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New Frontiers in Psoriatic Disease Research, Part I: Genetics, Environmental Triggers, Immunology, Pathophysiology, and Precision Medicine

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Abstract

Psoriasis is a chronic inflammatory condition characterized by systemic immune dysregulation. Over the past several years, advances in genetics, microbiology, immunology, and mouse models have revealed the complex interplay between the heritable and microenvironmental factors that drive the development of psoriatic inflammation. In the first of this two-part review series, the authors will discuss the newest insights into the pathogenesis of psoriatic disease and highlight how the evolution of these scientific fields has paved the way for a more personalized approach to psoriatic disease treatment.

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Introduction

Psoriasis is a chronic, inflammatory disease affecting an estimated 3 percent of the U.S. population (Rachakonda et al., 2014). In its skin manifestation, psoriasis most commonly presents with plaques as psoriasis vulgaris (PsV), but also includes rarer subtypes such as guttate, pustular, erythrodermic, and inverse psoriasis. Approximately 30 percent of patients with psoriasis have psoriatic arthritis (PsA) (Mease et al., 2013), which can manifest as synovitis, enthesitis, dactylitis, and spondylitis. Due to the overlap between the skin manifestation of psoriasis, PsA, and other comorbidities associated with the systemic inflammation from this immune-mediated disease state, some researchers, providers, and patients, as well as the National Institutes of Health, consider these conditions to be part of a spectrum of psoriatic disease. It has only been in the last few decades that researchers have truly begun to unravel the pathogenesis of psoriasis and PsA. Since then, this research has evolved rapidly.

While the mechanism of psoriasis is now understood to involve IL-23/IL-17 signaling, there is increasing recognition that psoriasis is driven by a complex interplay between numerous other intrinsic and extrinsic factors. Recent innovations in next generation sequencing and single cell profiling coupled with increases in computing power have enabled a multi-omics approach to understand the genetic landscape of psoriasis, tissue-specific immune micro-environments, and host-microbiome interactions. These data provide a more nuanced understanding of psoriasis and PsA, revealing novel pathways and mechanisms that contribute to the development of PsA, particular psoriatic disease subtypes, and characteristic patterns of inflammation.

In the first of this two-part review series, the authors highlight the latest developments in genetics, environmental triggers, and immunology of psoriasis and PsA, novel insights from mouse models, and how these new developments have enabled more personalized treatment for psoriatic disease.

The genetics of psoriasis and psoriatic arthritis

Genetic architecture of psoriasis

Genetic susceptibility to PsV is polygenic, according to the sum of multiple genetic risk factors. To date, genome-wide association studies (GWAS) have identified over 63 genetic risk loci, which account for 28% of PsV heritability (Tsoi et al., 2017) while broader genome-wide heritability for PsV is estimated at 50% (Li et al., 2020). There is significant genetic concordance between ethnic groups, but eleven risk loci differ in Han Chinese and Caucasian populations (Yin et al., 2015). GWAS have revealed valuable insights into disease pathogenesis (Table 1). Of particular importance are genes associated with antigen presentation, such as MHC class I: *HLA-C*06:02*, *HLA-C*12:03, HLA-B*57:01, HLA-B*38:01*, and *HLA-A*02:01*. Coding mutations in *ERAP1* and *ERAP2*, involved in peptide processing, have also been linked to PsV. Genetic risk loci have been identified in the NFκB pathway, which mediates keratinocyte (KC) proliferation and differentiation, production of pro-inflammatory cytokines in Th17 cells, clonal expansion of T cells, and Wnt signaling in osteoblasts (Goldminz et al., 2013, Ma and Hottiger, 2016, Takao et al.,

2003). These include genetic variants in *TRAF3IP2*, *CARD14*, *TNFSF15*, *TNIP1*, *IKBKE, CHUK, REL, NFKBIA*, and non-coding mutations in *TNFAIP3*. Other genetic risk loci, such as *IFIH1, DDX58, KLF4, ZC3H12C, CARD14* and *CARM1* are involved in type I interferon signaling and the innate immune response, while variants in *IL23R, IL12B, IL23A*, and *TYK2* play a role in adaptive (IL-23/IL-17) immunity. PsV genes also include those involved in host defense and maintenance of the skin epithelial barrier, such as beta-defensin and *LCE3B/LCE3C*.

