

FXYD3-IL-17 positive feedback loop promotes psoriasis exacerbation

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Commentary

Psoriasis is primarily a chronic skin disease characterized by keratinocyte hyperplasia, as well as a systemic inflammatory disease associated with numerous comorbidities, including rheumatological psoriatic arthritis, cardiovascular and psychiatric complications [1]. Approximately 2-3% of the global population is affected by psoriasis, and despite advances in the treatment, there are still limitations [1].

The disordered communication between immune cells and keratinocytes plays a crucial role in the initiation and exacerbation of psoriasis [2]. In particular, excessive production and response to interleukin-17 (IL-17) have been observed in psoriasis, making IL-17 a target for topical therapy [3]. The IL-17 family, consisting of IL17A-F, plays an essential role in the clearance of pathogens to protect the host from infection, but can also promote inflammatory pathology in autoimmune diseases. In psoriasis, IL-17 released from T cells (mainly Th17 subset), acts on the IL-17 receptor (IL-17R) of keratinocytes, stimulating keratinocytes to produce some defensins and chemokines, such as S100A8, S100A9, CXCL1 and CCL20, which then as positive feedback recruit more IL-17 producing T cells [4]. IL-17 or IL-17R blockers work favorably in patients with psoriasis, with around 90% reduction in baseline PASI (Psoriasis Area and Severity Index) value after 12 weeks treatment, whereas some side effects such as infections, outbreaks of inflammatory bowel disease or suicidal ideation merit further careful evaluation [2]. Further investigation into the regulatory mechanism of the IL-17 producing and responding loop could provide new insights into psoriasis treatment.

In a recent issue, we reported that FXYD3, a member of the FXYD domain-containing regulators of Na⁺/K⁺ ATPases family, was significantly induced in keratinocytes by IL-17 [5]. The increased FXYD3 enhanced the IL-17 signaling in keratinocytes, leading to psoriasis-like inflammation with higher levels of proinflammatory factors, including cytokines (such as IL-6), chemokines (such as CXCL1, CXCL2 and CCL 20) and alarmins (such as S100A8 and S100A9), which could recruit more IL-17 producing T cells in turn [5]. Our study revealed the key role of FXYD3 in the disordered communication (usually over-active) between IL-17 producing cells (mainly T cells) and IL-17 target cells (keratinocytes), in promoting psoriasis exacerbation (**Figure 1**) [5].

FXYD3, one of the seven members (FXYD1-7) in FXYD protein family, is overexpressed in multiple primary tumors, including human hepatocellular carcinoma, renal cell carcinoma, colorectal cancers, and pancreatic ductal adenocarcinoma, usually predicting a poor prognosis [6]. Our previous work suggested that FXYD3 was significantly upregulated in ER⁺ (estrogen receptor-positive) breast cancer stem cells in response to estrogen [7]. Estrogen signaling induced the nucleus localization of transcription factor SOX9, promoting FXYD3 expression. The induced FXYD3 then interacted with Src and ER α , forming a positive feedback to boost estrogen signaling and SOX9 nucleus entry. The SOX9/FXYD3/Src axis is crucial for maintaining the stem cell function and resistance to endocrine in ER⁺ breast cancer [7]. Besides tumor cells, FXYD3 is also widely expressed in various normal tissues, especially in the skin and colon. However, the biological and pathological roles of FXYD3 in skin or skin diseases, including psoriasis, remain largely unknown.

