The Relapse of Psoriasis: Mechanisms and Mysteries

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Over the past decades, tremendous success in the treatment of psoriasis has been achieved using biologics, such as neutralizing antibodies against TNF/TNFR, IL-23, and IL-17A/IL-17RA. Although psoriatic skin lesions appear to resolve after treatment with these biologics, lesions often recur after therapy is discontinued or during therapy. Memory T cells residing in the skin have been considered as the major driver of psoriasis relapse. However, whether structural cells in the skin such as keratinocytes and fibroblasts are involved in the relapse of psoriasis is unknown. In this review, we outline the therapeutic rationale of biologics used in the treatment of psoriasis, summarize different clinical features of psoriasis relapse on the basis of preclinical and clinical data, and specifically discuss how memory T cells and structural cells in the skin are involved in psoriasis relapse. Finally, we discuss the future challenges in the basic or clinical research on psoriasis.

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease characterized by epidermal hyperproliferation and sustained skin inflammation (Billi et al., 2019; Owczarek et al., 2021). Over the past two decades, enormous progress in the understanding of the pathogenesis of psoriasis has been achieved and then successfully translated into highly effective therapies in the treatment of psoriasis, which is best exemplified by the discovery and translation of the IL-23/IL-17 axis (Hawkes et al., 2017). Although psoriasis can be successfully treated using biologics, psoriatic skin lesions often recur after cessation of therapy (Carey et al., 2006; Owczarek et al., 2021). Therefore, psoriasis relapse is becoming the biggest challenge in the current therapies. In this review, we outline the most effective treatments for psoriasis, including biologics targeting TNF/TNFR, IL-23, and IL-17A/IL-17RA, summarize different clinical features of psoriasis relapse, and focus on discussing the possible mechanisms involved in psoriasis relapse. To the end, we will provide insights into the future directions and/or challenges in the basic or clinical research on psoriasis.

THE PATHOGENESIS OF PSORIASIS

The histology of the psoriasis plaque shows that epidermal keratinocytes (KCs) are hyperproliferative or aberrantly differentiated, and excessive immune cells infiltrate into the dermis and epidermis (Lowes et al., 2014; Ni and Lai, 2020; Rendon and Schäkel, 2019). Therefore, epidermal hyperplasia and sustained inflammation have been considered as the hallmarks of psoriasis (Lowes et al., 2014; Ni and Lai, 2020; Rendon and Schäkel, 2019). Several theories and models have been proposed to elaborate this immunopathology of psoriasis (Nestle et al., 2009; Nickoloff and Nestle, 2004). Among these, the most popular and acceptable theory is a feed-forward mechanism (Hawkes et al., 2017). In this mechanism, the crosstalk between KCs and immune cells plays key roles in shaping and maintaining the inflammatory milieu, thus leading to uncontrolled KC proliferation/differentiation and sustained inflammation in psoriasis (Ni and Lai, 2021). The detail of this feed-forward mechanism is as follows.

During trauma, injury, infection, or medication, various autoantigens such as nucleic acids, cationic antimicrobial peptides/proteins (AMPs), ADAMTSL-5, and PLA2G4D are released from stressed cells or damaged cells in prepsoriatic skin (Hawkes et al., 2017; Ni and Lai, 2020). Among these, cationic AMPs, including LL-37, human beta-defensin (hBD) 2 and hBD3, complex with DNA or RNA to form multimeric AMP–nucleic acid complexes, which activate toll-like receptor (TLR) 7 or 8 to induce the production of type I IFNs (IFN-α and IFN-β) in plasmacytoid dendritic cells (pDCs) or increase the amounts of IL-6 and TNF-α by myeloid dendritic cells (mDCs) (Ganguly et al., 2009; Lande et al., 2007). IL-6, together with TGFβ, induces $CD4^+$ naive T-cells differentiation into T helper (Th) 17 cells (Harrington et al., 2005; Park et al., 2005; Yang et al., 2007), whereas type I IFNs and TNF-α further activate mDCs to produce IL-12 and IL-23 (Lande et al., 2014; Nakajima et al., 2010; Sheibanie et al., 2004). Both IL-12 and IL-23 are essential in the cellular cascade of psoriasis pathophysiology. Because IL-12 induces $CD4^+$ naive T-cell differentiation into Th1 cells and IL-23 promotes Th17/T17 cells to become highly pathogenic or activates γδT cells and innate lymphoid cell 3 (ILC3s), all these cells produce high levels of IFN-γ, IL-17A/IL-17F, IL-22, and TNF-α (Aggarwal et al., 2003; Bielecki et al., 2021;

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Abbreviations: AMP, antimicrobial peptides/proteins; EpSC, epithelial stem cell; FDA, Food and Drug Administration; H3K27, histone 3 lysine 27; H3K27ac, histone 3 lysine 27 acetylation; H3K4me3, histone 3 lysine 4 trimethylation; hBD, human beta-defensin; ILC3, innate lymphoid cell 3; IMQ, imiquimod; KC, keratinocyte; mDC, myeloid dendritic cell; pDC, plasmacytoid dendritic cell; PGA, Physician Global Assessment; STAT3, signal transducer and activator of transcription 3; Th, T helper; TLR, toll-like receptor; Treg, regulatory T cell; T_{RM}, resident memory T cell

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Cai et al., 2011; Tait Wojno et al., 2019). IL-17A, together with other inflammatory cytokines, acts on KCs or other innate immune cells and induces these cells to constantly produce a variety of proinflammatory cytokines (Cai et al., 1998; Carrier et al., 2011; Moos et al., 2019; Teunissen et al., 1998), chemokines (Chiricozzi et al., 2011), and AMPs (Hegyi et al., 2012; Lai et al., 2012; Liang et al., 2006). The AMP such as REG3A induced by IL-17A inhibits KC differentiation to induce epidermal hypoplasia (Lai et al., 2012), whereas the inflammatory cytokines and chemokines induced by IL-17s in turn promote the expansion of IL-17–producing cells and recruit more neutrophils or IL-17–producing cells to the site of inflammation in the skin (Bielecki et al., 2021; Cai et al., 2011; Ha et al., 2014; Tortola et al., 2012), which comprises a feed-forward loop to further amplify local inflammatory responses and epidermal hyperplasia (Figure 1). Taken together, the dysregulation of the inflammatory circuit drives psoriasis development and maintains the pathophysiology of psoriasis.

