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INSIGHTS

Neutrophil IL-26 fuels autoinflammation

Krisztina Futosi[1,2] and Attila Mócsai[1,2]

Pustular psoriasis is an inflammatory skin disease with features of neutrophil-mediated sterile autoinflammation. In this issue of *JEM*, Baldo et al. (https://doi.org/10.1084/jem.20231464) show that this autoinflammation is driven by a vicious cycle through neutrophil-derived IL-26.

Autoinflammation is generally viewed as an inflammatory process without substantial involvement of adaptive immune system players or infection by microbial pathogens. However, the boundaries are difficult to define, especially given the large number of diseases with characteristic features of both autoimmunity and autoinflammation (Szekanecz et al., 2021).

Psoriasis, one of the most prevalent chronic inflammatory skin diseases, represents a spectrum of diseases with both autoimmune and autoinflammatory features (Liang et al., 2017). At the autoinflammatory end of the spectrum, pustular psoriasis is characterized by pus-filled sterile blister-like sores (pustules) under the skin surface. These pustules result from extensive neutrophil infiltration into the skin and may even coalesce to massive pustular regions ("lakes of pus") in the most severe and potentially life-threatening generalized form of the disease. Prior studies (Marrakchi et al., 2011; Onoufriadis et al., 2011; Marrakchi and Puig, 2022) have identified the role of the IL-36 cytokine in generalized pustular psoriasis. However, further details of the pathogenesis are still poorly understood.

IL-26 is a proinflammatory member of the IL-10 family, with Th17 cells being its most widely accepted cellular sources (Gilliet and Modlin, 2024). IL-26 has been shown to be important in a number of inflammatory diseases of both autoimmune and infectious origin. Additional unique features of IL-26 are its ability to directly kill extracellular bacteria by pore formation, and its involvement in TLR9-mediated sensing of DNA (Meller et al., 2015). Several studies have also suggested an important role for IL-26 in psoriasis, supposedly primarily by mediating the effects of Th17 cells (Itoh et al., 2019; Fries et al., 2023; Gilliet and Modlin, 2024). Thus, IL-26 appears to be a "double-edged sword" of the immune system, participating in antimicrobial host defense but also contributing to inflammation-induced tissue damage.

In this issue of *JEM*, Baldo et al. (2024) provide several unexpected twists on the role of IL-26 in autoinflammatory diseases with a focus on the various forms of pustular psoriasis. They show that IL-26 is expressed at much higher levels in pustular psoriasis than in the more common psoriasis vulgaris, suggesting a particular role for IL-26 in the autoinflammatory, rather than the autoimmune forms of psoriasis. Surprisingly, and in contrast to the mainly T cell–derived origin of IL-26 in psoriasis vulgaris, IL-26 in pustular psoriasis was apparently primarily derived from neutrophils. The authors went on and showed that IL-26 is constitutively present in neutrophils and stored in their primary granules, being released together with other primary granule proteins during degranulation of the cells.

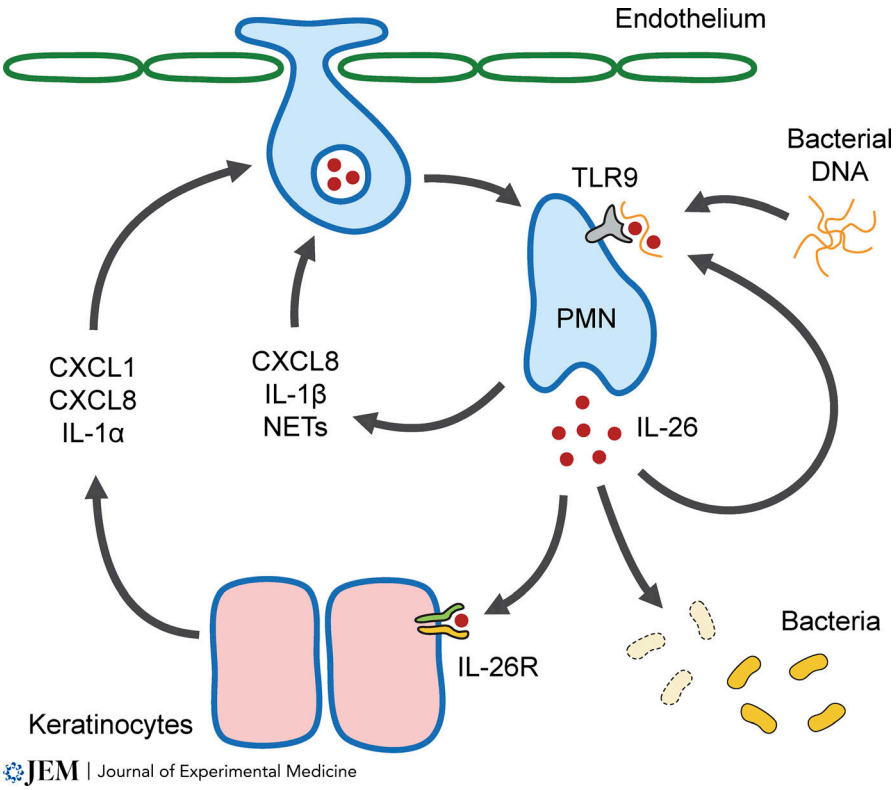
The authors then tested the biological role of IL-26 in the skin. They first showed that IL-26 triggers expression of IL-1α, CXCL1, and CXCL8 in skin explants of pustular psoriasis patients, supposedly by triggering the expression of those cytokines/chemokines in keratinocytes through the conventional IL-26 receptor (see figure). Supernatants of in vitro activated neutrophils exerted the same response.

