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Treating Psoriasis with a Light Touch

Makoto Sugaya[1]

Although several anticytokine antibodies and inhibitors are available for the treatment of psoriasis, more effective or better-tolerated alternatives would be of interest. In their article in the *Journal of Investigative Dermatology*, Michiels et al. (2021) propose a new strategy that targets an alternative activation pathway of the IL-22 receptor to attenuate murine psoriasis-like skin inflammation without affecting IL-22–dependent barrier defense in the gut.

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Psoriasis is a common chronic skin disease that is often associated with arthritis, cardiovascular diseases, and metabolic syndrome. The negative impact of the disease on patients' QOL can be immense. As a consequence of advances in research techniques, we now understand some aspects of psoriasis at the single-cell level (Liu et al., 2021). Although several anticytokine antibodies and inhibitors are available for the treatment of psoriasis, improved alternatives would be welcome. In their new article in the *Journal of Investigative Dermatology*, Michiels et al. (2021) propose a new strategy to treat imiquimod (IMQ)-induced psoriasis-like dermatitis in mice by targeting the noncanonical activation of signal transducers and activators of transcription (STAT) 3 that is downstream of IL-22 receptor activation in the skin without affecting IL-22–dependent barrier defense in the gut.

> "The suggestion that avoiding over-activation of signaling pathways through cytokine receptors with a 'light touch' to treat inflammatory diseases without losing beneficial effects that result from low level tonic cytokine signaling is exciting and will require further study."

Organ-specific function of cytokines

Some cytokines are ubiquitously expressed, whereas others are selectively expressed in different organs or cells. The functions and actions of most cytokines are shared between different cells in different organs. For example, TNF-α, IL-1β, and IL-6 are proinflammatory cytokines that activate many different kinds of cells, including immune cells, endothelial cells, and epithelial cells in various organs. In contrast, the expression of certain cytokines, including chemokines, is tissue specific. For example, CCL17 and CCL27 are chemokines that are predominantly expressed in the skin, and they are essential for the migration of skin-homing T cells. A variety of antibodies against cytokines are now available for clinical use, and we should consider the possibility of tissue-specific effects when using these biological agents.

Psoriasis is a common inflammatory skin disorder that involves cross-talk between epidermal keratinocytes (KCs), dermal vascular endothelial cells, dendritic cells, and T helper (Th) 17 cells. The key cytokines in psoriasis include TNF-α, IL-23, and IL-17. TNF-α has been reported to be involved in various diseases, and antibodies against this cytokine are effective for different inflammatory diseases such as psoriasis, rheumatoid arthritis, ulcerative colitis, and pyoderma gangrenosum. When utilizing anti–TNF-α antibodies in patients with psoriasis, systemic infections and development of malignancies are potentially severe side effects, whereas exacerbation of inflammatory diseases in other organs is very rare. In contrast, antibodies against IL-17A have the potential to initiate or exacerbate inflammatory bowel diseases, even though they rapidly clear psoriatic skin lesions (Fauny et al., 2020). These adverse events occur despite the fact that IL-17A levels within the lamina propria of patients with Crohn's disease are elevated (Fujino et al., 2003) and that it has been suggested that this cytokine could be a therapeutic target in patients with inflammatory bowel disease. A possible explanation is that although the IL-23–IL-17A axis is clearly involved in psoriasis (Li and Brown, 2017), anti–IL-23 antibodies moderately reduce Th17-mediated autoimmunity, whereas more effective neutralization of IL-17A adversely affects gut homeostasis and intestinal wall integrity (Whibley and Gaffen, 2015).

[1]*Department of Dermatology, Faculty of Medicine, School of Medicine, International University of Health and Welfare, Narita, Japan*

Correspondence: Makoto Sugaya, Department of Dermatology, Faculty of Medicine, School of Medicine, International University of Health and Welfare, Narita, Japan. E-mail: sugayamder@iuhw.ac.jp