BIOLOGICS USED FOR PSORIASIS TREATMENT

The in-depth understanding of the complex actions of cytokines and cytokine networks in the pathogenesis of psoriasis leads to the development of multiple biologics, such as neutralizing antibodies against TNF/TNFR, IL-17A/IL-17RA, and IL-23 (Table 1). To date, these biologics have revolutionized the clinical management of psoriasis, with a great enhancement in safety and efficacy (Brownstone et al., 2021; Hawkes et al., 2017; Lai and Dong, 2016). In this review, we outline the rationale and potential adverse effects of 11 biologics that are approved by the Food and Drug Administration (FDA) for psoriasis treatment in the clinic.

Biologics targeting TNF/TNFR

The increased level of TNF-α in lesional skin of patients with psoriasis has been well characterized. Therefore, multiple TNF or TNFR antagonists have been developed and used for psoriasis treatment. Currently, four anti–TNF-α antibodies and one TNFR inhibitor, including infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab, have been approved by FDA (Li et al., 2019). Four of them, including infliximab, etanercept, adalimumab, and certolizumab pegol (Table 1), have been approved for the treatment of psoriasis (Brownstone et al., 2021; Gerriets et al., 2021). Except etanercept targeting TNFR2, a receptor predominantly expressed on regulatory T cells (Tregs) and only recognizing a membrane-bound form of TNF-α (Yang et al., 2018), other three TNF biologics target both soluble and membrane-bound forms of TNF-α and showed good efficacies in the treatment of psoriasis on the basis of PASI. For instance, 80.4% of patients achieved a 75% reduction in PASI (i.e., PASI 75) after 10-week infliximab treatment (Reich et al., 2005), 82.8% of patients achieved a PASI 75 response after 12-week 400 mg of certolizumab pegol treatment (Reich et al., 2012), and 71.0% of patients achieved a PASI 75 response after 16-week adalimumab treatment (Menter et al., 2008), whereas a PASI 75 response was observed in only 47.3% of patients treated with 12-week etanercept (Papp et al., 2005; Tyring et al., 2006) (Table 1).

Despite the significant positive effects of blockade of TNF-α and its signaling in psoriasis, the percentage of patients

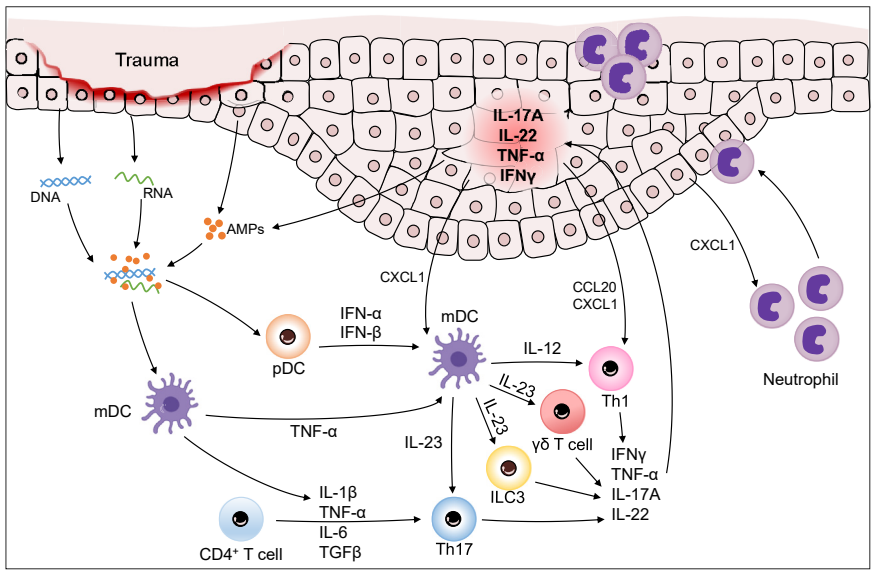

Figure 1. A feed-forward inflammatory loop in psoriasis. When trauma occurs, nucleic acids, AMPs, and other factors are released from stressed cells or damaged cells. Among these, AMPs complex with DNA or RNA to form multimeric AMP–nucleic acid complexes, which activate TLR7/8 to induce the production of type I IFNs in pDCs or increase amounts of IL-6 and TNF-α by mDCs. IL-6, together with TGFβ, induces $CD4^+$ naive T-cell differentiation into Th17 cells, and TNF-α and IL-1β further enhance Th17 differentiation, whereas type I IFNs and TNF-α activate mDCs to produce IL-12 and IL-23. IL-12 induces $CD4^+$ naive T-cell differentiation into Th1 cells that can produce IFN-γ, and IL-23 promotes Th17 cells, γδT cells, and ILC3 to produce high levels of IL-17A, IL-22, and TNF-α. All these cytokines act on keratinocytes to induce epidermal hyperproliferation or induce keratinocytes to constantly produce proinflammatory cytokines, chemokines, and AMPs. Again, AMPs complex with nucleic acids to activate pDCs or mDCs to express more IL-6, TNF-α, IL-12, IL-23, and type I IFNs for the expansion of IL-17–producing cells. Chemokines such as CCL20 and CXCL1 recruit more neutrophils or IL-17–producing cells to the site of inflammation in the skin. All these comprise a feed-forward loop to further amplify local inflammatory responses and epidermal hyperplasia. AMP, antimicrobial protein; mDC, myeloid dendritic cell; pDC, plasmacytoid dendritic cell; Th, T helper; TLR, toll-like receptor.

