Psoriasis: Past, Present, and Future

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Psoriasis is a chronic inflammatory disease of the skin, nails, and joints. In the last two decades, there has been enormous progress in our understanding of the genetics, immunology, and associated comorbidities (Figure 1). This has been accompanied by a marked improvement in the number of therapeutic agents and their effectiveness. Much of this progress has been outlined in numerous articles, commentaries and reviews in the *Journal of Investigative Dermatology* (*JID*) over the years (Figure 2). This commentary, which is part of the *JID Collections*, serves to outline how we have arrived at our present state of knowledge on psoriasis and provides an overview of some exciting future directions.

Historical perspective

For many decades, psoriasis was thought to be a disease characterized by keratinocyte hyperplasia (Figure 3). This was the main motivation for use of the anti-proliferative chemotherapy agent methotrexate for treatment of psoriasis (Weinstein and Frost, 1968; Weinstein and Velasco, 1972) (Figure 4). Its therapeutic benefit was attributed primarily to direct effects of methotrexate on the skin (Weinstein and McCullough, 1976).

Related to the focus on hyperproliferation of the psoriatic epidermis was research on cyclic AMP (Voorhees et al., 1972) and inhibitors of phosphodiesterases (PDE) as potential therapeutic agents in psoriasis (Rusin et al., 1978; Stawiski et al., 1975; Stawiski et al., 1979) – work that predated development and use of the PDE4 antagonist apremilast as a psoriasis therapy (Nast et al., 2015) by several decades.

As the discrete nature of psoriatic plaques suggested a local phenomenon, there was a hunt for a hormone or similar messenger directing localized genesis of lesions. While cyclic AMP garnered much attention, the arachidonic acid derivative leukotriene B_4 (LTB_4) also emerged as a likely candidate, as it was increased in psoriatic plaques (Brain et al., 1984; Brain et al., 1982; Grabbe et al., 1982) and had mitogenic effects on keratinocytes (Bauer et al., 1986; Kragballe et al., 1985). Cyclosporine, an inhibitor of phospholipase A_2 (Fan and Lewis, 1985) and therefore potential suppressor of LTB_4 production, thus surfaced as a potential anti-psoriatic agent.

In 1979, a small case series of four patients treated with cyclosporine was published in the New England Journal of Medicine (Mueller and Herrmann, 1979), followed 5 years later by a single case report in the Lancet in 1984 (Harper et al., 1984). In 1986, two clinical trials motivated in part by the LTB_4 findings demonstrated conclusively the clinical efficacy of cyclosporine for chronic plaque psoriasis (Ellis et al., 1986; Griffiths et al., 1986). While lesional LTB_4 was found to decrease with treatment (Ellis et al., 1986), the dramatic response prompted consideration of an alternative hypothesis – that the primary defect in psoriasis was not keratinocyte hyperproliferation but rather immunologic in nature. This represented a watershed moment in psoriasis research, rapidly shifting the focus toward the immune system, and particularly T cells, as a critical pathogenic driver (Gottlieb et al., 1992). Further work demonstrating disease improvement with selective blockade of activated T cells by interleukin (IL)-2 conjugated to diphtheria toxin fragments definitively implicated T cells in psoriasis pathogenesis (Gottlieb et al., 1995).

In 1991 Brian Nickoloff proposed the idea of the "cytokine network" in psoriasis (Nickoloff, 1991; Uyemura et al., 1993). In the "cytokine network" hypothesis, inflammatory cells and keratinocytes interact to drive the inflammatory process through secretion of various pro-inflammatory cytokines. Initial work focused primarily on the cytokines interferon (IFN)-γ and tumor necrosis factor (TNF)-α (Uyemura et al., 1993).

However, in 1998, IL-17A involvement was first recognized (Teunissen et al., 1998). Subsequently, psoriasis was shown to contain discrete populations of T helper (Th)1 and Th17 lymphocytes (Lowes et al., 2008). Whereas IL-12 is primarily responsible for driving Th1 responses, IL-23 has a key role in maintaining Th17 responses (Stritesky et al., 2008). IL-12 and IL-23 are closely related heterodimers (consisting of two subunits), each including a common p40 subunit, with IL-12 having a p35 subunit and IL-23 a p19 subunit (Lee et al., 2004). In 2004, it was noted that while the p40 and p19 subunits were prominently expressed in psoriatic skin, the p35 subunit was decreased (Lee et al., 2004), suggesting that IL-23 with its p19 subunit plays a more dominant role than IL-12, and therefore Th1 responses, in psoriasis.