Genetics of psoriatic arthritis and psoriasis subtypes

GWAS of PsA have found significant overlap with PsV (Bowes et al., 2015, Stuart et al., 2015). Surprisingly, only a few genetic variants so far have been identified as being discrepant between PsA and PsV, one of the main ones being HLA-C*06:02, which is a risk factor for PsV but protective for PsA, with other discrepant variants observed near *IL23R*, *TNFAIP3, LCE3A*, and *TNFRSF9* (Stuart et al., 2015). This may indicate a more prominent role for environmental factors in the development of PsA. Notably, mice expressing three distinct targeted mutations of ZF7 ubiquitin-binding motif of the *TNFAIP3* gene, were found to develop distal arthritis through IL-17-mediated NFκB activation (Razani et al., 2020). The genetic differences between psoriasis and PsA are also enriched in regulatory elements for lymphocytes, including $CD8^+$ T cells (Patrick et al., 2018), which are present in the synovial fluid of PsA patients and correlate with disease severity (Menon et al., 2014, Steel et al., 2020). Interestingly, different HLA alleles have been found to be preferentially associated with PsA features such as synovitis, sacroiliitis, dactylitis, and enthesitis (FitzGerald et al., 2015).

Regarding psoriasis subtypes, *HLA-C*06:02* has been found to be highly associated with guttate psoriasis (Gudjonsson et al., 2006). Coding mutations in *IL36RN*, *CARD14, AP1S3, SERPINA3*, and *MPO* that affect IL-1 and IL-36 signaling have been associated with the clinical spectrum of pustular psoriasis (Supplementary Table 1). Psoriasis genetic variants overlap with Crohn's disease (Ellinghaus et al., 2012) and several cardiovascular disease phenotypes (Lu et al., 2013) but share no common genetic features with atopic dermatitis (Baurecht et al., 2015).

Recent discoveries in genetics of psoriasis and psoriatic arthritis

Sequencing data from a large Chinese cohort has revealed a potentially important, unexpected role for small genomic insertions and deletions in psoriasis susceptibility (Zhen et al., 2019). As these variants are not adequately captured in GWAS, additional studies are warranted. Mendelian randomization (Emdin et al., 2017) has allowed researchers to demonstrate that obesity is not only associated with psoriasis, but that obesity is a causal risk factor for psoriasis (Budu-Aggrey et al., 2019, Ogawa et al., 2019). Future studies employing Mendelian randomization are likely to help define the directionality between psoriasis and its comorbidities. Finally, several studies have highlighted the potential powerful role of psoriatic genetics in precision medicine. A meta-analysis demonstrated that *HLA-C*06:02* is associated with favorable response of PsV patients to ustekinumab (van Vugt et al., 2019), while another study demonstrated that lack of *HLA-C*06:02* is associated with better response to adalimumab (Dand et al., 2019). Using a machine learning approach

involving ~200 genetic loci, researchers have developed a model to predict PsA with area under the receiver operator curve of 0.82 (Patrick et al., 2018).

Environmental triggers of psoriasis and psoriatic arthritis

The increased risk of PsV with smoking (Armstrong et al., 2014) may be modulated by interactions with genetic factors such as *HLA-C*06:02* and *CYP1A1* (Jin et al., 2009, Krämer and Esser, 2006). Although smoking is associated with a higher risk of PsA in the general population, amongst patients with psoriasis, there is either a decreased incidence of PsA or no significant relationship (Pezzolo and Naldi, 2019). Unlike smoking, the effects of alcohol consumption on psoriasis incidence is unclear (Brenaut et al., 2013, Dai et al., 2019).

Medications such as beta blockers, lithium, anti-malarials, imiquimod, nonsteroidal anti-inflammatory drugs, interferon-α, and terbinafine have been linked to the induction and exacerbation psoriasis (Balak and Hajdarbegovic, 2017, Kim and Del Rosso, 2010). More recently, paradoxical psoriasis induced by TNF-α inhibitors (Mazloom et al., 2018) has been shown to be associated with increased production of type I interferons by plasmacytoid dendritic cells in a T cell independent fashion (Conrad et al., 2018).

Obesity and diet are modifiable risk factors for psoriasis. Psoriasis patients have a higher prevalence and incidence of obesity (Armstrong et al., 2012). Animal studies have shown that diet-induced obese mice have more severe psoriasiform dermatitis, suggesting that the chronic inflammatory state caused by adipokines in excessive fat tissue could be a pathogenic link between obesity and psoriasis (Kanemaru et al., 2015). A meta-analysis demonstrated that weight loss through dietary intervention in obese individuals improves pre-existing psoriasis and prevents *de novo* psoriasis (Mahil et al., 2019).

However, more recent studies suggest that mechanisms other than obesity may mediate the impact of diet on psoriasis. For example, an increase of saturated fatty acids (SFAs) in healthy, lean mice alone was sufficient to induce an exacerbation of psoriasiform inflammation, and reduction of nutritional saturated fatty acids diminished the psoriatic phenotype in non-obese mice (Herbert et al., 2018). Another study showed that exposure to a high-sugar and moderate-fat Western diet (WD), even in the absence of obesity, was enough to induce skin inflammation in mice in as little as 4 weeks through the recruitment of IL-17A-producing γδ-type T cells (Shi et al., 2020). Interestingly, WD-induced skin inflammation was blocked by systemic antibiotic treatment, suggesting a critical role of gut dysbiosis in diet-induced inflammation. Further studies are warranted to determine if specific diets, in the absence of weight reduction, would bring meaningful clinical improvement in psoriasis and PsA.