Table 1. Biologics Targeting TNF/TNFR, IL-17/IL-17RA, or IL-23 Used

Biologic	Mechanism	PASI 75 Response	Median Time to Relapse
TNF			
Infliximab	Mouse–human chimeric IgG1κ mAb binding to soluble and transmembrane forms of TNF-α	80.4% (242 of 301) (Reich et al., 2005)	182 days (Giunta et al., 2007)
Etanercept	Recombinant protein containing the TNFR2 fused to the constant end of the IgG1 antibody	47.3% (147 of 311) (Tyring et al., 2006)	51 days or 7.3 weeks (51.1 days) (Griffiths et al., 2010; Ortonne et al., 2009)
Adalimumab	Human mAb against TNF-α	71.0% (578 of 814) (Menter et al., 2008)	141 days (Papp et al., 2011)
Certolizumab pegol	Monovalent, humanized TNF-α Fab antibody fragment conjugated to a polyethylene glycol	74.6% (44 of 59, 200 mg) or 82.8% (48 of 58, 400 mg) (Reich et al., 2012)	154 days (200 mg) or 140 days (400 mg) (Reich et al., 2012)
IL-17/IL-17RA			
Secukinumab	Humanized IgG1κ mAb against IL-17A	91.6% (471 of 514) (Reich et al., 2019)	140 days (150 mg per dose) or 168 days (300 mg) (Mrowietz et al., 2015)
			196 days (300 mg) (Blauvelt et al., 2017c)
Ixekizumab	Humanized IgG4κ mAb that selectively binds and neutralizes IL-17A	88.5% (651 of 736, every 2 weeks) or 81.0% (594 of 733, every 4 weeks) (Gordon et al., 2016)	142.8 days (every 2 weeks) or 140.7 days (every 4 weeks) (Blauvelt et al., 2017b)
Brodalumab	Humanized IgG2 mAb against IL-17RA	83.3% (185 of 222, 210 mg) (Papp et al., 2016)	46 days (Masson Regnault et al., 2017)
IL-23			
Ustekinumab	Human IgG1κ mAb that specifically binds to the p40 subunit of IL-12/IL-23	66.7% (273 of 409, 45 mg) or 75.7% (311 of 411, 90 mg) (Papp et al., 2008)	100.8 days (45 mg) or 126.7 days (90 mg) (Griffiths et al., 2010)
			201 days (Chiu et al., 2019)
Tildrakizumab	Humanized IgG1κ, mAb targeting IL-23 p19 subunit	63.8% (197 of 309, 100 mg) or 62.3% (192 of 308, 200 mg) (Reich et al., 2017)	168 days (100 mg or 200 mg) (Kimball et al., 2020)
Guselkumab	Human IgG1λ mAb that selectively blocks IL-23 by binding to its p19 subunit	89.3% (477 of 534) (Reich et al., 2019)	282 days (Rivera et al., 2021)
Risankizumab	Humanized IgG1 mAb that inhibits IL-23 by specifically targeting the p19 subunit	88.7% (361 of 407) (Blauvelt et al., 2020)	295 days (as PGA $\geq$ 3) (Blauvelt et al., 2020)

Abbreviation: PGA, Physician Global Assessment.

with remarkable improvement in their skin lesions is lower than the percentage of those treated with anti–IL-17A, anti–IL-17RA, and some of anti–IL-23 antibodies (Hawkes et al., 2017). This lower efficacy of TNF biologics in the treatment of psoriasis indicates that TNF-α, as an early released inflammatory cytokine, is at key steps of disease development but may not be fundamental to the disease pathogenesis (Lai and Dong, 2016). Paradoxically, some anti-TNF antibodies have been reported to elicit psoriatic eruptions or worsen pre-existing psoriatic skin disease during treatment of patients with psoriasis (Conrad et al., 2018; Li et al., 2019). For example, infliximab elicited de novo psoriasis at different localizations or with a different morphology from initial psoriasis during treatment (Joyau et al., 2012). One speculation of this paradoxical side effects of infliximab and other anti–TNF-α biologics is that inhibition of TNF-α abrogates the inhibitory effect of TNF-α on the production of type I IFNs by skin pDCs (Conrad et al., 2018; Nestle et al., 2005; Psarras et al., 2021), thus increasing the number of IFN-γ–secreting Th1 and IL-17–secreting T17 cells (Sherlock et al., 2013; Tillack et al., 2014). The other speculation is that patients receiving anti–TNF-α therapy have an increased risk for infection, which is known to trigger or manifest psoriasis (Fry and Baker, 2007). Therefore, understanding how anti-TNF/TNFR biologics exert their pleiotropic effects is key to avoiding their undesirable effects and selecting the most appropriate therapy for patients who have failed or are otherwise intolerant to anti-TNF/TNFR biologics.

Biologics targeting IL-17A/IL-17RA

The importance of the IL-23/IL-17 axis in the pathogenesis of psoriasis suggests that this axis is a good target to develop novel agents in the treatment of psoriasis. As a key effector cytokine produced by pathogenic Th17, γδT cells, and ILC3, IL-17A and its receptor IL-17RA have been thought as one of the best targets in the treatment of psoriasis (Tse, 2013). Therefore, several mAbs targeting IL-17A and IL-17RA have been developed. To date, three antibodies targeting IL-17A/IL-17RA, including secukinumab, ixekizumab, and brodalumab, have been developed and approved by United States FDA for the treatment of moderate-to-severe plaque psoriasis (Table 1). Each biologic is highly effective and helped over 80% of treated patients to achieve a PASI 75 response (Table 1). Among these three biologics, brodalumab had been speculated to be superior to two others (Bartlett and Million, 2015) because IL-17RA is the most common signaling subunit in the IL-17 pathway and form heterodimeric receptor complexes with several other IL-17 receptors, including IL-17RB, IL-17RC, IL-17RD, and IL-17RE, which transduce IL-17A, IL-17C, IL-17E, and IL-17F signals. Recent reviews on several multicenter, double-blind randomized controlled trials partially confirmed this speculation and show that brodalumab was superior to ixekizumab and secukinumab only for long-term PASI 90 response but had a similar probability of short-term PASI 90 response to two others on the basis of the treatment effectiveness (Armstrong et al., 2021; Wade et al., 2019).

Although targeting IL-17A/IL-17RA is successful in the treatment of psoriasis, several adverse effects, including *Candida albicans* mucocutaneous infections, upper respiratory tract infections, headache, diarrhea, and gastrointestinal disorders, have been reported in clinical trials. The infections and gastrointestinal disorders caused by IL-17 blockade are likely due to a crucial role of IL-17A in the control of fungi and extracellular but not intracellular bacterial infections (Dubin and Kolls, 2008). Therefore, these adverse effects need to be carefully considered when anti–IL-17A/IL-17RA biologics are used to treat patients with psoriasis with some bacterial infections or inflammatory bowel disease. Furthermore, events of suicidal ideation and behavior in several participated patients were reported in the AMAGINE trials for brodalumab, although no causal relationship was ever shown (Hawkes et al., 2017). To avoid these adverse effects, blocking IL-17–producing cell responses but not universal IL-17 cytokine signaling might be more secure and optimistic, and targeting key transcription factors that determine the lineage commitment of IL-17–producing cells might be an alternative option.

