Insert to practical dermatology July 2021

Sponsored by UCB

The Complex Circuitry of Psoriasis Pathogenesis:

Convergence of the Innate and Adaptive Immune System

For decades, psoriasis was believed to be a surface-level disorder of keratinocytes. Over time, research has shed light on specific immune cell-derived cytokines that drive keratinocyte activation and proliferation, resulting in the clinical symptoms of the disease.[1] We now know that there is an intricate web of proinflammatory cytokines that regulate inflammation in psoriatic skin. A unique way to depict this pathogenesis is as a complex electric circuit with different pathways and loops to stimulate and amplify the inflammatory process. Throughout this article, we will build on the image of a circuit board to illuminate our current understanding of how keratinocytes and immune cells interact within this pathway and visualize the cycle of inflammation behind psoriasis immunopathology (Figure 1).

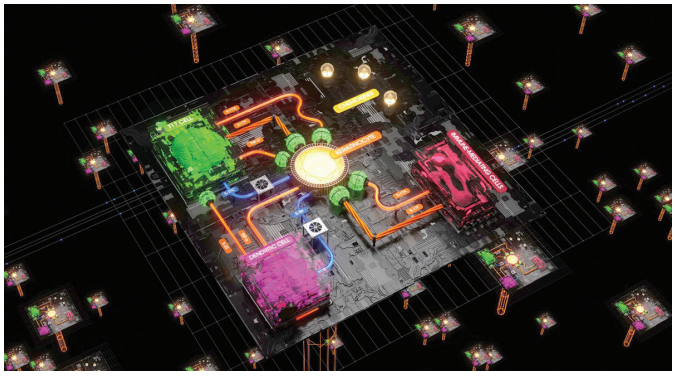

Figure 1. Cytokine pathways in psoriasis pathogenesis can be depicted as an electric circuit board.

CYTOKINES ELEVATED IN PSORIATIC LESIONS AMPLIFY KERATINOCYTE HYPERPROLIFERATION

Psoriasis is an outward manifestation of an internal inflammatory cascade produced in response to genetic susceptibility, stress, and environmental triggers.[1] These triggers lead to increased infiltration of immune cells including dendritic cells, T cells, and neutrophils into the skin. While the proinflammatory cytokine tumor necrosis factor alpha (TNFα) has long been known to play a role in psoriasis, cytokines involved in the interleukin (IL)-17/23 axis, including IL-23, IL-17A, and IL-17F, have also been implicated as key mediators of psoriatic inflammation.[1,2]

The discovery of TNFα as a prevalent cytokine in psoriatic lesions was one of the first indications of psoriasis as an immunopathologic disorder. The subsequent finding of increased IL-23 levels in psoriatic skin revealed how multi-faceted the immune cell interactions behind psoriasis pathogenesis appear to be. Activated dendritic cells and other antigen-presenting cells initially produce many cytokines, including IL-23, a known regulator of the T17 differentiation pathway. Once stimulated by IL-23, T17 cells release IL-17 cytokines.[1]

The presence of T17 cells and levels of IL-17 cytokines were found to correlate clinically with the severity of psoriasis. There are six known members of the IL-17 cytokine

family, two of which have been found to be key drivers of psoriasis: IL-17A and IL-17F.[1] Both are elevated in psoriatic skin and function as both homodimers and heterodimers, binding to the IL-17RA/IL-17RC receptor complex on keratinocytes and triggering their activation.[1,3] The IL-17/23 pathway represents the interplay between the innate and adaptive immune system, ultimately driving psoriatic inflammation.[2] Of note, blocking IL-23 may only partially reduce inflammation resulting from the innate immune system; it does not completely inhibit IL-17 production, because other cells including a range of innate-like lymphocytes (such as γδ T cells and innate lymphoid cells) may secrete IL-17A and IL-17F independently of IL-23.[2,4,5]

All of these cytokines—TNFα, IL-23, IL-17A, and IL-17F—activate the keratinocytes, eliciting inflammation in the skin.[1]

KERATINOCYTE-PRODUCED FACTORS POWER THE FEEDBACK LOOP IN THE INFLAMMATORY CYCLE

Once activated, keratinocytes in turn release a wide variety of cytokines that perpetuate the inflammatory cycle in psoriasis. In particular, keratinocytes produce IL-17C, another member of the IL-17 cytokine family that is elevated in psoriatic skin. IL-17C binds to the IL-17RE/IL-17RA receptor complex on T17 cells to further increase IL-17A/F production, resulting in a feedback loop between T17 cells and keratinocytes.[6-8]

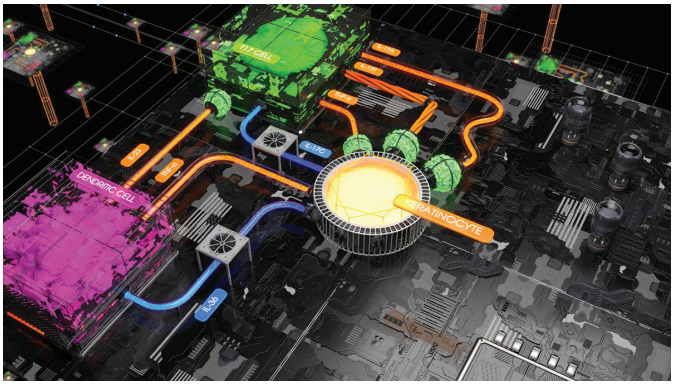

Figure 2. Keratinocyte-produced factors power the feedback loops in the amplification of inflammation (feedback pathways shown in blue).

