From Empirical to Pathogenesis-Based Treatments for Psoriasis

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Since the foundation of the European Society for Dermatological Research, pathogenesis of psoriasis has been studied by many research groups, focusing on various compartments of the skin. Understanding of the pathogenesis of psoriasis has evolved into a branching model of innate and acquired immunity. Insights in the genetics of psoriasis proved to be compatible with this model. Inspired by these insights, pathogenesis-based treatments have emerged with unprecedented efficacy and sustainability. In particular, the cytokine network harbors major treatment targets for biologics with TNF-α, the IL-17 family, IL-23 and, in the case of generalized pustular psoriasis, IL-36. Furthermore, the Jak TYK2, PDE-4, and AHR are targets for new small molecules in the treatment of psoriasis. Psoriasis research is a showcase par excellence of translational medicine, resulting in pathogenesis-based treatments.

Journal of Investigative Dermatology (2022) 142, 1778–1785; doi:10.1016/j.jid.2022.01.014

Editor’s Note

This Review is part of a series of articles invited from lectures presented at the 2021 Meeting of the European Society for Dermatological Research, in celebration of its 50th Anniversary.

INTRODUCTION TO THE HISTORY OF DRUG DISCOVERY IN PSORIASIS

Psoriasis is an inflammatory disease involving the skin, joints, cardiovascular system, and CNS. Psoriasis of the skin is characterized by erythema, induration and scaling, reflecting inflammation, epidermal hyperproliferation, and abnormal epidermal differentiation. Genetic factors predispose for psoriasis, and triggering factors may aggravate the disease.

The European Society of Dermatological Research (ESDR) celebrated its 50th anniversary during the annual meeting on 23–25 September 2021. In this review, we will overview 50 years of research on the pathogenesis of psoriasis. During the first 25 years of the ESDR, research groups focused on various fields of interest: epidermal growth and differentiation, inflammation, and immune mechanisms. The evidence in favor of immunopathogenesis and a central role for the T cells have been accumulating during these years. Subsequently, during the next 25 years, immunopathogenesis has been the unifying principle in the research and treatment development of psoriasis.

The innovations in psoriasis are a showcase for translational medicine: the transition from empirical innovations to drug discovery on the basis of insights into the pathogenesis of the disease.

PSORIASIS, A T CELL DRIVEN DISEASE

Several observations have convinced researchers that T cells are crucial in the pathogenesis of psoriasis. The first observation is that T cells accumulate in early psoriatic lesions (Braun-Falco and Christophers, 1974). Furthermore, clusters of activated HLA-DR+ immunocompetent cells have been observed in the psoriatic lesion, suggesting an ongoing immune response (Baker et al., 1984; de Boer et al., 1994). HLA-DR molecules are present on keratinocytes (KCs), suggesting that KCs may activate T cells (Gottlieb et al., 1986).

Further support for the hypothesis that psoriasis is a T-cell driven disease is the increased numbers and activation of non-Langerhans antigen-presenting cells (APCs) in the psoriatic lesion (Baadsgaard et al., 1989) and the expression of ICAM-1 and interferon-gamma inducible protein-10 on KCs (Gottlieb, 1990). Finally, injection of CD4 cells into pre-psoriatic skin engrafted onto severe combined immunodeficiency (SCID) mice induces psoriasis (Nickoloff and Wrona-Smith, 1999).

The potent efficacy of ciclosporin in psoriasis (Ellis et al., 1986; Griffiths et al., 1986) has lent important support for the actual relevance of targeting T cells as pathogenesis-based treatment of psoriasis. Ciclosporin binds to cyclophilin and inhibits calcineurin, resulting in inhibition of NFAT transcription factor for the IL2 gene in T cells. The efficacy of blockade of activated T cells by IL-2 conjugated to diphtheria toxin fragments in psoriasis shows that specific inhibition of this pathway improves psoriasis (Gottlieb et al., 1995), which is compelling evidence for the relevance of this pathway to the pathogenesis of psoriasis. Furthermore, the antipsoriatic efficacy of anti-CD4 and CTLA-4–Ig (Abrams et al., 2000; Nicolas et al., 1991) provide robust evidence for T-cell targeting as a pathogenesis-based treatment principle.
EPIDERMAL CHALLENGES STIMULATE DENDRITIC CELLS, RESULTING IN ACTIVATION OF T HELPER 1 AND 17 CELLS