Biologics targeting IL-23

IL-23 is a heterodimeric cytokine composed of the p19 and the p40 subunits and shares the p40 subunit with IL-12. Given the key role of IL-23 in driving pathogenic Th17, γδT, and ILC3 cells to produce high levels of IL-17A, IL-23 definitely is a superior target to develop biologics for psoriasis treatment. Early in 1998, IL-12 was considered as a key cytokine in psoriasis pathogenesis owing to the observation of enhanced *IL12p40* mRNA in lesional skin of patients with psoriasis (Yawalkar et al., 1998). Therefore, ustekinumab (Table 1), a human monoclonal IgG1 antibody targeting the p40 subunit, was firstly developed for the treatment of patients with moderate-to-severe psoriasis (Benson et al., 2011). However, subsequent studies showed that IL-23 but not IL-12 was elevated in lesional skin of patients with psoriasis because *IL23p19* mRNA, not *IL12p35* mRNA, was increased in the lesional skin of patients with psoriasis (Lee et al., 2004). Moreover, injection of IL-23 in murine skin induced psoriasis-like phenotype, whereas IL-12 did not promote the same pathology (Lee et al., 2004; Tonel et al., 2010). The evidence suggests that targeting IL-12p40 indeed is inhibiting IL-23. Therefore, several IL-23–specific antibodies antagonizing the p19 subunit, including tildrakizumab, guselkumab, risankizumab, LY2525623, AMG139, and LY3074828, have been developed (Teng et al., 2015). Currently, three humanized mAbs targeting IL-23p19 subunit, including guselkumab, tildrakizumab, and risankizumab (Table 1), have also been approved by FDA for the treatment of psoriasis (Crowley et al., 2019; Ghazawi et al., 2021). Among these, guselkumab and risankizumab were highly effective in the treatment of moderate-to-severe plaque psoriasis because nearly 90% of patients achieved a PASI 75 response after 16-week guselkumab (Reich et al., 2019) or risankizumab (Blauvelt et al., 2017a) treatment. Notably, relatively long-term treatment responses were also observed in some patients with just a single dose of guselkumab or risankizumab treatment (Krueger et al., 2015; Sofen et al., 2014). This impressive rapid clinical response might be due to the transdifferentiation of Th17 cells into Treg after IL-23 inhibition (Gagliani et al., 2015; Hawkes et al., 2017).

Although IL-23 is not as important as IL-17A in host defense, upper respiratory tract infections and soft-tissue abscesses were reported in phase 3 trials with guselkumab (Hawkes et al., 2017). These adverse effects are probably because IL-23 is required for the production of IL-17A and IL-17F by IL-17–producing cells and because IL-17A/F plays key roles in protecting hosts from *Mycobacterium* and *Candida* infections (Khader et al., 2005; Lai and Dong, 2016; Puel et al., 2012). Moreover, a few patients were under the risk of a breakdown in tumor surveillance and had nonmelanoma skin cancers in phase 3 trials with guselkumab (Hawkes et al., 2017) owing to the hierarchy of dominance between IL-12's tumor suppression and IL-23's tumor promotion (Dunn et al., 2006; Ngiow et al., 2013). Therefore, further investigation to evaluate the long-term efficacy and safety profiles of IL-23 biologics is required.

DEFINITIONS AND CLINICAL FEATURES OF PSORIASIS RELAPSE

Although psoriatic skin lesions appear to resolve by treatment with the aforementioned biologics, lesions often recur in the same locations after therapy is discontinued. Multiple factors, such as the type of biologics, biologic naivety, initial PASI, and patients with or without comorbidities, influence the time to relapse. To standardize the definition of psoriasis relapse, the National Psoriasis Foundation Medical Advisory Board defines psoriasis relapse as a 50% loss of PASI improvement from baseline. In addition, FDA suggests using the Physician Global Assessment (PGA) $\geq$3 as another standard of psoriasis relapse (Gordon et al., 2005). Therefore, the time to relapse can be defined as the time in which patients lose 50% of improvement of PASI score or achieve PGA $\geq$ 3 once the treatment is discontinued. Accumulating evidence from preclinical and clinical trials shows that the time to relapse in patients with psoriasis ranges from a few months to more than a year after biologic treatment is discontinued (Mu et al., 2019; Owczarek et al., 2021; Umezawa et al., 2019).

Relapse within 3 months or less after complete control and withdrawal of therapy

Although all the aforementioned biologics are effective for patients with psoriasis and usually achieve satisfied efficacy, psoriasis relapse occurs within a few months after discontinuation of some biologics. For example, all patients who had successful brodalumab treatment experienced a relapse after cessation of treatment. The duration between brodalumab discontinuation and psoriasis relapse in some patients was around 2 weeks in a monocentric retrospective study of 139 patients, and the severity of psoriasis of these relapsed patients was higher than the severity at baseline (Khemis et al., 2018). In another study of 77 patients who received successful brodalumab treatment, some patients experienced a relapse within a few days, about half of the patients experienced a relapse within 50 days after withdrawal of brodalumab, and the median time to relapse was 46 days (Masson Regnault et al., 2017) (Table 1). Moreover, in a trial on etanercept, some patients achieved PGA $\geq$ 3 in <2 months

(51 days) after the 50 mg of etanercept twice-weekly treatment pause (Ortonne et al., 2009). In another trial on etanercept in which 347 patients with psoriasis also received 50 mg of etanercept twice-weekly treatment, the median time to relapse for patients with treatment success was 7.3 weeks (Griffiths et al., 2010) (Table 1).