Insights from Krisztina Futosi and Attila Mócsai.

The authors finally tested the effect of IL-26 on neutrophils themselves. Although IL-26 alone did not trigger neutrophil activation, combination of IL-26 with bacterial DNA fragments caused robust release of IL-1β and CXCL8 from neutrophils in a TLR9-dependent manner (see figure). Interestingly, this was specific for bacterial DNA as eukaryotic DNA did not trigger the same response. To further support the role of bacterial DNA in neutrophil-mediated autoinflammation, the authors showed a strong correlation between CXCL1, CXCL8, and bacterial but not eukaryotic DNA content in human suction blisters. Even more direct evidence came from strongly reduced CXCL1 and CXCL8 concentration in the blister fluid upon pretreatment of the skin with wide-spectrum antibiotics.

[1]Department of Physiology, Semmelweis University School of Medicine, Budapest, Hungary; [2]HUN-REN–SU Inflammation Physiology Research Group, Hungarian Research Network and Semmelweis University, Budapest, Hungary.

Correspondence to Attila Mócsai: mocsai.attila@semmelweis.hu.



The proposed role of neutrophil-derived IL-26 in pustular psoriasis. IL-26 derived from neutrophils (PMN) drives several autoamplification loops by keratinocyte activation through the conventional IL-26 receptor (IL-26R) and ligation of TLR9 on neutrophils by IL-26 in complex with bacterial DNA. IL-26 also exerts direct antimicrobial functions.

Taken together, the authors conclude that neutrophil-derived IL-26 plays a critical role in triggering a vicious cycle driving autoinflammation in pustular psoriasis (see figure). IL-26 triggers two amplification loops through different mechanisms. On one hand, it triggers keratinocyte activation through the conventional IL-26 receptor, leading to IL-1α and CXC chemokine release and concomitant neutrophil recruitment. On the other hand, IL-26 bound to bacterial DNA activates neutrophils through TLR9, leading to further activation of the recruited neutrophils.

One of the key findings of the study is the identification of neutrophils as a major source of IL-26 in the autoinflammatory forms of psoriasis. This challenges the current view that Th17 cells are the sole principal players driving the autoinflammation process. The high expression of IL-26 by neutrophils also suggests that the primary role of Th17 cells in IL-26–mediated disease processes needs to be revisited, as well.

Another intriguing finding is the fact that the autoinflammatory process is driven by amplification through bacterial DNA fragments. This provides an interesting novel aspect on the role of the microbiota to autoinflammation and suggests that the definition of autoinflammation as a non-infectious sterile inflammation may need to be revisited and, possibly, refined.

IL-26 is widely expressed in various vertebrates from fish to humans, but it is surprisingly absent from mice and rats. Though many investigators would see this as a major technical obstacle, the authors have been able to turn this into an opportunity to perform an entirely human, yet highly informative set of experiments. They did so by testing human patient skin samples, human skin explants, and keratinocyte cultures, as well as by the analysis of in vivo human suction blisters. The next obvious step would be to test neutralizing anti-IL-26 antibodies, initially supposedly as a topical treatment, to possibly attenuate disease pathology in pustular psoriasis. It would also be interesting to know what mechanisms take over IL-26 function in mice and rats.

Likely related to the need of rapid response to invading pathogens, there are a large number of examples indicating positive feedback amplification of neutrophil function at the autocrine, paracrine, and more complex levels (Németh and Mócsai, 2016). The two IL-26–mediated amplification loops (neutrophils–IL-26–keratinocytes–chemokines–neutrophils and neutrophils–IL-26–DNA–TLR9–neutrophils) provide further examples for such positive feedback amplification mechanisms (see figure).

