating these recent results clarifies our concept of psoriasis pathogenesis (Figure 1). Early danger signals induce T helper type 17 (or ILC3) differentiation. These cells migrate into skin, recognize autoantigens that are presented by distinct major histocompatibility complex class I molecules (Prinz, 2018), and secrete IL-17A/F, IL-21, and IL-22. Keratinocytes respond to IL-17 homo- or heterodimers via a

dimeric receptor that includes IL-17RA (Eyerich et al., 2017). After IL-17 receptor ligation, keratinocytes secrete antimicrobial peptides and neutrophil-attracting chemokines (CXCL1 in mice and CXCL8 in humans). This initiates a pro-inflammatory circuit and recruits neutrophils into the epidermis. Moos and colleagues (2019) speculate that IL-22–producing cells might also depend on IL-17–induced keratinocyte signals. This might explain why therapeutic neutralization of IL-17A in psoriasis also diminishes acanthosis, which is thought to be induced by IL-21 and IL-22 rather than by IL-17A/F.

In addition to the central cascade illustrated in Figure 1, there may be other inflammatory feedback loops that enhance and/or perpetuate psoriasis-like inflammation in skin. One example may involve the IL-17 family member IL-17C, which engages IL-17RA like its sister cytokines IL-17A and IL-17F, and elicits similar intracellular signaling. Unlike IL-17A/F, IL-17C can be produced by keratinocytes after stimulation with TNF- α or toll-like receptor agonists. Neutralization of IL-17C leads to marked improvement of psoriasis-like inflammation in murine models (Vandeghinste et al., 2018), suggesting that IL-17C is indeed relevant to disease pathogenesis.

Both the vehicle used in the study by Moos and colleagues (2019) and the active compound itself (imiquimod) can trigger IL-17RA–independent inflammation. Imiquimod has been reported to trigger the inflammasome independent of toll-like receptor 7/8 ligation (Gross et al., 2016). The vehicle in the preparation of imiquimod that is most widely used, Aldara cream, may also have IL-17–independent pro-inflammatory effects (Walter et al., 2013) that involve activation of the inflammasome. The net result is recruitment of innate immune cells, such as monocytes. In the study by Moos and colleagues (2019), an inflammatory infiltrate consisting mostly of monocytes could still be detected, whereas hallmarks of psoriasis, such as acanthosis and neutrophilic inflammation, were absent when keratinocytes did not have functional IL-17RA. This additionally validates the importance of

¹Department of Dermatology and Allergy, Technical University of Munich, Biedersteiner Munich, Germany

Correspondence: Kilian Eyerich, Department of Dermatology and Allergy, Technical University of Munich; Biedersteiner Strasse 29, 80802 Munich, Germany. E-mail: kilian.eyerich@tum.de

© 2019 The Authors. Published by Elsevier, Inc. on behalf of the Society for Investigative Dermatology.

Clinical Implications

- Psoriasis is a prototypical T helper type 17–mediated inflammatory disease.
- Keratinocytes are central and essential players in psoriasis pathogenesis.
- The role of keratinocytes in psoriasis comorbidities needs to be further investigated.

IL-17A/C/F signaling via IL-17RA in keratinocytes in psoriasiform cutaneous inflammation.

Insights into the involvement of epithelial cells in IL-17–mediated inflammation help explain clinical observations made in patients with rare monogenetic diseases featuring reduction or absence of type 17 cytokine signaling, such as chronic mucocutaneous candidiasis (Eyerich et al., 2008). In patients with chronic mucocutaneous candidiasis, type 17 cytokine signaling is attenuated due to mutations in transcription factors STAT1 or STAT3 that are downstream of the IL-17 receptor, the existence of circulating antibodies that neutralize IL-17A/F, or mutations in IL-17RA. Patients with chronic mucocutaneous candidiasis are very susceptible to chronic and severe infections that are caused by yeasts, such as *Candida* species, but only at skin and mucosal surfaces and not in the circulation. This highlights the fact that, in this setting, protective IL-17RA–mediated signaling occurs in epithelial cells of the skin and gut rather than in leukocytes.

Psoriasis can be conceptualized as an exaggerated physiological response to epithelial damage or wounding, and we now know that keratinocytes are essential and central players in this response (Figure 1). Like most informative studies, the results reported by Moos et al. (2019) allow for speculations and suggest new questions. Could a future therapeutic strategy aim to neutralize IL-17 signaling selectively in keratinocytes? Such an approach might obviate the worsening of inflammatory bowel disease that we occasionally observe after systemic neutralization of IL-17A or IL-17RA.