Relapse in >3 months after completion control and withdrawal

Except for brodalumab and etanercept, the median time to relapse of other biologics is generally longer than 3 months after therapy is stopped (Table 1). Particularly, biologics targeting to IL-23p19 subunit exhibit terrific durability. For example, the median time to relapse in a phase 3 study on patients who were deemed responders to 150 mg risankizumab was 42 weeks (295 days, 54 weeks from the last dose), showing superior durability of risankizumab response after withdrawal (Blauvelt et al., 2020). In a reSURFACE 1 trial, the median time to loss of PASI 75 was 142 days with 100 mg tildrakizumab or 172 days with 200 mg tildrakizumab (Warren et al., 2021), whereas in another trial on tidrakizumab, the median time to loss of PASI 50 was 6 months (24 weeks) irrespective of doses (Kimball et al., 2020), suggesting that the duration might not be dose dependent. Trials with guselkumab showed that 30.6% of patients experienced a loss of PASI 50 by week 52, 49.1% by week 60, and 67.6% by week 72, whereas 32.4% of patients did not lose response over week 72 (Gordon et al., 2019); the median time to relapse is 282 days (Rivera et al., 2021). In addition to the aforementioned three biologics specifically targeting IL-23p19, ustekinumab, a biologic specifically targeting IL-12/IL-23p40, showed its good durability, and the median time to relapse for patients who received 45 or 90 mg ustekinumab was 14.4 or 18.1 weeks, respectively (Griffiths et al., 2010). More recently, a trial on ustekinumab indicated that a relapse time was 6.7 $\pm$ 4.1 months (range = 3−30.8 months) (Chiu et al., 2019).

Biologics targeting IL-17A or TNF-α show excellent durability as well. In a trial on secukinumab, the median time to relapse was 5 months (20 weeks) for patients who received 150 mg secukinumab initially or 6 months (24 weeks) for those who received 300 mg secukinumab initially (Mrowietz et al., 2015), and the median relapse time of 7 months (28.0 weeks) was also observed in another 300 mg secukinumab trial (Blauvelt et al., 2017c). A trial on ixekizumab showed that relapse time was 20.4 or 20.1 weeks for patients who received drugs every 2 or 4 weeks, respectively (Blauvelt et al.,b). Several trials also show that the biologics targeting TNF-α have excellent durability. The median time to relapse was 6.07 months (182 days) for infliximab (Giunta et al., 2007), 4.7 months (141 days, interquartile range = 93–202 days) for adalimumab (Papp et al., 2011), and 5.1 months (154 days) for 200 mg certolizumab pegol or 4.7 months (140 days) for 400 mg certolizumab pegol (Reich et al., 2012).

Relapse with disease control and on therapy

Clinical trials indicate that relapse can occur during treatment. In a multicenter, double-blind, placebo-controlled trial, 249 patients with severe plaque psoriasis were randomly assigned to receive intravenous infusions of either 3 or 5 mg/kg of infliximab or placebo given at weeks 0, 2, and 6. At week 10, the maximum response was observed for both infliximab treatment groups. A total of 72% of patients treated with 3 mg/kg of infliximab and 88% of patients treated with 5 mg/kg of infliximab achieved a $\geq$75% improvement from baseline in PASI score. However, this high level of response began to decline at week 14, and some patients experienced relapse around week 22, although they were still given infliximab treatment (Gottlieb et al., 2004).

Moreover, some special cases of relapse, including but not limited to continuous recording on relapse, medication switching in case of unobtrusive response to initial therapy, and so on, have been observed. For example, a patient aged 28 years affected by moderate-to-severe plaque psoriasis who had previously failed to respond to a traditional therapy received brodalumab treatment. Within only 4 weeks, the patient achieved impressive clinical improvement. However, half a year later, the patient skipped his medication owing to work commitments and then experienced a relapse within 1 month in a guttate-plaque form mainly involving the face. Surprisingly, patients presented no improvement after 3-month brodalumab administration owing to unknown reasons (Burlando et al., 2020). Another intriguing case happened in a patient aged 33 years who also failed to respond to conventional treatments. This patient received the 300 mg subcutaneous sekukinumab as an induction dose, and his psoriasis plaques disappeared completely after four-dose treatment. However, when he received the fifth dose, the form of guttate-style erythematous-scaled lesions occurred at a distance from the patient's extensor surface of upper left extremity, and then lesions turned into linear character along the Blaschko line after topical steroids and a combination of calcipotriol and corticosteroids were applied (Demirbaş et al., 2020). These two special cases indicate that inhibition of IL-17A/IL-17RA by biologics makes some patients more susceptible to group A *Streptococcus* infection that has been shown to trigger guttate psoriasis (Dileepan et al., 2011; Rendon and Schäkel, 2019; Telfer et al., 1992).

THE UNDERLYING MECHANISMS OF PSORIASIS RELAPSE

Because relapse after cessation of biologic treatment is common, lots of attention have been paid to exploring the underlying mechanism of psoriasis relapse. At present, the most prevailing notion is that all the aforementioned biologics and other conventional therapies for psoriasis treatment only suppress the activity of pathogenic immune cells but do not eradicate these cells; withdrawal of active therapy thereby makes these pathogenic immune cells reactivate and reinitiate inflammatory lesions (Behr et al., 2018; Benezeder and Wolf, 2019; Suárez-Fariñas et al., 2011). Among these pathogenic immune cells, memory T cells residing in the skin are considered as a major driver of psoriasis relapse (Gallais Sérézal et al., 2018; Matos et al., 2017; Saczonek et al., 2020). In addition to skin resident memory T (T_{RM}) cells, memory-like $\gamma\delta$T cells (Hartwig et al., 2015), and skin structural cells with inflammatory memory (Larsen et al., 2021; Naik et al., 2017) have also been proposed to involve in psoriasis relapse.