The role of neutrophil-derived IL-26 in pustular psoriasis also raises the possibility of its role in other forms of neutrophil-mediated (auto)inflammatory diseases. Those include a large number of joint, skin, lung, kidney, and other disease states (Németh et al., 2020). In addition, the identification of IL-26 as a component of primary granules of neutrophils, which are thought to contain a large fraction of the antimicrobial armamentarium of the cells, also raises the possibility that IL-26 may play a critical role in the primary function of neutrophils in antimicrobial host defense. Such a function could be mediated by any of the three mechanisms (see figure) shown by this group: a supposedly paracrine effect of IL-26 on other cells; an autocrine-like effect of IL-26–DNA complexes on neutrophil TLR9; or the direct antimicrobial effect of IL-26 (Meller et al., 2015; Baldo et al., 2024). These are obvious research directions that may further extend the relevance and scope of the Baldo et al. (2024) paper.

Several prior reports suggested IL-36 to be critical for the development of certain forms of pustular psoriasis (Marrakchi and Puig, 2022). This conclusion was mainly based on the genetic deficiency of IL-36 receptor antagonist (IL36RA) in generalized pustular psoriasis patients (Marrakchi et al., 2011; Onoufriadis et al., 2011) and has led to the development of spesolimab, an IL-36 receptor–blocking antibody, as an effective treatment of generalized pustular psoriasis (Bachelez et al., 2021). The identification of IL-26 as a critical player of pustular psoriasis immediately suggests IL-26 as another potential therapeutic target in this severe disease. Importantly, a neutralizing anti-IL-26 monoclonal antibody has already been developed and showed a therapeutic effect in a transgenic mouse model of IL-26–mediated psoriasis (Hatano et al., 2019).

Testing this or other IL-26–blocking antibodies in human patients would provide an immediate clinical relevance of the findings of Baldo et al. (2024). However, given the critical role of neutrophils, and a possible role of neutrophil-derived IL-26, in antibacterial host defense, special attention should be paid to the potentially detrimental effect of IL-26–targeted therapies on neutrophil-mediated innate host defense. In that respect, it is interesting to note that the above-mentioned IL-26–neutralizing monoclonal antibody did not affect the direct antimicrobial function of IL-26 (Hatano et al., 2019).

Another interesting aspect of the Baldo et al. (2024) paper is that it further blurs the boundaries of autoinflammatory diseases. Except for a few disease states (including monogenic autoinflammatory diseases and gout), it is often difficult to clearly differentiate autoinflammatory from autoimmune diseases (Szekanecz et al., 2021). The role of microbial DNA from the commensal flora in pustular psoriasis adds another dimension of blurred boundaries, in this case making it difficult to separate autoinflammatory and infectious disease processes. Although the issue of the role of the commensal microbiota in immune-mediated diseases is not entirely new (Van de Wiele et al., 2016; Lupfer et al., 2017), the Baldo et al. (2024) paper provides important novel molecular details in the field of autoinflammatory diseases. At the same time, it also raises novel questions, e.g., whether the commensal flora is involved in smoldering background inflammation or rather in acute exacerbations during the autoinflammatory disease process; or whether autoinflammation requires the ongoing presence of live microbes or rather debris of dead bacteria is sufficient to fuel the autoinflammation process. Those and other questions will keep the scientific community busy deciphering the full significance and medical implication of this beautiful study.

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References

Bachelez, H., et al. 2021. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2111563
Baldo, A., et al. 2024. *J. Exp. Med.* https://doi.org/10.1084/jem.20231464
Fries, A., et al. 2023. *Nat. Commun.* https://doi.org/10.1038/s41467-023-39484-4
Gilliet, M., and R.L. Modlin. 2024. *J. Invest. Dermatol.* https://doi.org/10.1016/j.jid.2023.10.038
Hatano, R., et al. 2019. *MAbs.* https://doi.org/10.1080/19420862.2019.1654305
Itoh, T., et al. 2019. *J. Invest. Dermatol.* https://doi.org/10.1016/j.jid.2018.09.037
Liang, Y., et al. 2017. *Curr. Opin. Immunol.* https://doi.org/10.1016/j.coi.2017.07.007
Lupfer, C.R., et al. 2017. *FEBS J.* https://doi.org/10.1111/febs.14076
Marrakchi, S., et al. 2011. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1013068
Marrakchi, S., and L. Puig. 2022. *Am. J. Clin. Dermatol.* https://doi.org/10.1007/s40257-021-00655-y
Meller, S., et al. 2015. *Nat. Immunol.* https://doi.org/10.1038/ni.3211
Németh, T., and A. Mócsai. 2016. *Trends Immunol.* https://doi.org/10.1016/j.it.2016.04.002
Németh, T., et al. 2020. *Nat. Rev. Drug Discov.* https://doi.org/10.1038/s41573-019-0054-z
Onoufriadis, A., et al. 2011. *Am. J. Hum. Genet.* https://doi.org/10.1016/j.ajhg.2011.07.022
Szekanecz, Z., et al. 2021. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-021-00652-9
Van de Wiele, T., et al. 2016. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/nrrheum.2016.85