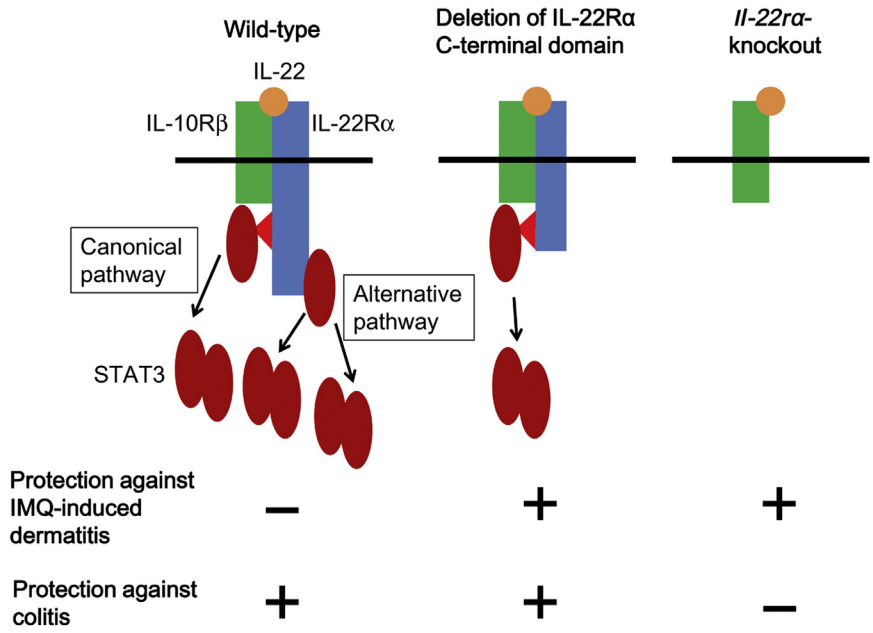

Figure 1. A light touch through the IL-22 receptor lacking the C-terminal domain of IL-22Rα provides protection against both IMQ-induced dermatitis and colitis. IL-22 activates STAT3 through the phosphorylation of membrane-proximal Y residues of the receptor (canonical pathway) and the C-terminal domain of IL-22Rα (alternative pathway). Massive STAT3 activation through both pathways protects mice from colitis but not from IMQ-induced dermatitis. Mice totally deficient in IL-22Rα are protected from IMQ-induced dermatitis, but they are sensitive to colitis. Mice with deletion of the C-terminal part of IL-22Rα, abrogating only the noncanonical pathway, are resistant to both IMQ-induced dermatitis and colitis. IMQ, imiquimod; STAT3, signal transducers and activators of transcription 3.

IL-22 is another cytokine that is produced by Th17 cells, Th22 cells, γδ cells, and innate lymphoid cells type III. IL-22 is involved in the development of psoriasis by inducing the proliferation of KCs and augmenting the production of antimicrobial peptides. Similar to IL-17A, IL-22 is important for barrier defense and tissue repair in various organs, including the skin, gut, lung, and liver (Wolk et al., 2004). Although clinical trials of a human mAb directed against IL-22 (fezakinumab) for the treatment of psoriasis were terminated, IL-22–deficient and anti–IL-22–blocking antibody–treated mice are resistant to IMQ-induced dermatitis and other mouse psoriasis models (Ma et al., 2008; Van Belle et al., 2012). Fezakinumab is thought to be promising for the treatment of atopic dermatitis (AD). Thus, the possible side effects of anti–IL-22 antibodies on the gut are of interest.

Signaling pathway downstream of the cytokine receptors

Cytokines activate many signaling pathways downstream of their receptors. Blocking the enzymatic activity of signaling molecules such as Jaks or MAPKs with small-molecule inhibitors is in some ways easier than blocking the interactions between cytokines, and inhibitors are already available for most signaling pathways. Blocking signaling molecules is a double-edged sword. Although dominant signaling pathways in diseases can often be abrogated, side effects may occur because relevant signaling pathways may have homeostatic roles in many types of cells. IL-22 signals through a receptor that is composed of two chains: IL-22Rα and IL-10Rβ. After binding to its receptor, IL-22 activates the Jak–STAT pathway and, to a lesser extent, the MAPK and protein kinase B pathway. The classical Jak–STAT pathway requires the SH2 domain of STAT and involves the phosphorylation of Y residues in the IL-22 receptor. However, in some cases, STAT activation occurs in a phosphotyrosine-independent manner. In the case of IL-22Rα, the C-terminal domain is constitutively associated with STAT3 (Dumoutier et al., 2009). This noncanonical pathway leads to massive STAT3 activation. In their report, Michiels et al. (2021) show that signaling through the C-terminal part of IL-22Rα plays a major role in IL-22 signaling in the skin and in the liver but only a minor role in the ileum. Mice expressing IL-22 receptor that lacks the C-terminal part of IL-22Rα, abrogating only the noncanonical pathway, were resistant to the development of IMQ-induced dermatitis and were also resistant to colitis induced by *Citrobacter rodentium*. The authors concluded that the different responses to IL-22Rα truncation in the skin and in the ileum resulted from the organ-specific level of involvement of the noncanonical pathway. Mice that were totally deficient in IL-22Rα were also partially protected from IMQ-induced dermatitis, but they were sensitive to *C. rodentium*–induced colitis. Therefore, modest activation of cytokine signaling via a light touch may allow desirable treatment effects of IL-22 blockade in the skin without unwanted side effects in the gut (Figure 1).