T_{RM} cells in the relapse of psoriasis

Mounting evidence shows that resolved psoriatic skin lesions contain a population of T_{RM} cells that are responsible for local relapse of psoriasis (Cheuk et al., 2014; Di Meglio et al., 2016; Gallais Sérézal et al., 2018; Matos et al., 2017; Saczonek et al., 2020; Suárez-Fariñas et al., 2011). Early in 2002, Bhushan et al. (2002) showed that E-selectin inhibitors were not efficacious in preventing psoriasis, indicating that nonmigratory immune cells can mediate disease. Subsequently, Boyman et al. (2004) showed that immunodeficient AGR129 mice engrafted with prepsoriatic human skin containing T cells and other immune cells spontaneously developed psoriasis, suggesting that immune cells residing in the skin are sufficient for inducing psoriasis and that resident T cells might be the major disease-initiating/relapsing pathogenic T cells in psoriasis. After 7 years, immune cells were found to retain in resolved lesions in patients with psoriasis after 3 months of etanercept treatment (Suárez-Fariñas et al., 2011), and epidermal $CD8^+$ T_{RM} cells were identified as one of the major immune cells retained in resolved psoriatic lesions (Cheuk et al., 2014). This population of $CD8^+$ T_{RM} cells lacks CD49a but expresses CD103, the αEβ7 integrin that interacts with E-cadherin expressed by KCs (Kurihara et al., 2019; Milner and Goldrath, 2018) and is capable of producing IL-17A (Cheuk et al., 2017, 2014). Recently, using high-throughput screening of the CDR3 region of TCR and immunostaining, Clark group has found that IL-17–producing αβT cells with psoriasis-specific antigen receptors exist in clinically resolved psoriatic skin lesions and to some extent in nonlesional skin but not in healthy controls (Matos et al., 2017). Gallais Sérézal et al. (2019, 2018) confirmed through NanoString analysis that these pathogenic IL-17–producing αβT cells in resolved psoriatic lesions were $CD49a^-CD103^+CD8^+$ T_{RM} cells and were capable of triggering psoriasiform tissue response. All these findings suggest that IL-17–producing $CD49a^-CD103^+CD8^+$ T_{RM} cells are responsible for psoriasis relapse (Figure 2).

In addition to αβT cells, γδT cells have been found in low (1%) but detectable frequencies in resolved psoriatic lesions (Laggner et al., 2011; Matos et al., 2017). This population of γδT cells might have the memory capacity and plays an important role in psoriasis relapse. In 2015, $Vγ4^+Vδ4^+$T cells, one population of γδT cells, were identified as a long-lived memory γδT cells in imiquimod (IMQ)-induced inflamed murine skin and produced IL-17A/F to mediate an exacerbated secondary inflammatory response in psoriasis-like mice (Figure 2) (Hartwig et al., 2015). However, γδT cells are the main source of IL-17A in the mouse model of IMQ-induced psoriasiform dermatitis but not in patients with psoriasis, and $Vγ4^+Vδ4^+$T cells can travel through the blood to distant skin sites and lymph nodes where they persist as memory-like cells capable of altering the set point for induction of inflammation (Ramírez-Valle et al., 2015). Therefore, whether $Vγ4^+Vδ4^+$T cells would trigger psoriasis relapse in previously affected skin areas of patients with psoriasis warrant further investigation.

KCs with inflammatory memory in the relapse of psoriasis

Although inflammatory memory is usually confined to T and B cells, the findings of trained immunity or innate immune memory within macrophages, NK cells, fibroblasts, and KCs with stemness suggest that both innate immune cells and some nonimmune cells can also have immune memory or inflammatory memory (Kamada et al., 2018; Naik et al., 2017; Netea, 2013; Petit et al., 2019). This memory of innate immune cells has been shown to be mainly involved in host defense by enhancing responsiveness to subsequent triggers. Interestingly, recent progress suggests that immune memory of structural cells is potentially detrimental to chronic inflammatory diseases (Dakin et al., 2017; Larsen et al., 2021; Naik et al., 2017; Netea et al., 2020). For instance, tendon-derived stromal fibroblasts seemed to be trained to mount much stronger inflammatory responses to inflammation than healthy tendon cells, which are involved in the development of chronic inflammation and recurrent tendinopathy (Dakin et al., 2017). Psoriasis is also a chronic inflammatory disease, and psoriasis lesions preferentially recur in the same anatomic locations once therapy is discontinued; whether skin structural cells in resolved lesions will gain memory to predispose to recurrence of lesions in the same locations was under veil. Most recent progress that skin epithelial stem cells (EpSCs) have the ability to acquire prolonged memory of inflammation may uncover this mysterious veil and suggest that KCs with inflammatory memory also contribute to the recurrence of lesions in the same anatomic locations of patients with psoriasis (Larsen et al., 2021; Naik et al., 2017). In this review, we discuss how KCs with inflammatory memory are potentially involved in psoriasis relapse.

EpSCs are basal KCs that reside in the innermost layer of skin epithelium and can self-renew or undergo a terminal differentiation program to form an epithelial barrier (Blanpain and Fuchs, 2014; Bordon, 2017). Although the ability of epithelial barrier against different external stimuli is well defined (Larsen et al., 2020), whether EpSCs or basal KCs in skin epithelium have the capacity to remember an inflammatory event and participate in psoriasis relapse remains unknown. Two studies by Elaine Fuchs group have shown that EpSCs can gain inflammatory memory in the context of psoriasis-like skin inflammation and mount robust inflammatory responses on a second challenge such as wounding or infections (Larsen et al., 2021; Naik et al., 2017). Using IMQ-induced psoriasis-like skin inflammation reporter mice model, Fuchs et al. (2017) traced EpSCs for up to 180 days and found that EpSCs were long lived in the inflamed skin after the resolution of inflammation in psoriasis-like mice. During wounding, these psoriasis-like mice with resolved skin inflammation were able to heal the wound faster than control mice independently of immune cells such as resident T cells and macrophages (Naik et al., 2017), suggesting that EpSCs are key cells directly sensitized by inflammatory stimuli and subsequently control the faster response to wounding. Given the role of epigenetic modification in innate immune memory (Netea et al., 2016), the authors then tested chromosomal accessibility in EpSCs using Transposase Accessible Chromatin with high-throughput sequencing and found that IMQ exposure increased the accessibility in genes related to inflammation and hyperproliferation in EpSCs. Further investigation revealed that the acquired faster response to wounding particularly relied on AIM2 inflammasome and its downstream components in EpSCs because