Biomechanical stress is another major microenvironmental factor in psoriatic inflammation (Belasco and Wei, 2019). For example, animal models show that hind limb unloading reduced Achilles tendon inflammation (Jacques et al., 2014). Furthermore, mechanical stress induced expression of IL-17A by entheseal T cells at anatomic locations commonly affected by arthritis in mice (Reinhardt et al., 2016). Local biomechanical stress is also thought

to promote differentiation of murine osteoclasts in the joint (Gracey et al., 2020). This is supported by a recent study demonstrating that erosive disease in mice is confined to mechano-sensitive regions and driven by mesenchymal cells that recruit monocytes via CXCL1 and CCL2 prior to differentiation into mature osteoclasts (Cambre et al., 2018). The pathogenic importance of exogenous mechanical loading suggests that rather than inherent genetic predisposition, dynamic interplay between the immune system and microenvironmental factors plays a major role in the development of PsA.

Various infections have been known to trigger or worsen psoriasis. HIV has been linked to a higher prevalence of psoriasis (Ceccarelli et al., 2019), worsening of pre-existing psoriasis, eruptive onset of de novo psoriasis (Duvic et al., 1987), and more recalcitrant disease (Menon et al., 2010), which may be due to an increased $CD8^+$ to $CD4^+$ T cell ratio, HIV viral protein superantigens (Ceccarelli et al., 2019), and a shared genetic architecture of the MHC I region (Chen et al., 2012). Preceding streptococcal pharyngitis (Telfer et al., 1992), possibly through similarities between streptococcal antigens and keratinocyte proteins, may induce cross-reactivity in streptococcal specific T cells leading to activation of psoriasis (Prinz, 2001). Periodontitis has also been associated with psoriasis, with psoriasis patients demonstrating more gingival inflammation, alveolar bone loss, and missing teeth (Qiao et al., 2019), and showing a significant reduction in psoriasis severity following non-surgical periodontitis treatment (Ucan Yarkac et al., 2020).

Emerging research now suggests that interactions between the skin and gut microbiome and the host immune system may play a key pathogenic role in the development of psoriasis and PsA (Supplementary Table 1). Bacteria play crucial roles in host IL-17 mediated mucosal barrier immunity, Th17 cell development, and $ROR\gamma t^+$ Treg immune homeostasis (Zheng et al., 2020). PsV skin is enriched in pro-inflammatory *Streptococcus* and *Staphylococcus*, though not all studies observed this enrichment. Both *Streptococcus* and *Staphylococcus aureus* elicit a strong Th17-type response in skin T effector cells resulting in induction of IL-17A, IL-17F, and IL-22 cytokines in murine models (Okada et al., 2020). Interestingly, murine models of PsA and PsV do not develop inflammatory disease when treated with antibiotics or raised in a germ free environment (Rath et al., 1996, Zákostelská et al., 2016). In addition to increased pro-inflammatory bacteria, there is a reduction in immunomodulatory *Propionibacterium*, a major producer of propionate (Yan et al., 2017), a short chain fatty acid (SCFA) that promotes regulatory T cell homeostasis (Smith et al., 2013).

Similarly, the gut microbiome in PsV has demonstrated a decrease in *Bacteroides* and *F. prausnitzii*, a gut commensal that produces the immunomodulatory SCFA, butyrate (Furusawa et al., 2013). The only study of the gut microbiome in PsA showed decreases in *Akkermansia*, *Ruminococcus*, and *Pseudobutyrivibrio*, which were associated with decreased levels of immunomodulatory medium-chain fatty acids (MCFA) (Scher et al., 2015).

In addition to its role in disease pathogenesis, the microbiome may also be a modulator of therapeutic response. Gut bacteria are not only involved in drug metabolism, but also indirectly influence drug efficacy through effects on host gene expression and interactions

between drugs and bacterial metabolites (Scher et al., 2020). For example, PsV and PsA patients who responded to secukinumab, had a higher abundance of intestinal *Citrobacter*, *Staphylococcus*, and *Hafnia/Obesumbacterium* (Yeh et al., 2019). However, there was no difference in the gut microbiome between responders and non-responders to ustekinumab (Yeh et al., 2019).