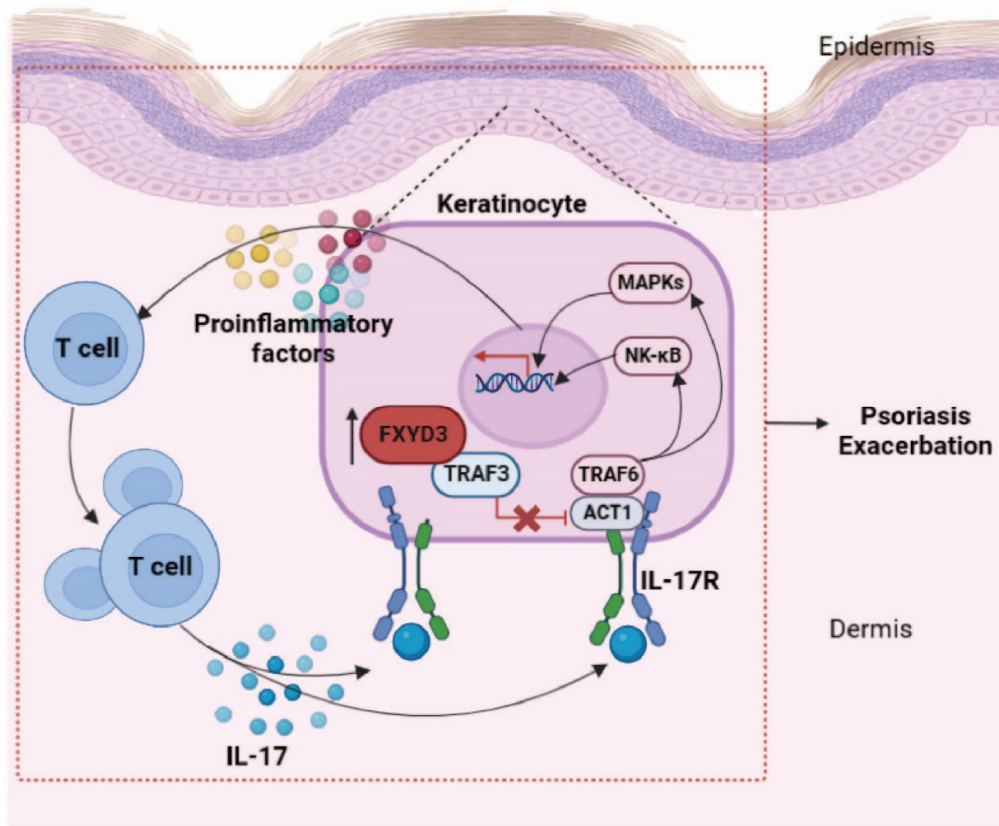


Figure 1. FXYD3 contributes to the form IL-17 signal-based inflammatory circuit in psoriasis. Upon IL-17 stimulation, keratinocytes upregulate the expression of FXYD3, which directly interacts with TRAF3 to ameliorate the suppression of TRAF3 on IL-17R-ACT1 activation complex, leading to enhanced IL-17 downstream pathways. The amplified IL-17 signaling by FXYD3 then promotes the release of more proinflammatory factors (including proinflammatory cytokines such as IL-6, chemokines such as CXCL1, and alarmins such as S100A8) from keratinocytes, which in turn recruit more IL-17 producing T cells.

To investigate the potential involvement of FXYD3 in psoriasis, we first examined its expression pattern in skin tissue. Immunofluorescent staining assay of human skin biopsies indicated that FXYD3 was predominantly expressed in keratinocytes. Notably, FXYD3 expression was significantly increased in skin tissue samples from psoriasis patients and imiquimod (IMQ)-induced psoriasis mice when compared to their respective healthy controls. Moreover, we demonstrated that IL-17, the key cytokine involved in psoriasis initiation and exacerbation, played a critical role in regulating FXYD3 expression. Specifically, IL-17A was capable of inducing FXYD3 expression in the NHEK cell line (normal human epidermal keratinocytes). Of clinical relevance, treatment with anti-IL-17 receptor antibodies resulted in a reduction of FXYD3 in the skin of patients with psoriasis [5]. These findings highlight a potential correlation between FXYD3 and the progression of psoriasis, inspiring us to investigate the function of FXYD3 in the epidermis *in vivo*.

K14^{cre}FXYD3^{fl/fl} mice (hereafter referred to as cKO), in which FXYD3 was selectively deleted in keratinocytes, showed less severe IMQ-induced psoriasis-like pathological phenotype compared to littermate controls (WT mice) [5]. We also depicted the immune landscape of skin from cKO and WT mice in IMQ-induced psoriasis

model. The counts of several immune cell populations, including neutrophils, monocytes, macrophages and $\gamma\delta$ T-cell, as well as the levels of multiple inflammatory factors, were all decreased in psoriatic skin in cKO mice. FXYD3 deficient keratinocytes had impaired IL-17A downstream signaling, with decreased phosphorylation of p65, p38, and ERK1/2. Moreover, IL-17A blockage ameliorated the psoriatic phenotype in WT mice to comparable level observed in cKO mice, implying that FXYD3 contributed to the psoriasis-like inflammation via promoting IL-17-mediated downstream signaling.

The IL-17 family signals via their correspondent receptors on the target cells, recruiting the receptor-proximal adaptor ACT1 (an NF- κ B activator 1) to activate downstream pathways, including NF- κ B and MAPKs (mitogen-activated protein kinases), to induce the expression of defensins, cytokines and chemokines [8]. To gain the mechanistic insight, we screened the interaction of FXYD3 with multiple known mediators or regulators in the IL-17 signaling pathway, including IL-17R, ACT1, and TRAF2-5. We found that only TRAF3 could interact with FXYD3, meanwhile IL-17 stimulation could enhance the interaction. TRAF3, one of the six members in TRAF (TNF receptor associated factor) family, contains ring finger, zinc finger, coil-coil, and TRAF domains [9]. TRAF3 has been reported as an essential negative regulator in IL-17 signaling [10],

directly interacting with IL-17R to interfere with the formation of the receptor signaling activation complex IL-17RA-ACT1-TRAF6. TRAF3 binds to IL-17R, relying on its TRAF domain, which as we revealed was also required for the interaction between TRAF3 and FXYD3. Thus, we speculated whether FXYD3 competed with IL-17R to interact with TRAF3. Indeed, overexpression of FXYD3 suppressed IL-17-induced interaction between IL-17R and TRAF3, but enhanced the formation of the IL-17R-ACT1 complex. Consistently, the IL-17-induced binding of ACT1 to IL17R was also weaker in FXYD3-KO primary keratinocytes than in WT cells, leading to the suppression of IL-17 downstream pathways.

In summary, we have identified FXYD3 as a key mediator in psoriasis exacerbation by facilitating the disordered communication between IL-17 producing immune cells (likely T cells) and IL-17 target cells (mainly keratinocytes) (**Figure 1**). IL-17-induced FXYD3 competes with IL-17R to interact with the negative regulator TRAF3, promoting IL-17 signaling in keratinocytes. The abnormal IL-17 activation caused by FXYD3 enhances the production of proinflammatory factors, contributing to the recruitment of more IL-17 producing cells. FXYD3-IL-17 forms an inflammatory circuit and provides potential targets for the psoriasis treatment. Some interesting questions require further exploration, for instance, how IL-17 induces the upregulation of FXYD3 in keratinocytes; and the possible roles of FXYD3 in maintaining immune homeostasis in other tissue, such as in the intestine.

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Contributions

MX drafted and edited the manuscript. QQW critically reviewed the manuscript.

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