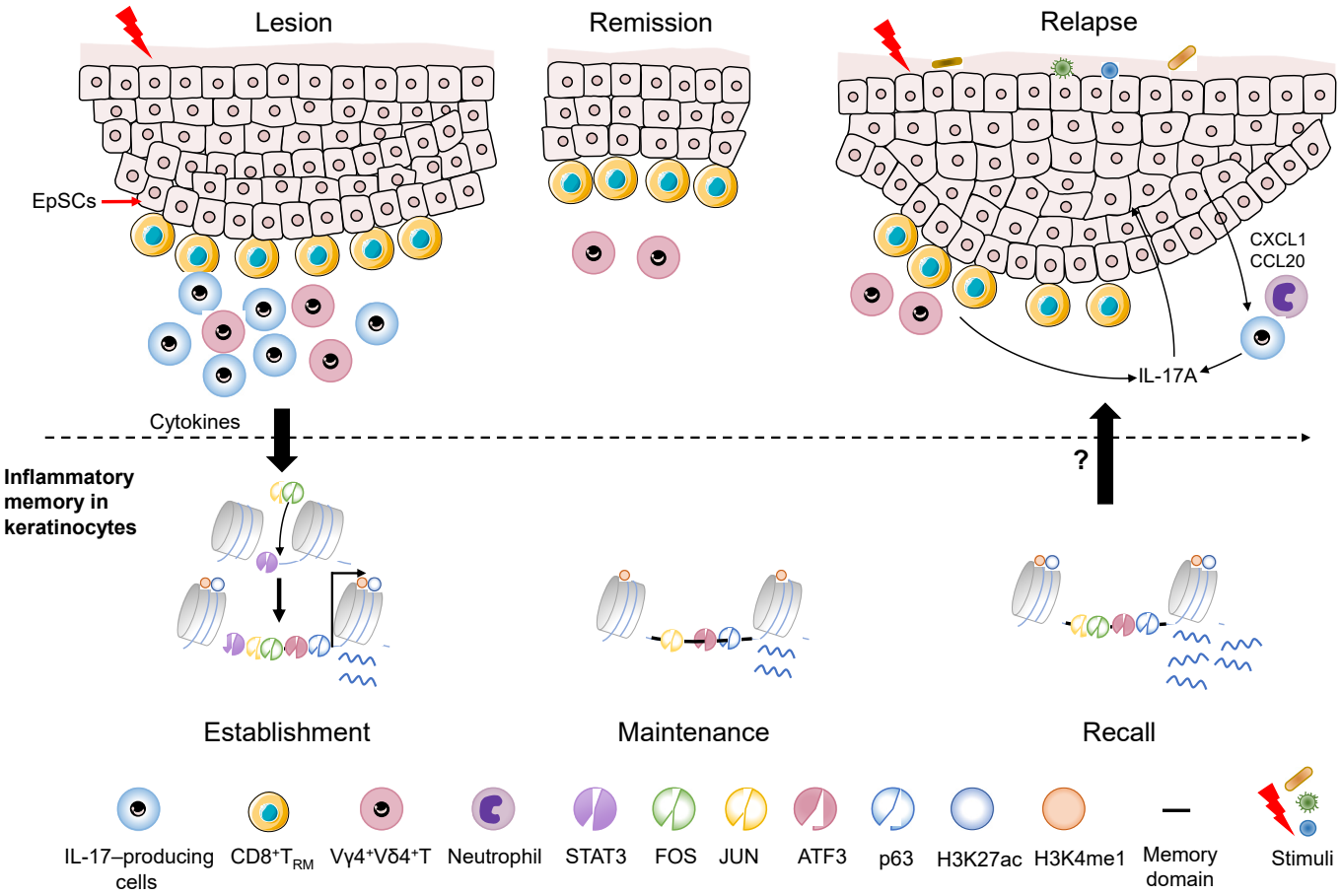

Figure 2. CD8$^+$ T_{RM} cells and keratinocytes with inflammatory memory in psoriasis relapse. In skin lesions, IL-17–producing cells, CD8$^+T_{RM}$, and Vγ4$^+$Vδ4$^+$T cells are activated to produce multiple cytokines, including IL-23, IL-17A, and IL-22, which activate STAT3 and general stress-responsive transcription factors FOS and JUN in EpSCs (also named basal keratinocytes). Moreover, several inflammatory cytokines promote H3K27ac at distal enhancers or H3K4me3 at the promoters of stimulated genes, thus increasing the chromatin accessibility in EpSCs. FOS partners with JUN, and then STAT3 directs FOS–JUN to MDs, the chromatin regions that gain accessibility during the inflammatory response and remain so after resolution, for establishing inflammatory memory in EpSCs. After resolution of inflammation, CD8$^+T_{RM}$ and Vγ4$^+$Vδ4$^+$T cells retain in resolved skin, and STAT3 and FOS are released from the MDs, but H3K4me1, monomethylated H3K4 derived from H3K4me3, and JUN with other homeostatic transcriptional factors such as ATF3 and p63 remain on MDs to maintain chromatin opening in EpSCs. On secondary challenges such as wounding and infections, FOS is rapidly rerecruited to MDs and couples with JUN to reactivate gene expression in EpSCs, and CD8$^+T_{RM}$ and Vγ4$^+$Vδ4$^+$T cells produce IL-17A, thus reinitiating inflammatory loops in the skin and triggering psoriasis relapse. The bottom panel is adapted from Larsen et al. (2021). EpSC, epithelial stem cell; H3K27ac, histone 3 lysine 27 acetylation; H3K4, histone 3 lysine 4; H3K4me3, histone 3 lysine 4 trimethylation; MD, memory domain; STAT3, signal transducer and activator of transcription 3; T_{RM}, resident memory T cell.