Regarding new questions, the pathogenesis of psoriasis comorbidities, such as cardiovascular disease, is not completely understood. There is evidence that neutralization of IL-17A diminishes vascular inflammation (Schuler et al., 2018). Are keratinocytes (or other epithelial cells) central to, or even participants in, vascular inflammation? This might be the case if pro-inflammatory cytokines, chemokines, or growth factors such as vascular endothelial growth factor diffuse from

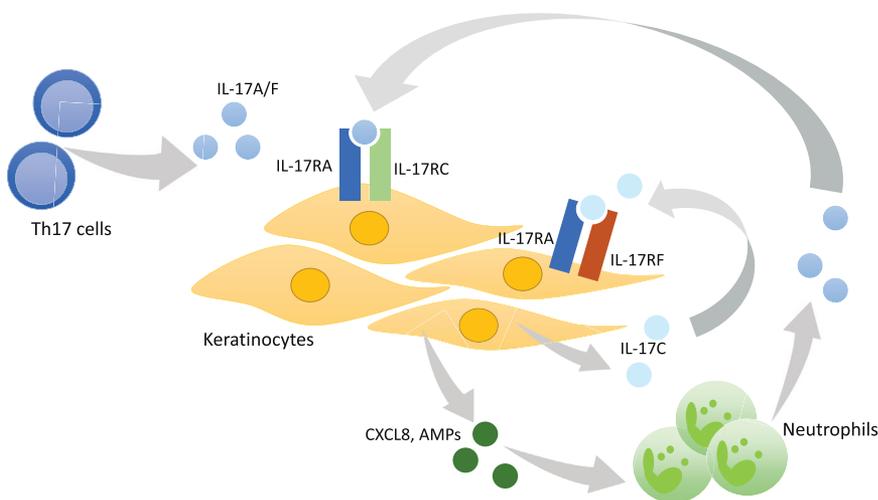


Figure 1. Keratinocytes (yellow) are central to induce full-blown psoriasis. Upon stimulation by Th17 cells, keratinocytes secrete antimicrobial peptides (AMPs) and CXCL8 that recruits neutrophils to the epidermis. This circuit is further promoted by an autocrine feedback loop involving IL-17C.

the skin into the systemic circulation. Or, in contrast to the cutaneous hallmarks of psoriasis, do psoriasis comorbidities depend on the ability of non-epithelial cells to respond to IL-17? These and other important questions need to be answered via future studies.

CONFLICT OF INTEREST

NG-S reports speaker's fees and advisory board membership of AbbVie, Novartis, UCB

KE reports speaker's fees and advisory board membership of AbbVie, Almirall, Berlin Chemie, Celgene, Galapagos, Hexal, Janssen, Leo, Lilly, Novartis, Sanofi, UCB.

REFERENCES

Eyerich K, Dimartino V, Cavani A. IL-17 and IL-22 in immunity: driving protection and pathology. *Eur J Immunol* 2017;47:607–14.

Eyerich K, Eyerich S. Immune response patterns in non-communicable inflammatory skin diseases. *J Eur Acad Dermatol Venereol* 2018;32:692–703.

Eyerich K, Foerster S, Rombold S, Seidl HP, Behrendt H, Hofmann H, Ring J, Traidl-Hoffmann C. Patients with chronic mucocutaneous candidiasis exhibit reduced production of Th17-associated cytokines IL-17 and IL-22. *J Invest Dermatol* 2018;128:2640–5.

Garzorz-Stark N, Lauffer F, Krause L, Thomas J, Atenhian A, Franz R, et al. Toll-like receptor 7/8 agonists stimulate plasmacytoid dendritic cells to initiate Th17-deviated acute contact dermatitis in human subjects. *J Allergy Clin Immunol* 2018;141:1320–33.e11.

Gross CJ, Mishra R, Schneider KS, Medard G, Wettmarshausen J, Dittlein DC, et al. K(+) efflux-independent NLRP3 inflammasome activation by small molecules targeting mitochondria. *Immunity* 2016;45:761–73.

Hawkes JE, Gudjonsson JE, Ward NL. The snowballing literature on imiquimod-induced skin inflammation in mice: a critical appraisal. *J Invest Dermatol* 2017;137:546–9.

Lauffer F, Jargosch M, Krause L, Garzorz-Stark N, Franz R, Roenneberg S, et al. Type I immune response induces keratinocyte necroptosis and is associated with interface dermatitis. *J Invest Dermatol* 2018;138:1785–94.

Moos S, Mohebiany AN, Waisman A, Kurschus FC. Imiquimod-induced psoriasis in mice depends on the IL-17 signaling of keratinocytes. *J Invest Dermatol* 2019;139:1110–7.

Prinz JC. Human leukocyte antigen-class I alleles and the autoreactive T cell response in psoriasis pathogenesis. *Front Immunol* 2018;9:954.

Schuler R, Brand A, Klebow S, Wild J, Veras FP, Ullmann E, et al. Antagonization of IL-17A attenuates skin inflammation and vascular dysfunction in mouse models of psoriasis. *J Invest Dermatol* 2018.

Vandeghinste N, Klattig J, Jagerschmidt C, Lavazais S, Marsais F, Haas JD, et al. Neutralization of IL-17C reduces skin inflammation in mouse models of psoriasis and atopic dermatitis. *J Invest Dermatol* 2018;138:1555–63.

Walter A, Schafer M, Cecconi V, Matter C, Urošević-Maiwald M, Belloni B, et al. Aldara activates TLR7-independent immune defence. *Nat Commun* 2013;4:1560.