Not surprisingly, the microbiome is now a prime target for novel therapeutics. Already, clinical trials are investigating the efficacy of probiotic supplements for the treatment of psoriasis. One double-blinded, placebo-controlled clinical trial did not find any significant clinical improvement in PsV with a probiotic containing *Lactobacillus* (Kaur et al., 2007). However, a different study found that PsV patients who received an oral probiotic cocktail were more likely to achieve PASI-75 at 12 weeks (Navarro-López et al., 2019). Oral supplements of *Bifidobacteria infantis* have also been found to reduce serum levels of TNF-α and C-reactive protein in PsV patients (Groeger et al., 2013). Intriguingly, a recent case report described a patient who developed sustained remission of her PsA after undergoing fecal microbiota transplantation (FMT) for a *Clostridium difficile* infection (Selvanderan et al., 2019). The therapeutic efficacy of FMT in patients with PsA is now under investigation through a double-blind, randomized, placebo-controlled trial (Kragsnaes et al., 2018).

The immunology of psoriasis and psoriatic arthritis

Data from GWAS and other preclinical studies suggest that while certain immunopathogenic mechanisms may be shared, there are likely also tissue specific microenvironmental factors that contribute to the phenotypic heterogeneity of psoriasis and PsA. The IL-23/IL-17 axis is common to the pathogenesis of both cutaneous psoriasis, PsA, and enthesitis (Iwakura and Ishigame, 2006, Sherlock et al., 2012). Binding of IL-23 to the heterodimeric IL-23R/IL-12Rβ1 receptor activates Tyk2 and Jak2 dependent STAT3 signaling, which promotes the expansion of Th/Tc17 cells that secrete IL-17A, IL-17F, and TNF (Hile et al., 2020). Components of innate immunity also facilitate the inflammatory cascade in cutaneous psoriasis and PsA in which plasmacytoid and conventional dendritic cells are activated in the skin (Nestle et al., 2005) and synovial fluid (Penkava et al., 2020), respectively, and produce inflammatory cytokines, including IL-23, to facilitate priming and proliferation of Th/Tc17 cells. Antimicrobial peptides, most notably cathelicidin (LL37), bind to self-DNA and stimulate plasmacytoid dendritic cells via TLR9 or serve as autoantigen presented to T cells by HLA-C*06:02. IL-17A can be also produced by group 3 innate lymphoid cells (ILC3) that are abundant in PsV and PsA (Polese et al., 2020, Soare et al., 2018).

In addition to heightened pro-inflammatory signaling, PsO involves suppression of anti-inflammatory pathways. Both psoriasis and PsA demonstrate decreased numbers of $CD73^+$ T regulatory cells (Tregs) (Han et al., 2018), expansion of dysfunctional $ROR\gamma t^+$ Tregs with Th17 potential (Liu Y. et al., 2020, Scher et al., 2019), and decreased levels of the anti-inflammatory cytokine IL-38 (Mercurio et al., 2018), and reduction in ILC2s (Soare et al., 2018).

Differences in tissue-specific cues result in the activation of unique pathogenic pathways in the skin and synovium. In the skin, IL-17 and IL-22 stimulate keratinocyte hyperplasia

as well as CXCL8-dependent neutrophil recruitment and microabscess formation (Liang et al., 2017). In the joints, local inflammatory cytokines and growth factors promote osteoclast-osteoblast decoupling and RANKL-mediated destructive bone remodeling in PsA (Paine and Ritchlin, 2018). Chronic psoriatic inflammation also upregulates Wnt signaling (*RUNX1*, *FUT8*, and *CTNNAL1*) (Patrick et al., 2019) in osteoblasts of PsA patients. A recent study utilizing an *in vitro* cell culture system to mimic local inflammatory microenvironment of bone-forming sites validated the link between Wnt signaling and inflammation, establishing that constitutive low-intensity stimulation with TNF induces persistent expression of Wnt proteins, causing increased bone formation through NFκB signaling (Li et al., 2018). Furthermore, binding of osteoclast derived RANK to osteoblastic RANKL leads to activation of RUNX2, which mediates bone remodeling and bone formation in RANKL mutant mice (Ikebuchi et al., 2018).

Locally presented antigens are another element of the immune microenvironment that may play a key role in psoriatic inflammation. In PsV, a large proportion of cutaneous $CD8^+$ T cells is oligoclonal, with oligoclonality usually confined to lesional skin. To date, putative autoantigens in psoriasis including LL-37, a disintegrin and metalloprotease domain containing thrombospondin type 1 motif-like 5 (ADAMTSL5)(Fuentes-Duculan et al., 2017, Yuan et al., 2019), keratin 17 (KRT17)(Yunusbaeva et al., 2018), and neolipids generated by phospholipase A2 group IVD (PLA2G4D)(Cheung et al., 2016).