Unsolved problems and further studies

Although the authors suggest a fascinating strategy, there are unsolved problems. The decreases in the skin inflammation induced by IMQ were much less in mice with the deletion of IL-22Rα C-terminal domain than in *Il-22rα*–knockout mice, suggesting that the canonical activation of the Jak–STAT pathway downstream of IL-22 is important in the skin. In addition, some parameters were altered in the *C. rodentium*–induced colitis model when the noncanonical pathway was abrogated. The authors concluded that the absence of the alternative pathway could be tolerated because mice lacking the C-terminal domain of IL-22Rα did not lose significantly more weight than their wild-type counterparts. Defining the best conditions to get the benefit of blocking noncanonical STAT3 activation without affecting IL-22–dependent barrier defense will be challenging. Exactly how selective targeting would be accomplished in mice or humans who express full-length IL-22Rα also remains to be determined. Finally, although IMQ-induced dermatitis in mice has some characteristics that are similar to those in human psoriasis, other mouse psoriasis models should be tested. Moreover, IL-22 signaling should be investigated in AD models because

antibodies against IL-22 have been developed for this disease. The suggestion that avoiding overactivation of signaling pathways through cytokine receptors with a light touch to treat inflammatory diseases without losing beneficial effects that result from low-level tonic cytokine signaling is exciting and will require further study.

ORCID
Makoto Sugaya: http://orcid.org/0000-0002-1618-329X

CONFLICT OF INTEREST
MS received a speaking fee from Mitsubishi Tanabe Pharma and Sanofi.

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A Possible Role for PAI-1 Blockade in Melanoma Immunotherapy

Mario Del Rosso[1], Gabriella Fibbi[1], Anna Laurenzana[1], Francesca Margheri[1] and Anastasia Chillà[1]

In their new article in the *Journal of Investigative Dermatology*, Tseng et al. (2021) confirm that the sensitivity of melanoma cells to anti–PD-L1 checkpoint inhibitor therapy is correlated with high PD-L1 surface expression. By blocking PD-L1 membrane clearing, controlled by LRP1 and PAI-1, the expression of high-cell-surface levels of PD-L1 was maintained.

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Background and novelty

Immune checkpoint inhibitors (ICIs) have changed the landscape of cancer treatment. In particular, the PD-1 and PD-L1 immune checkpoint molecules are significantly involved in the evasion of tumors from immune control, and the use of anti–PD-L1 mAbs has revolutionized the treatment of various types of cancer, including melanoma. However, despite initial enthusiasm, several clinical trials have shown that although treatment with anti–PD-L1 mAbs in advanced melanoma showed higher, more durable responses in a subset of patients, there was no difference between survival and that observed when conventional chemotherapy was used (Wang et al., 2017). In their new article in the *Journal of Investigative Dermatology*, Tseng et al. (2021) show that targeting extracellular PAI-1 through the PAI-1 inhibitor tiplaxtinin (TPX) synergizes with anti–PD-L1 checkpoint blockade in a model of murine melanoma, thus paving the way for potentially more effective melanoma treatment. This work stems from two different lines of previous investigations indicating that improved clinical outcomes in patients with melanoma subjected to anti–PD-L1 therapy are associated with high PD-L1 positivity (Patel and Kurzrock, 2015) and that a temporary inhibition of PD-L1 and EGFR–clathrin–mediated endocytosis potentiated the response of human tumors to ICIs (Chew et al., 2020). As reported in this article, using immunohistochemical analysis of a significant number of paraffin-embedded sections from patients with melanoma, Tseng et al. (2021) showed that individuals with low PAI-1 expression and high levels of PD-L1 were associated with early melanoma stages (stages I and II), whereas high PAI-1/PD-L1 ratios were associated with late stages (stages III and IV), supporting the data obtained in vitro and in animals.

Following up on the observation that extracellular PAI-1 promoted the internalization of surface-expressed PD-L1 in melanoma cells by inducing clathrin-mediated endocytosis, Tseng et al. (2021) tested the hypothesis that PD-L1 was translocated to lysosomes by PAI-1–dependent mechanisms, showing that such transport is mediated by LRP1.

Role of LRP1 in the regulation of extracellular proteolysis and PD-L1

LRP1 is a very sociable multipurpose molecule that belongs to the family of

[1]*Department of Experimental and Clinical Biomedical Sciences, School of Human Health Sciences, University of Florence, Florence, Italy*

Correspondence: Mario Del Rosso, Department of Experimental and Clinical Biomedical Sciences, School of Human Health Sciences, University of Florence, Florence 50134, Italy. E-mail: mario.delrosso@unifi.it