An injury or friction of the skin may trigger a psoriatic lesion. Virus or autologous DNA binds to the cathelicidin-derived antimicrobial peptide LL-37 (Lande et al., 2007). LL-37 was shown to enhance DNA-induced IFN-γ responses in a toll-like receptor (TLR) 7- and TLR8-dependent manner in plasmacytoid dendritic cells (pDCs) (Ganguly et al., 2009; Lande et al., 2007). In clinical practice, IFN-γ is a well-known trigger for psoriasis. The TLR7 agonist imiquimod proved to trigger psoriasis and represents an animal model for psoriasis (van der Fits et al., 2009). IFN-γ stimulates myeloid DCs (mDCs), which release IL-12 and IL-23 upon stimulation (Lowes et al., 2014, 2007). IL-12, in the context of other cytokines, stimulates activation and proliferation of T helper (Th) 1 cells. This pathway will be explored later under activation and trafficking of Th1 cells.

Increased expression of IL-23 has been shown in the psoriatic lesion (Lee et al., 2004). IL-23 induces proliferation and activation of Th17 cells in a concerted action with other cytokines, including TNF-α. TNF-α activates mDCs, which synthesize IL-23. One can conclude from the suppression of IL-23 signaling by the TNF-α inhibitor etanercept that TNF-α signaling is relevant to the IL-23/IL-17 cascade (Zaba et al., 2009, 2007). Ustekinumab, targeted against the p40 chain, which IL-12 and IL-23 have in common, is a biologic with a well-appreciated efficacy in psoriasis. Biologics that selectively target the p19 chain of IL-23 have an even higher clinical efficacy.

After stimulation by LL-37–DNA complexes, DCs from psoriatic plaques are potent stimulators of T-cell proliferation. The important role of DCs in the pathogenesis of psoriasis and the efficacy of anti–IL-23 treatments converge to the conclusion that IL-23 is a master cytokine in psoriasis and a relevant therapeutic target.

IL-17–AND IL-22–Producing CELLS

Th17 cells differentiate from naive CD4 cells in a milieu of IL-6 and TGFβ with IL-23 as a critical stimulator (Morishima et al., 2009). Th17 cells release IL-17A, IL-17F, and IL-22 on stimulation (Liang et al., 2006). In addition to Th17 cells, IL-17–producing CD8 cells (Tc17) have been shown in the psoriatic epidermis (Ortega et al., 2009). After successful treatment, IL-17–producing T-cell clones are still present in the apparently symptomless psoriatic skin, which suggests that these cells belong to the most persistent T cells of the psoriatic lesion (Matos et al., 2017). Th22 cells also differentiate from naive CD4 cells, and these cells are stimulated by IL-23, TNF-α, and IL-6 to release IL-22 (Fujita, 2013). Th22 cells release IL-22 on activation.

In addition to the Th/Tc17 lineage, several other cell types may produce IL-17:

1. Regulatory T cells (Tregs) may differentiate to IL-17–producing cells. In the psoriatic lesion, IL-17+ CD4+CD25highFoxP3+ Tregs have been identified (Bovenschen et al., 2011).

2. Innate lymphocytes, NK cells, and NKT cells have been shown to produce IL-17 (Coquet et al., 2008; Polese et al., 2020; Villanova et al., 2014).

3. Neutrophils have been shown to contain IL-17, although transcription of IL17 by these cells has not been shown convincingly (Keijser et al., 2014; Lin et al., 2011).

IL-17 is a crucial cytokine in psoriasis (Krueger et al., 2012; Lowes et al., 2008, 2007). IL-17 can be produced by several immunocytes in psoriasis. Both IL-17A and IL-17-F are considered to be relevant in psoriasis. The robust efficacy of anti–IL-17 treatments confirms the relevance of this pathway to psoriasis and psoriatic treatment. IL-22 is produced by Th17 and Th22 cells. In contrast to anti–IL-17 treatments, anti–IL-22 treatment was not successful in psoriasis but was effective in atopic dermatitis (Guttman-Yassky et al., 2018).