Mouse models of psoriasis and psoriatic arthritis

Preclinical mouse models are a valuable tool for investigating the pathogenic role of pathways, genes, or transcripts identified in genetic analyses and other studies. These approaches model one or more components of human psoriasis, but none to date replicate the disease in its full complexity. Mouse models of psoriasis can be broadly classified as spontaneous, xenotransplants, induced/acute, and genetically engineered (reviewed in (Gudjonsson et al., 2007, Schon et al., 2020). The first models of psoriasis involved spontaneous gene mutations in *Scd, Sharpin* ,or *Ttc* resulting in a “flakey skin” phenotype (Gates and Karasek, 1965, HogenEsch et al., 1993, Sundberg et al., 1994). However, the use of these models was limited as they lacked T cell infiltration.

Other early approaches used grafts of uninvolved skin from psoriasis patients onto immunodeficient mice (athymic nude, AGR), which triggered conversion into a psoriatic plaque (Boyman et al., 2004, Fraki et al., 1982, Krueger et al., 1981). Xenografts and *ex vivo* psoriasis skin explants (Billi et al., 2020, Ward et al., 2015) are the most translatable approach for studying treatment efficacy and the role of skin resident versus circulating immune cells. However, they are challenging to develop, require full-thickness patient skin, and some require autologous activated T cells (Nickoloff and Wrone-Smith, 1999).

The most widely used model involves topical application of imiquimod (IMQ) a TLR7 agonist. Since 2009 (van der Fits et al., 2009), over 600 publications have used this approach and interpreted their findings, often incorrectly, as critical for psoriasis pathogenesis (Hawkes et al., 2017). However, non-lesional skin from PsV patients treated with IMQ has

different transcriptomic signatures compared to lesional skin, suggesting that IMQ models recapitulate only limited aspects of psoriasis (Vinter et al., 2015).

Investigators have also studied the effects of cytokines through intradermal injections of IL-17C (Ramirez-Carrozzi et al., 2011), IL-17A (Vasseur et al., 2016), IL-36 (Foster et al., 2014), IL-21 (Caruso et al., 2009), IL-23 (Chan et al., 2006) either alone or in combination (Guilloteau et al., 2010). These models reproduce some features of psoriasis and provide insight into the pathogenic role of individual cytokines and their synergistic effects. However, the need for repeated injections limits their utility for long-term study. The development of novel DNA minicircles allowing for sustained transgenic expression of IL-23 (Sherlock et al., 2012) reproduces chronic psoriasiform skin inflammation, enthesitis, arthritis, and vascular inflammation in mice, providing an innovative model for studying psoriatic comorbidities.

Recently, advances in genetic engineering have led to the development of transgenic and knockout animal models, which have provided novel insights into psoriasis. For example, the CD18 hypomorphic model (*CD18*^{hypo} PL/J background; CD18*(Itgb2*^{tm1Bay})) helped define the role of skin-infiltrating T cells (Bullard et al., 1996) and TNF-α-producing macrophages (Wang et al., 2009).

The growing interest in keratinocytes and their derived factors resulted in an influx of KC-specific transgenic models: VEGF-A (Kunstfeld et al., 2004, Xia et al., 2003), TGF-β1 (Li et al., 2004), IL-17C (Johnston et al., 2013), ectopic Tie2 (Wolfram et al., 2009) and IL-17A (Karbach et al., 2014) all resulted in flakey skin phenotypes. The Tie2, IL-17A and IL-17C models also developed cardiovascular disease (CVD), including vascular inflammation (Karbach et al., 2014, Schuler et al., 2019, Wang et al., 2009) and thrombosis (Golden et al., 2015, Wang et al., 2016), which are also seen in psoriasis patients (Gelfand et al., 2006). These models will be helpful in identifying the cellular mechanisms underlying CVD comorbidities.

The newest murine model of psoriasis overexpresses a serine protease, called kallikrein 6 (KLK6). *Klk6* mice (*Klk6*+) develop severe psoriasiform dermatitis and arthritis that are *Klk6*- and protease-activated receptor 1- (PAR1; *F2R*) dependent (Billi et al., 2020). Other models develop PsA-like disease, including KC-overexpression of constitutively active *Stat3c* (Yamamoto et al., 2015), *RAC1* (Winge and Marinkovich, 2019), and *Il17a* (Croxford et al., 2014) and KC-deletion of *JunB/c-Jun* (Uluckan et al., 2016, Zenz et al., 2005). These models demonstrate how epidermal factors can cause arthritis.

Precision medicine

While major advances in the treatment of psoriasis have been made over the last few decades, many patients are treatment refractory, especially those with PsA (Ritchlin and Scher, 2019), and achieving long term remission remains a significant challenge. Precision medicine can be used to address these gaps in care, by tailoring treatment based on individual patient characteristics.