Genetic studies align with these observations, showing association between psoriasis and variants close to the p40 gene (*IL12B*) and within the IL-23 receptor (*IL23R*) (Nair et al., 2008), as well as NF-κB (Nair et al., 2009) and the IL-17 signaling pathway (Ellinghaus et al., 2010).

This has consolidated the view of the cytokine network in psoriasis anchored by IL-23/IL-17/TNF responses (Martin et al., 2013), not only in chronic plaque psoriasis but also in other psoriasis subtypes (Xing et al., 2016). The

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Abbreviations: HLA, human leukocyte antigen; Psa, psoriatic arthritis; TCR, T cell receptor

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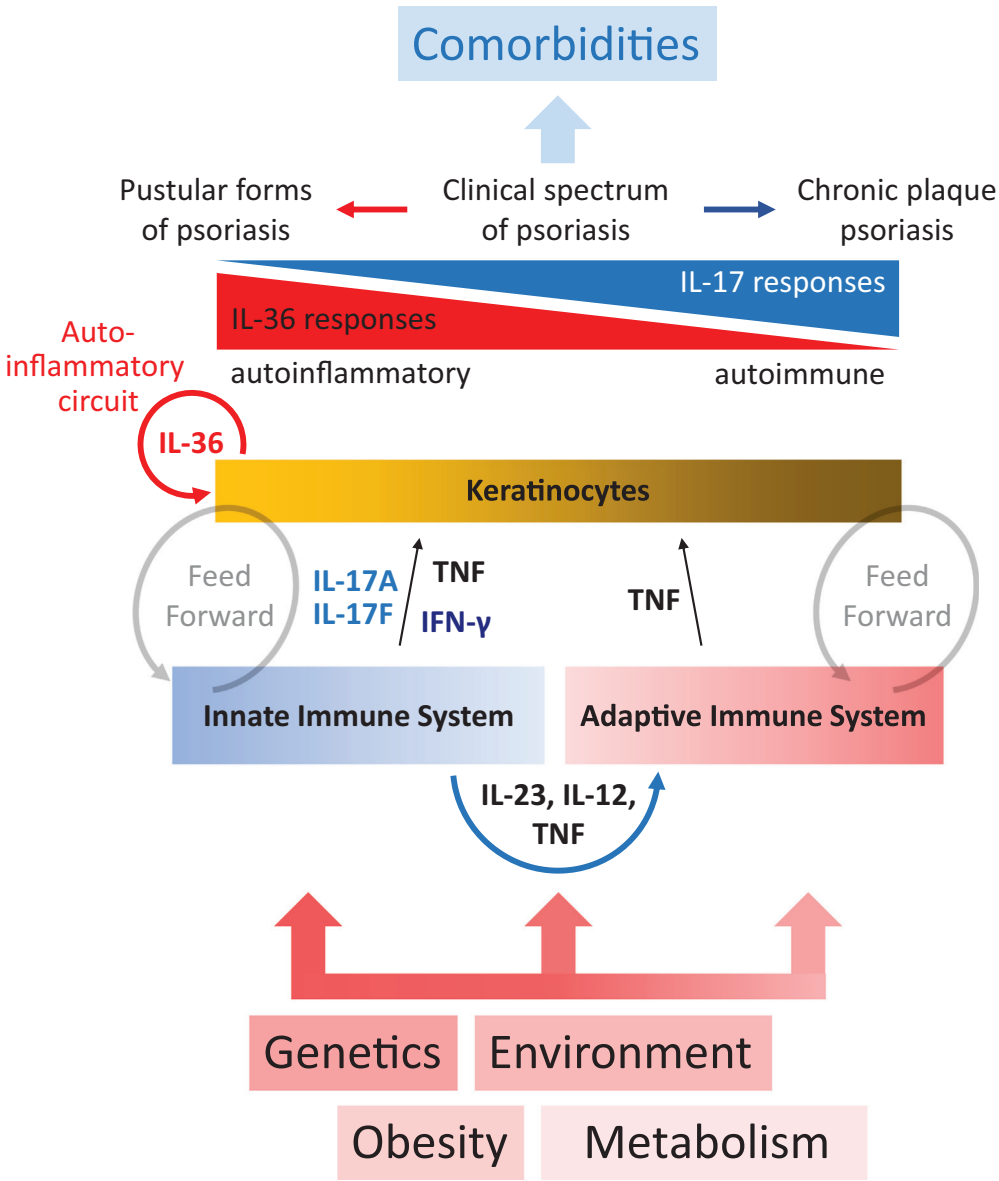