AIM2-deficient mice lost the ability to recollect inflammation and failed to accelerate wound repair in previously inflamed skin, whereas induced expression of epidermal AIM2 promoted wound repair in the absence of prechallenge with IMQ (Bordon, 2017; Naik et al., 2017). Most recently, Fuchs et al. (2021) have further revealed the molecular mechanisms guiding the establishment, maintenance, and recall of EpSC inflammatory memory using a series of elegant transcriptomic and chromatin profiling techniques coupled with mouse genetics (Larsen et al., 2021). They also used an IMQ-induced psoriasis-like skin inflammation mouse model to show that >1,000 DNA regions in EpSCs acquired accessibility at the apex of inflammation during psoriasis. Among these genes, the general stress-responsive transcription factor FOS partners with JUN and signal transducer and activator of transcription 3 (STAT3), a key transcription factor activated by IL-23, IL-17A, and IL-22 in psoriasis (Nakajima et al., 2019; Sano et al., 2005; van der Fits et al., 2009; Zheng et al., 2007), directs FOS–JUN to memory domains—the chromatin regions that gain accessibility during the inflammatory response and remain so after resolution—for establishing inflammatory memory. After resolution of the inflammatory condition, STAT3 and FOS were released from the memory domains, whereas JUN with other transcriptional factors such as ATF3 and p63 remained on memory domains, which are sufficient to maintain the chromatin open at the memory domains and facilitate rapid FOS rerecruitment and gene reactivation on secondary challenges such as wounding and infections (Figure 2) (Larsen et al., 2021; Nguyen and Aragona, 2021). Altogether, these two findings show that EpSCs or basal KCs with stemness gain long-term epigenetic memory during psoriasis, and this inflammatory memory enables EpSCs more robustly in response to a broad range of stressors such as infections and wounding, which potentially contributes to the recurrence of skin inflammation in psoriasis.

During the establishment of inflammatory memory, an open chromatin state is required for both stimulus-specific transcription factors such as STAT3 and generic stress-responsive transcription factors such as FOS–JUN to have access to memory domains. Two key epigenetic markers are involved in chromatin accessibility. One is the acquisition of histone 3 lysine 27 acetylation (H3K27ac) at distal enhancers because the addition of acetyl group neutralizes the positive charge of histone 3 lysine 27 (H3K27) and results in weaker interactions between histone and DNA and then the opening of chromatin (Zeng et al., 2021). The other is the consolidation of histone 3 lysine 4 trimethylation (H3K4me3) at the promoters of stimulated genes (Netea et al., 2020) because H3K4me3 can associate with nucleosome remodeling factor to mediate adenosine triphosphate–dependent chromatin remodeling (Wysocka et al., 2006). Larsen et al. discovered that memory domains in EpSCs were marked by H3K27ac at the apex of inflammation (day 6) and retained histone 3 lysine 4 monomethylation marking on day 30 when the skin was restored to homeostasis (Figure 2) (Larsen et al., 2021), both of which drive or keep the opening of the specific memory domains. However, what causes these epigenetic modifications in EpSCs remains unaddressed. Multiple metabolites have been shown to participate in histone modifications by either serving as cosubstrates or modulating the activity of chromatin-modifying enzymes (Dai et al., 2020; Donohoe and Bultman, 2012). For instance, α-ketoglutarate generated from glutaminolysis promoted JMJD3-dependent demethylation of H3K27 trimethylation and induced anti-inflammatory activation of macrophages (Liu et al., 2017), whereas accumulation of fumarate upregulated histone 3 lysine 4 methylation by inhibiting KDM5 (Arts et al., 2016). Psoriasis is associated with multiple metabolic syndromes, including obesity, type 2 diabetes, and so on (Boehncke and Schön, 2015; Gisondi et al., 2018). A different metabolic profile or increased expression of metabolic checkpoints such as MYC and HIF has been observed in skin lesions of patients with psoriasis compared with that in symptom-free psoriatic and/or healthy control skin (Cibrian et al., 2020). Among these metabolites, glutamic acid, choline, valine, glucose, and myo-inositol appear to be associated with hyperproliferative KCs (Dutkiewicz et al., 2016; Kim et al., 1989). Particularly, glucose metabolism has been shown to be selectively involved in KC hyperproliferation in lesional skin of individuals with psoriasis (Zhang et al., 2018). We (unpublished data) and other groups also found that glycolysis pathway and amino acid metabolic activity were upregulated in lesional skin and serum from patients with psoriasis and that lactic acid is a major glycolytic metabolite elevated in psoriatic lesions (Cibrian et al., 2020; Kang et al., 2017; Liu et al., 2021). Lactic acid has been shown to promote the acetylation of histone lysine residues by inhibiting histone deacetylases and stimulating gene transcription from chromatin (Latham et al., 2012). We have also discovered that lactic acid was increased in KCs and psoriatic lesional skin by several inflammatory cytokines and then promoted H3K27ac in KCs and induced KCs more robustly in response to different secondary stimuli (unpublished data), suggesting that KCs can gain its inflammatory memory through histone acetylation. However, further investigations are required for determining whether KCs and fibroblasts, other skin structural cells, can gain inflammatory memory through histone acetylation or other histone modifications. Moreover, whether KCs or fibroblasts with inflammatory memory would participate in psoriasis relapse warrant further investigation.

PERSPECTIVES

The appreciation and recognition of the importance of inflammatory circuits in psoriasis pathogenesis lead to the development of multiple biologics successfully used in the treatment of psoriasis. Although these biologics have revolutionized the clinical management of psoriasis, psoriasis relapse after withdrawal of biologic treatment is still a conundrum. The importance of skin epidermal $CD8^+$ T_{RM} cells in psoriasis relapse has long been appreciated; the recent discovery of basal KCs with inflammatory memory also advances our understanding of the underpinnings of psoriasis relapse. However, whether these findings will ultimately lead to eradicating psoriasis relapse is completely unknown because the following questions still remain mysterious. How are $CD8^+$ T_{RM} cells in resolved psoriatic skin activated to reinitiate inflammation? Will KCs with inflammatory memory be involved in regulating the function of $CD8^+$ T_{RM} cells in psoriasis? How could the potentially nonspecific functions of metabolites have locus- and/or gene-specific effects on memory domains in KCs with stemness? How should psoriasis relapse be controlled by manipulating $CD8^+$ T_{RM} cells and KCs with inflammatory memory? Could the future therapeutic strategy aim to block specific metabolic pathways such as glycolysis in KCs or combine metabolic inhibition with biologic treatment? To address these questions, more efforts are required for a better understanding of the signaling pathways that allow long-term survival of T_{RM} cells and deciphering the intrinsic cellular and molecular mechanisms by which KCs gain inflammatory memory in psoriasis. Moreover, a mouse or rodent model that can exactly resemble human psoriasis relapse is required owing to heterogenic differences between human and mouse. To this end, we hope that the aforementioned investigations will ultimately lead to novel therapies capable of either eradicating $CD8^+$ T_{RM} cells or turning off the capacity of memory KCs in response to stress, thus inducing long-term remissions in psoriasis.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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