Clinical features, serologic factors, and “omics” datasets can help us classify patients into subpopulations based on their likelihood to respond to a specific therapy or their probability of developing systemic comorbidities (van Vugt et al., 2018). For example, patients with nail and scalp involvement have a higher likelihood of developing PsA (Scher et al., 2019, Wilson et al., 2009). Factors such as therapeutic levels and neutralizing anti-drug antibodies levels can also help guide clinicians when assessing the initial response and sustained efficacy of a drug (Loeff et al., 2020, Pan et al., 2020, Tsakok et al., 2019). However, in the near future clinicians will be able to utilize more sophisticated approaches that integrate clinical phenotypic data with predictive or diagnostic classifiers constructed from “omic” datasets, such as for the transcriptome (Le et al., 2019, Li et al., 2014, Merleev et al., 2018, Tsoi et al., 2019), genome (Supplementary Table 1), microbiome (Supplementary Table 1), lipidome (Sorokin et al., 2018, Zeng et al., 2017), glycome (Li et al., 2019, Maverakis et al., 2015, Park et al., 2018), proteome (Broome et al., 2003, Carlen et al., 2005), and metabolome (Alonso et al., 2016, Kamleh et al., 2015, Zeng et al., 2017). Recent technologies such as single cell RNA-seq have begun to identify novel cell subsets in the skin and synovium (Cheng et al., 2018, Croft et al., 2019, Liu J. et al., 2020, Orange et al., 2018, Stephenson et al., 2018). Already, some promising biomarkers and predictive models are starting to emerge (Supplementary Table 2).

Further advancements in “omic” datasets will give rise to more precise clinically relevant psoriasis models in the future. Complementing these technologies are the advances driven by big data analysis and machine learning, which has been applied to improve the diagnostic accuracy of tissue pathology (Correa da Rosa et al., 2017, Emam et al., 2020, Foulkes et al., 2019, Orange et al., 2018, Tomalin et al., 2020, Zhang et al., 2019). The last critical element is to improve high throughput capture of multimodal clinical data from the EMR, a major requirement in the development of precision medicine (Haendel et al., 2018).

Conclusion

The latest developments in psoriatic research suggest that a multitude of interconnected factors is responsible for the heterogeneous presentation of psoriatic disease (Figure 1). Numerous genetic variants and the interactions occurring in the microenvironment between immune cells, keratinocytes, osteoclasts, and the microbiome determine the development of psoriatic disease, disease severity, therapeutic response, and the development of comorbidities such as inflammatory arthritis and cardiometabolic conditions. These advances have not only revealed novel therapeutic targets, but also provide data to optimize treatment for the individual patient. The next frontier lies in harnessing this information in the clinical setting to deliver more timely, effective, and personalized care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest:

Dr. Gudjonsson has received grant support from AbbVie, Almirall, BMS/Celgene Novartis, Eli Lilly, and Kiowa-Kirin, and served as an advisor to Almirall, Novartis, Eli Lilly, and AnaptysBio. Dr. Scher has consulted for Abbvie, Janssen, Novartis, Sanofi, Eli Lilly, UCB, Amgen, Pfizer and received research grant support from Pfizer, Amgen.