Keratinocytes also produce two additional cytokines, IL-36α and IL-36γ, that feed back to activate dendritic cells and stimulate the IL- 23/17 pathway for IL-17A and IL-17F production, as demonstrated by the expression of CD83 and CD86 on their cell surface (Figure 2).[9,10]

Chemokines, such as CXCL1, IL-8, and CCL20, are released by keratinocytes to recruit additional immune cells into psoriatic lesions. In vitro assays of dermal cells treated with T17 supernatant showed increased migration by T cells, monocytes, and most notably, neutrophils. Neutrophils can release the T17 differentiation cytokine IL-23 or trap IL-17A and IL-17F, and then, when stimulated, release these cytokines along with proteases, all of which further stimulate keratinocytes and power the inflammatory feedback mechanism (Figure 3).[1,11,12]

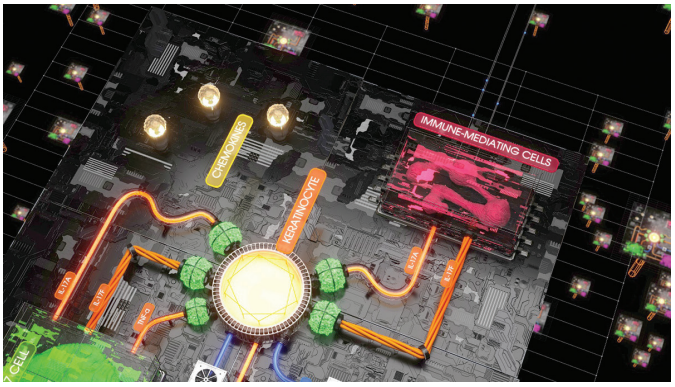

Figure 3. Keratinocytes release chemokines that recruit additional immune-mediating cells, perpetuating the cycle of inflammation.

SUMMARY: A DEEPER LOOK AT THE IL-17/23 AXIS IN PSORIASIS PATHOGENESIS

The convergence of the innate and adaptive immune systems in psoriasis pathogenesis shows the key roles that all proinflammatory cytokines play in the complex circuit of inflammation.[2] The initiation of the inflammatory cascade via the IL-17/23 axis, as well as the persistent feedback loops, all culminate in keratinocyte activation and hyperproliferation. The visual consequences of these immunopathogenic mechanisms are embodied as skin plaques, causing clinical symptoms of pain, itching, and a burning sensation, which can greatly impact the quality of life for patients with psoriasis.[1,13,14] As the science continues to evolve, a better understanding of the pathogenesis can contribute to advancements in the psoriasis landscape, for a brighter future.

1. Lynde CW, Poulin Y, Vender R, et al. Interleukin 17A: Toward a new understanding of psoriasis pathogenesis. J Am Acad Dermatol. 2014;71(1):141-50.
2. Armstrong AWR, C., Leonardi CL, Kircik LH. IL-23 versus IL-17 in the pathogenesis of psoriasis: There is more to the story than IL-17A. J Drugs Dermatol. 2019;18(8 Suppl 2):s202-08.
3. Johansen C, Usher PA, Kjellerup RB, et al. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. Br J Dermatol. 2009;160(2):319-24.
4. Jin W, Dong C. IL-17 cytokines in immunity and inflammation. Emerg Microbes Infect. 2013;2(9):e60.
5. Cole S, Simpson C, Okoye R, et al. MAIT Cell Derived IL-17A and IL-17F Production Is IL-23 Independent and Biased Towards IL-17F. Presented at IGAS 2019.
6. Johnston A, Fritz Y, Dawes SM, et al. Keratinocyte overexpression of IL-17C promotes psoriasiform skin inflammation. J Immunol. 2013;190(5):2252-62.
7. Ramirez-Carrozzi V, Sambandam A, Luis E, et al. IL-17C regulates the innate immune function of epithelial cells in an autocrine manner. Nat Immunol. 2011;12(12):1159-66.
8. Maggi L, Santarlasci V, Capone M, et al. Distinctive features of classic and nonclassic (Th17 derived) human Th1 cells. Eur J Immunol. 2012;42(12):3180-8.
9. Pfaff CM, Marquardt Y, Fietkau K, et al. The psoriasis-associated IL-17A induces and cooperates with IL-36 cytokines to control keratinocyte differentiation and function. Sci Rep. 2017;7(1):15631.
10. Foster AM, Baliwag J, Chen CS, et al. IL-36 promotes myeloid cell infiltration, activation, and inflammatory activity in skin. J Immunol. 2014;192(12):6053-61.
11. Glatt S, Baeten D, Baker T, et al. Dual IL-17A and IL-17F neutralisation by bimekizumab in psoriatic arthritis: evidence from preclinical experiments and a randomised placebo-controlled clinical trial that IL-17F contributes to human chronic tissue inflammation. Ann Rheum Dis. 2018;77(4):523-32.
12. Minns D, Smith KJ, Alessandrini V, et al. The neutrophil antimicrobial peptide cathelicidin promotes Th17 differentiation. Nat Commun. 2021;12(1):1285.
13. Strober BE, van der Walt JM, Armstrong AW, et al. Clinical Goals and Barriers to Effective Psoriasis Care. Dermatol Ther (Heidelb). 2019;9(1):5-18.
14. Mayo Clinic. Psoriasis: Symptoms and Causes. 2 May 2020. https://www.mayoclinic.org/diseases-conditions/psoriasis/symptoms-causes/syc-20355840 [Last accessed 20 April 2021].