HOW KCs ARE AFFECTED BY T CELLS AND CYTOKINES

Activated T cells affect KCs in various ways. Lesion-derived T-cell clones can induce growth of KCs in culture; IFN-γ, although a growth inhibitor on its own, acts cooperatively with other T-cell cytokines to cause KC growth induction (Bata-Csorgo et al., 1995). It is intriguing that IFN-γ is not a treatment target in psoriasis.

T-cell–derived cytokines, including IL-17 and IL-22, activate KCs to produce host defense proteins, cytokines, and chemokines. IL-17 and IFN-γ synergize in the enhancement of proinflammatory cytokine production by human KCs (Teunissen et al., 1998), in particular CXC, CXCL, and CCL20 chemokines, which enhances tracking of neutrophils, T cells, and DCs (Harper et al., 2009). IL-22 upregulates the expression of host defense proteins in KCs, downregulates the expression of at least seven genes associated with differentiation of KCs, and induces epidermal hyperproliferation (Boniface et al., 2005; Wolk et al., 2004).

IL-6 is expressed in high levels in the psoriatic lesion. It is a pleiotropic proinflammatory cytokine that is produced by a variety of cells such as fibroblasts, macrophages, endothelial cells, and KCs in response to a variety of stimuli, which include other cytokines such as IL-1, TNF-α, and PDGF (Grossman et al., 1989). IL-6 stimulates the proliferation of human KCs. Anti–IL-6 therapies, which are effective for rheumatoid arthritis, are either ineffective for psoriasis or can induce new-onset psoriasis-like disease (Fritz et al., 2017).

KCs in allergic contact dermatitis and in psoriasis have been shown to express both TNF-α and IL-17 receptors (Albanesi et al., 1999; Boniface et al., 2007). The synergism of TNF-α and IL-17 signaling has been studied by Chiricuzzi et al. (2011). This synergism revealed a much larger set of significant disease-signature genes in the psoriatic transcriptome than that in TNF-α and IL-17 in isolation.

In the psoriatic lesion, IL-17A, IL-17F, IL-22, TNF-α, IFN-γ, and IL-6 are integrated into a cytokine network. These cytokines induce epidermal proliferation, premature keratinization, expression of host defense proteins, and chemokines.

TRAFFICKING AND ACTIVATION OF TH1 CELLS

As explained earlier, activation and proliferation of Th1 cells result from IL-12—producing mDCs, which have been stimulated by an epidermal challenge. Injection of CD4 cells into
prepsoriatic skin engrafted onto SCID mice induces psoriasis (Nickoloff and Wrone-Smith, 1999). Injection of these cells seems to be essential in the elicitation of early psoriasis. These accumulations of CD4 cells in the dermis are followed by CD8 cell activation and recruitment, accumulating in the epidermis. The Th1 cells are likely to participate in an earlier stage of psoriasis pathogenesis by inducing CCL20 and IL-23 production in mDCs, thus playing a role upstream of the proinflammatory cascade controlled by the IL-23/IL-17 axis (Diani et al., 2016).

The uncommitted T cell may differentiate into a Th1 cell in a milieu of IL-12 and IL-18 or into a Th2 cell in a milieu of IL-4. Th1 cells release Th1 cytokines such as TNF-α, INF-γ, and IL-2. Th2 cells release Th2 cytokines such as IL-4, IL-5, IL-10, and IL-13. Psoriasis is a disease with Th1 cytokine dominance (Austin et al., 1999; Schlaak et al., 1994). In addition to the Th1 cell dominance, cytotoxic T-cell dominance has been observed as well by Austin et al. (1999). In contrast, atopic dermatitis is a disease with Th2 cytokine dominance. Studies on T-cell populations in biopsies taken from psoriatic lesions and atopic dermatitis lesions in the same patient revealed distinct T-cell infiltrates compatible with the Th1/Th2 paradigm (Eyerich et al., 2011). Th1 cytokines dominance implies a strong cell-mediated immunity, whereas Th2 cell dominance is associated with attenuated cell-mediated immunity. This explains why bacterial infections of the skin are seldom seen in patients with psoriasis and are frequent in patients with atopic dermatitis. Although psoriasis and atopic dermatitis were supposed to be mutually exclusive (Christophers and Henseler, 1987), atopic dermatitis and psoriasis may present in the same individual, both simultaneously and consecutively, and coexistence of disease may occur at a level equal to or lower than expected (Cunliffe et al., 2021).