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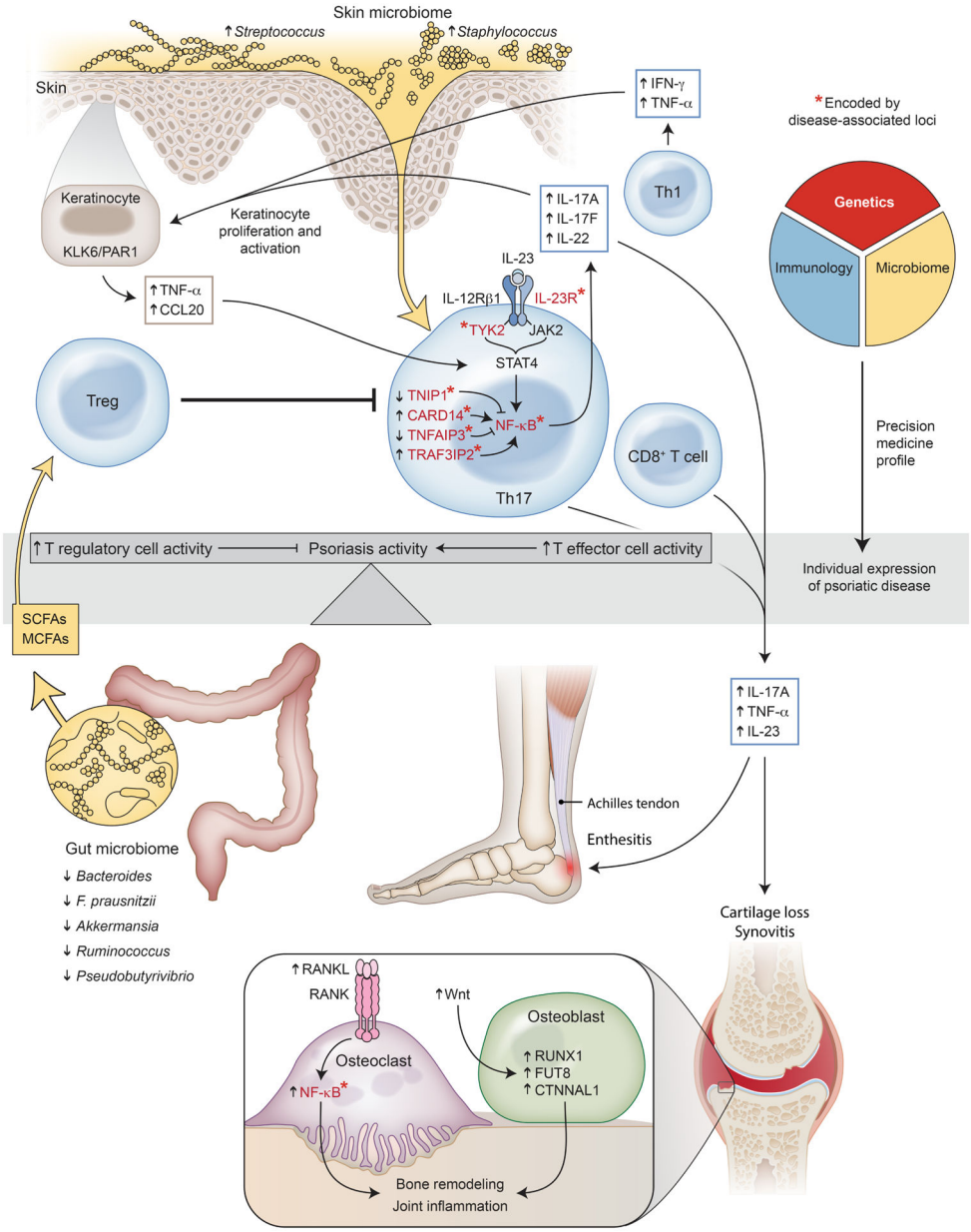

Figure 1. The multifactorial pathogenesis of psoriatic disease.

The development of psoriasis and psoriatic arthritis is influenced by a combination of genetic risk loci (red), many of which are involved in regulation of IL-23 receptor signaling and the NF-kB pathway, imbalances in Treg/T17 immunity (blue), as well as changes in the gut and cutaneous microbiome (yellow). *Illustration assistance provided by Heather McDonald, BioSerendipity, LLC, Elkridge, MD.*

Table 1.

Major identified genetic risk loci for psoriasis and their associated pathways.