The relevance of Th1 cells to the pathogenesis of psoriasis has been confirmed by the efficacy of anti–IL-2 blockade of activated T cells by IL-2 conjugated to diphtheria toxin fragments in the treatment of psoriasis (Gottlieb et al., 1995). However, later studies showed that IL-2 can be produced by CD8+ cells as well.

Anti–TNF-α molecules have revolutionized the treatment of psoriasis between 2000 and 2010, resulting in a long-term improvement of psoriasis in at least half of the patients. As a result, the number of hospital beds for psoriasis was substantially reduced in Europe. Although originally anti–TNF-α was considered to be a treatment targeted at Th1 cells, TNF-α signaling is involved in various components of the pathogenesis of psoriasis, and anti–TNF-α is by no means a treatment targeted specifically against Th1 cells (Gottlieb et al., 2005). Cytokine, GF, and chemokine production by lymphocytes, neutrophils, DCS, and KCs are all affected by TNF-α. TNF-α activates mDCs that synthesize IL-23 and other regulators of T-cell development (Zaba et al., 2009, 2007). The TNF-α inhibitor etanercept has been shown to suppress the IL-23/IL-17 axis (Zaba et al., 2009, 2007).

On the basis of the Th1/Th2 paradigm, IL-10 treatment has been investigated and a significant but modest clinical improvement has been shown in patients with psoriasis (Asadullah et al., 2000). It remains intriguing that IFN-γ, a Th1 cytokine, is not a target for antipsoriatic treatments.

Th1 cells and not Th2 cells contribute to the pathogenesis of psoriasis. Immunodeviation from Th1 to Th2 dominance proved to be a therapeutic principle for psoriasis.

T-CELL TRAFFICKING INTO THE EPIDERMIS IS MANDATORY FOR THE PSORIATIC LESION

Activated T cells invading the epidermis of patients with psoriasis express heterodimeric integrin α1β1, the receptor for collagen I, which is a component of the basement membrane. Blocking α1β1, using a neutralizing mAb, prevented both the accumulation of epidermal T cells and the development of psoriatic lesions in a xenotransplantation mouse model (Conrad et al., 2007). These studies strongly suggest that interaction between T cells and KCs is required for the development of the disease. New strategies in psoriasis treatment focusing on T-cell–extracellular matrix interactions seem to be promising. T cells residing in the epidermis have a highly relevant role in the pathogenesis of psoriasis.

In particular, in the chronic psoriatic lesion and during the resolution of the psoriatic lesion, intraepidermal entry and activation of CD8 cells have been observed (Baker et al., 1984). When peripheral blood–derived mixtures of CD4/CD8 cells are injected into symptomless psoriatic skin engrafted onto SCID mice, psoriatic lesional skin is characterized by preferential migration of CD8 cells into the hyperplastic epidermis (Wrone-Smith and Nickoloff, 1996). In the epidermis of the psoriatic plaque, CD8 cells prevail, whereas CD4 cells are the predominant cells in the dermis. Psoriatic epidermis exhibits a pronounced CD8 cell epidermotropism with accompanying epidermal hyperproliferation and abnormal keratinization, and the changes are only minimally expressed in atopic dermatitis and lichen planus (Bovenschen et al., 2005).

Epidermal T cells are highly activated in psoriasis, and a high proportion of CD8 cells belong to the tissue-resident memory T (TRM) cells. CD8+ TRM cells have been ascribed a role in immunity after resolved viral skin infections, and these cells may express TRM markers, including CD69, CD103, and CD49a. CD8+CD49a+ TRM cells produce IFN-γ, and CD8+CD49a− TRM cells produce IL-17. Selective retention of CD8+ TRM cells in resolved psoriatic lesions explains why psoriatic lesions often recur at the same sites. TRM cells are a potential biomarker for residual disease activity versus deep remission (Cheuk et al., 2014; Benezeder and Wolf, 2019).