Type of Variant	Gene Loci
Non-Coding SNP	
IL23/IL17	***IL23R*** (Gupta et al., 2016), ***IL23A*** (Nair et al., 2009, Stuart et al., 2015), ***TYK2*** (Genetic Analysis of Psoriasis et al., 2010, Tsoi et al., 2012), ***IL12RB2*** (Gupta et al., 2016, Nair et al., 2009, Tsoi et al., 2012)
NF-kB	***NFKBIA*** (Stuart et al., 2015), ***TNFAIP3*** (Nair et al., 2009, Stuart et al., 2015), ***CARD14*** (Gupta et al., 2016, Tsoi et al., 2012), ***TRAF3IP2*** (Ellinghaus et al., 2010, Stuart et al., 2015), ***IKBKE*** (Tsoi et al., 2017)
Innate immune	***IFIH1*** (Stuart et al., 2015), ***TNIP1*** (Nair et al., 2009), ***FUT2*** (Tsoi et al., 2017), ***CHUK*** (Tsoi et al., 2017), ***KLRK1*** (Tsoi et al., 2017), ***TRIM65*** (Tsoi et al., 2017), ***DDX58*** (Tsoi et al., 2012), ***GJB2*** (Sun et al., 2010), ***SERPINB8*** (Sun et al., 2010), ***NOS2*** (Stuart et al., 2010), ***IL28RA*** (Tsoi et al., 2012), ***FBXL19*** (Stuart et al., 2010), ***RNF114*** (Tsoi et al., 2012)
Adaptive immune	***ERAP1*** (Sun et al., 2010), ***ERAP2*** (Tsoi et al., 2012), ***MICA*** (Tsoi et al., 2012), ***TNFRSF9*** (Stuart et al., 2015, Tsoi et al., 2012), ***FASLG*** (Tsoi et al., 2017), ***PTPN2*** (Tsoi et al., 2017), ***CFL1*** (Tsoi et al., 2017), ***KLF4*** (Tsoi et al., 2012), ***RUNX3*** (Tsoi et al., 2012), ***IRF4*** (Tsoi et al., 2012), ***SOCS1*** (Tsoi et al., 2012), ***ETS1*** (Tsoi et al., 2012), ***STAT3*** (Tsoi et al., 2012), ***IL-4*** (Tsoi et al., 2012), ***IL-13*** (Tsoi et al., 2012), ***IL-31*** (Tsoi et al., 2017)
Other	***IL28RA*** (Tsoi et al., 2012), ***PTEN*** (Tsoi et al., 2017), ***ZNF365*** (Tsoi et al., 2017), ***UBAC2*** (Tsoi et al., 2017), ***RP11*** (Tsoi et al., 2017), ***FUBP1*** (Tsoi et al., 2017), ***CAMK2G*** (Tsoi et al., 2015), ***MBD2*** (Tsoi et al., 2012), ***ILF3*** (Tsoi et al., 2012), ***ZC3H12C*** (Tsoi et al., 2012), ***ELMO1*** (Tsoi et al., 2012), ***TAGAP*** (Tsoi et al., 2012), ***B3GNT2*** (Sun et al., 2010), ***CSMD1*** (Sun et al., 2010), ***PTTG1*** (Sun et al., 2010), ***ZNF816A*** (Sun et al., 2010), ***ZNF365*** (Tsoi et al., 2017)
Coding SNP	
IL23/IL17:	***IL23R*** (Tang et al., 2014), ***TYK2*** (Dand et al., 2017), ***IL12B*** (Zuo et al., 2015)
NF-kB	***NFKBIA*** (Zuo et al., 2015), ***CARD14*** (Jordan et al., 2012, Mossner et al., 2018, Tsoi et al., 2012), ***TRAF3IP2*** (Tsoi et al., 2012)
Innate immune:	***IFIH1*** (Dand et al., 2017), ***TNFSF15*** (Dand et al., 2017), ***TNIP1*** (Zuo et al., 2015), ***FUT2*** (Tang et al., 2014), ***IL36RN**** (Marrakchi et al., 2011، Onoufriadis et al., 2011، Setta-Kaffetzi et al., 2013), ***AP1S3**** (Setta-Kaffetzi et al., 2014), ***SERPINA3**** (Frey et al., 2020), ***MPO**** (Haskamp et al., 2020, Vergnano et al., 2020), ***GJB2*** (Tang et al., 2014)
Adaptive immune:	***IL-13*** (Dand et al., 2017), ***ERAP1*** (Genetic Analysis of Psoriasis et al., 2010)
Other	***LNPEP*** (Cheng et al., 2014), ***LCE3D*** (Tang et al., 2014, Zuo et al., 2015), ***LIPK*** (Yang et al., 2020), ***PPP4R3B*** (Yang et al., 2020), ***BBS7*** (Yang et al., 2020), ***GSTCD*** (Yang et al., 2020), ***ZNF816A*** (Tang et al., 2014)
HLA Allele	***HLA-C*06:02***** (Feng et al., 2009, Nair et al., 2006, Okada et al., 2014, Tiilikainen et al., 1980), ***HLA-C*12:03*** (Okada et al., 2014), ***HLA-B*57:01*** (Chen et al., 2012, Feng et al., 2009), ***HLA-B*40*** (Feng et al., 2009), ***HLA-B*38:01*** (Chen et al., 2012, Okada et al., 2014), ***HLA-B*27:05*** (Chen et al., 2012, Okada et al., 2014), ***HLA- B*39:01*** (Chen et al., 2012, Okada et al., 2014), ***HLA-B*08:01*** (Chen et al., 2012), ***HLA-B*14:02*** (Chen et al., 2012), ***HLA-B*55:01*** (Chen et al., 2012) ***HLA-A*02:01*** (Chen et al., 2012), ***HLA-DQα1*** (Okada et al., 2014)
Copy Number Variation	***LCE3C/LCE3D*** (de Cid et al., 2009, Li et al., 2011), ***DEFB*** (Hollox et al., 2008, Stuart et al., 2015)
Small Insertions/ Deletions	***IFIH1*** (Zhen et al., 2019), ***ERAP1*** (Zhen et al., 2019), ***ERAP2*** (Zhen et al., 2019), ***LNPEP*** (Zhen et al., 2019), ***UBLCP1*** (Zhen et al., 2019), ***STAT3*** (Zhen et al., 2019), ***GJB2*** (Zhen et al., 2019), ***ZNF816A*** (Zhen et al., 2019)

* These genes are associated with pustular psoriasis

** Associated with psoriasis vulgaris and guttate psoriasis