Intraepidermal accumulation of CD8 cells is mandatory for the development of the psoriatic lesion. In particular, the CD8+ TRM cells persist after clinical resolution of the lesion and may be a biomarker to differentiate between partial versus deep remission.

AUTOANTIGEN PRESENTATION AND COSTIMULATORY PATHWAYS

Not an epidermal challenge but the presentation of auto-antigens may initiate and maintain the psoriatic lesions. In antigen presentation, the primary interaction is between the major histocompatibility complex (MHC) of DCs and TCRs.
DCs and T cells interact in an antigen-specific manner. In addition, other cells of the epidermis, including KC and melanocyte may interact with CD8 cells through MHC class I–TCR binding. The oligoclonal T-cell expansion in psoriasis, analyzing TCR usage on the infiltrated T cells, provides clear evidence in favor of an antigen-specific T-cell response in the psoriatic lesion (Chang et al., 1994; Menssen et al., 1995).

The following candidate epidermal autoantigens have been proposed:

1. KC proteins with similarity to streptococcal antigens (Besgen et al., 2010; Valdimarsson et al., 2009);
2. lipid antigens generated by PA24D: PA24D generated lipid antigen activates CD1a Langerhans cells, and these bind to CD1a-reactive T cells, which generate IL-17 and IL-22 (Cheung et al., 2016);
3. melanocyte autoantigen ADAMTS5 (Prinz, 2017): through MHC class I, melanocytes bind to the TCR of CD8 cells, and On activation, these T cells release IL-17; and
4. host defense protein IL-37 (Fuentes-Duculan et al., 2017; Lande et al., 2014): IL-37–specific T cells belong to both CD4 and CD8 cells, resulting in Th1 and Th17 secretion ability.

The interaction between TCR and MHC may be a future target for drug development. CD4 and CD8 molecules bind to the MHC molecule, stabilizing the TCR–MHC interaction. It has been shown that anti-CD4 treatments have therapeutic efficacy in psoriasis (Nicolas et al., 1991). Because the majority of T cells in the epidermis are CD8 cells, therapeutic approaches to reduce CD8 cells seem promising.

Furthermore, so-called costimulatory pathways are critically required for the process of T-cell activation, comprising antigen-dependent and antigen-independent T-cell activation. Costimulatory pathways have been identified to be relevant to psoriasis because selective inhibitors proved to improve psoriasis clinically:

1. Alefacept inhibits the activation of memory effector T cells (CD45RO T cells) by blocking the costimulatory interaction between LFA-3 and CD2 (Krueger, 2002). LFA-3 is localized on APCs and CD2 on memory effector T cells. CD2–LFA-3 interaction may activate T cells in the absence of TCR triggering. Another mechanism of alefacept in the treatment of psoriasis is inducing apoptosis of memory effector T lymphocytes and depletion of CD2 cells by binding to NK cells through its Fc region. Alefacept has been registered by Food and Drug Administration but not by European Medicines Agency.
2. Efalizumab is an IgG1 antibody against the CD11a subunit of LFA-1 and blocks LFA-1/ICAM-1 interaction (Leonardi, 2004). Efalizumab reversibly blocks LFA-1/ICAM-1 interaction, resulting in reduced T-cell activation and impaired T-cell trafficking. Efalizumab was withdrawn from the market because of reported cases of progressive multifocal leukoencephalopathy in patients on efalizumab treatment.

Autoantigens may be initiators of psoriasis. The interaction between APCs and T cells represent treatment targets.

PSORIASIS, A DISEASE OF BRANCHING INNATE AND ACQUIRED IMMUNITY

The various components of the immunopathogenesis provide an integrated system of innate and acquired immunity. In Figure 1, the segments of research on the pathogenesis of psoriasis have been integrated. After an epidermal challenge, stimulation of DCs results in IL-12 and IL-23 release, which activate Th/Tc1 and Th/Tc17 cells. Autoantigens may be presented to T cells, also resulting in IL-17 release. IL-17, in concerted action with other cytokines, including TNF-α, IFN-γ, IL-22, IL-2, and IL-6, induces epidermal proliferation and parakeratosis and releases host defense proteins and chemokines, which induce accumulation of neutrophils, T cells, macrophages, and DCs. Persistence and disease memory of psoriasis is mediated by CD8⁺ Tc17 cells.

In individual patients, some segments of the pathogenesis may be more dominant than others, which may explain the heterogeneity of psoriasis when comparing individual patients.

PSORIASIS SUSCEPTIBILITY GENES ARE ASSOCIATED WITH IMMUNE MECHANISMS IN PSORIASIS

Psoriasis is a polygenic disease. More than 80 psoriasis risk loci have been reported (Zhu et al., 2021). Several of these genes are associated with the biological mechanisms as explained earlier. Some susceptibility genes are associated with antigen presentation, IL-23/IL-17 axis, type 1 IFN signaling, NF-κB signaling, and skin barrier (Dand et al., 2020). Outcomes of studies on the genetics of psoriasis are entirely compatible with a key role of the aforementioned signaling pathways. At present, research on the genetics of psoriasis has identified far more genes, which will be reported in future publications.

PATHOGENESIS-BASED BIOLOGICS AND SMALL MOLECULES

The biologics, which are available for the treatment of psoriasis, have been listed in Box 1.

Long-term effective and safe control of psoriasis can be achieved with the available biologics. Anti-TNF treatments are realizing a 75% improvement of PASI in the majority of patients and antibodies against the IL-17 family, and anti–IL-23 biologics are permitting a 100% improvement of disease severity in about half of the patients, illustrating the relevance of the IL-23/IL-17 signaling in psoriasis. The efficacy of biologics has been compared and contrasted in network meta-analyses (Armstrong et al., 2020).

In addition to the revolutionary development of new biologics in psoriasis, several small molecules are in various stages of development (Box 2):

1. The gene for the Jak TYK2 proved to be a susceptibility gene for psoriasis (Dand et al., 2017). This Jak is associated with IFN-α, IL-12, and IL-23 signaling. Deucravacitinib, a TYK2 inhibitor, proved to be effective in psoriasis; PASI 90 was reached by 44% of the patients (Papp et al., 2018).
2. PDE-4 inhibits the breakdown of the second messenger cAMP in immunocytes, resulting in protein kinase A activation, resulting in activation of NF-κB and inhibition of CRE-binding protein and ATF-1. This modulation of transcription factors results in a dominance of IFN-γ, IL-12, IL-17, IL-22, and IL-23 in comparison to IL-6 and IL-10. PDE-4 inhibitors restore this distorted balance: apremilast is available as a systemic treatment (Forchhammer and Ghoreschi, 2015; Papp et al., 2015) and roflumilast is in development as a topical treatment (Lebwohl et al., 2020).

3. The AHR is activated by several exogenous ligands such as polycyclic aromatic hydrocarbons and digoxin-like

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Figure 1. An integrated concept of innate and acquired immunity. After an epidermal challenge, self-DNA is complexed with the host defense protein LL-37. LL-37 was shown to enhance DNA-induced IFN-α responses in a TLR7- and TLR8-dependent manner in pDCs. As a result, mDCs are activated, and this activation is reinforced by an autocrine TNF-α loop. mDCs migrate to lymph nodules and release IL-12 and IL-23, which promote the differentiation and proliferation of Th1, Th17, and Th22 cells from naive T cells. These T cells migrate to the skin and remain stimulated by mDCs. Th1 cells release IL-2, TNF-α, and IFN-γ; Th17 cells release IL-17A, IL-17F, IL-22, and TNF-α; and Th22 cells IL-22. Autoantigens may be presented to T cells. The melanocyte autoantigen ADAMTS5 binds to TCR of CD8 cells through MHC class I. On activation, these T cells release IL-17. PLA2G4AAg activates CD1α Langerhans cells, and these bind to CD1α-reactive T cells, which generate IL-17 and IL-22. IL-17A and IL-17F, in concerted action with other cytokines, including TNF-α, IFN-γ, IL-22, and IL-2, induce epidermal proliferation and parakeratosis and release host defense proteins and chemokines, which results in accumulation of neutrophils, T cells, macrophages, and dendritic cells in the established lesion. Several of these inflammatory cells such as neutrophils contribute to IL-17 production. Epidermal cells release IL-37, which activates IL-8, IL-8 is a potent chemottractant for neutrophils. Enhanced IL-36 signaling is a crucial pathway in pustular psoriasis. The established psoriatic lesion continues to release self-DNA which binds LL-37 and again stimulates the pDCs. The cytokine IL-36, released by the epidermis of the psoriatic lesion, also activates pDCs. The pathogenesis of psoriasis is an activation loop. In the chronic lesion, CD8 cells prevail and may differentiate to CD8+ TRM cells, which mediate persistence and disease memory of psoriasis. MHC, major histocompatibility complex; mDC, myeloid dendritic cell; pDC, plasmacytoid dendritic cell; T1, type 1 T cell, T17, type 17 T cell; T22, type 22 T cell; TLR, toll-like receptor; T<sub>RM</sub>, tissue-resident memory T cells. Illustration assistance provided by Heather McDonald, BioSerendipity, LLC, Elkridge, MD.
comparable. There is evidence that crude coal tar therapy may show some efficacy by activation of the AHR. AHR is a transcription factor, which is translocated into the nucleus. Subsequently, gene transcription is modulated, comprising downmodulation of cytokines including those relevant to psoriasis and atopic dermatitis, an antioxidant response, and finally improved barrier formation by FLG upregulation (Bissonnette et al., 2021; Di Meglio et al., 2014). Tapinarof is an AHR agonist and as topical therapy proved to result in a 75% improvement of PASI in 36–47% of the patients (Robbins et al., 2019).

Box 1. Biologics for the Treatment of Psoriasis

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<th>Anti-TNF-α:</th>
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<tr>
<td>Etanercept</td>
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<td>Ixekizumab</td>
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<td>Anti-IL-17A/F</td>
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<td>Bimekizumab</td>
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<tr>
<td>Anti-IL-17 receptor</td>
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<tr>
<td>Brodalumab</td>
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<tr>
<td>Anti-IL-12/23 (p40 chain)</td>
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<td>Ustekinumab</td>
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<td>Anti-IL-23p19 chain</td>
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<td>Risankizumab</td>
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<td>Guselkumab</td>
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| 1Approved by European Medicines Agency and not yet by Food and Drug Administration.

Box 2. Small Molecules for the Treatment of Psoriasis

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<th>Phosphodiesterase inhibitors</th>
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<td>Apremilast systemic</td>
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<td>Roflumilast topical</td>
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<tr>
<td>TYK2 inhibitors</td>
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<tr>
<td>Deucravacitinib systemic</td>
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<td>PF-06826647 systemic</td>
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<td>Brepocitinib systemic</td>
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<td>Aryl hydrocarbon receptor agonist</td>
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<td>Tapinarof</td>
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CONCLUSION

During the previous 50 years, our insights in the immuno-pathogenesis of psoriasis have been evolved into a branching model of innate and acquired immunity. Insights into the genetics of psoriasis have revealed a constellation of susceptibility loci, entirely congruent to this model. Inspired by these insights, pathogenesis-based treatments have emerged with unprecedented efficacy and sustainability, reconfirming that these steps in pathogenesis are relevant to the disease. Psoriasis research and development are a showcase par excellence of translational medicine.

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Disclaimer

The contents of this review have been presented at the virtual meeting of the European Society for Dermatological Research 2021.

CONFLICT OF INTEREST

PCMvdK received fees for consultancy service or lectureships from Almirall, AbbVie, Eli Lilly, Novartis, Janssen Pharmaceuticals, Leo Pharma, Bristol Mayer Squibb, UCB, Boehringer Ingelheim, and Dermavant Sciences. PCMvdK is a chief medical officer at International Psoriasis Council.

ACKNOWLEDGMENTS

The author wishes to acknowledge Rogier Trompert Medical Arts for providing the license to publish Figure 1 in the Journal of Investigative Dermatology.

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