Figure 1. Simplified overview of interrelation between psoriasis predisposing factors, inflammatory mechanisms, clinical manifestations, and consequences. Crosstalk between the innate and adaptive immune systems involves secretion of IL-12 and IL-23, which are important for priming and maintaining Th1 and Th17 responses. Inflammatory responses prime keratinocytes that in turn amplify the inflammatory response and "feed forward," creating a sustaining cycle of inflammation. These inflammatory responses shape the clinical manifestations of psoriasis, which exist between pustular forms (dominated by higher IL-36 responses) and plaque psoriasis (characterized by high IL-17A).

foundational role of the "cytokine network" in psoriasis has been conclusively demonstrated by the remarkable efficacy of drugs targeting various cytokines in psoriasis including TNF, IL-17A and more recently IL-23 (Chaudhari et al., 2001; Gordon et al., 2015; Gordon et al., 2018; Langley et al., 2014; Leonardi et al., 2012; Papp et al., 2012; Reich et al., 2017; Reich et al., 2019).

Recently, a "feed forward" mechanism as a driver of psoriasis pathogenesis has been proposed by James Krueger and colleagues (Hawkes et al., 2017). This proposed mechanism links together the "cytokine network" with the epidermal responses and hyperplasia, as follows: activation and increased expression of IL-17 in pre-psoriatic skin produces a feed forward inflammatory response in keratinocytes that is self-amplifying and drives the development of psoriatic plaques through induction of epidermal cell proliferation, hyperplasia, and further recruitment of inflammatory cells into the skin (Hawkes et al., 2017). This model more readily enables incorporation of other inflammatory mediators and processes such as for the epidermal derived cytokines such as IL-17C (Fritz et al., 2017; Guttman-Yassky and Krueger, 2018), the IL-36 family of cytokines (Carrier et al., 2011; Johnston et al., 2011), and signaling pathways such as TNFAIP3 (Devos et al., 2019), CARD14 (Mellett et al., 2018), and MCPIP1, a regulator of IL-17A and IL-17C responses in psoriatic epidermis (Monin et al., 2017; Ruiz-Romeu et al., 2016), into the pathogenesis of psoriasis.

Thus, the pathogenesis of psoriasis continues to evolve after decades of intense study, and pathogenesis

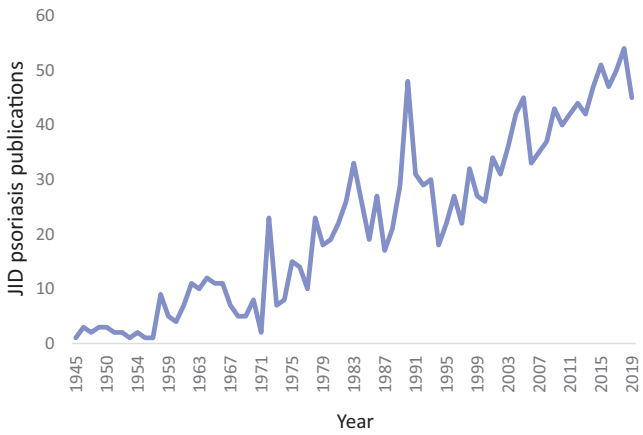

Figure 2. Number of psoriasis publications in the *Journal of Investigative Dermatology* (*JID*) per year since 1945.

remains the most highly represented area of investigation in the *JID*'s body of recent psoriasis literature (Figure 5).

Comorbidities of psoriasis

Due to strong associations with a multitude of comorbidities, psoriasis is increasingly conceptualized as a systemic inflammatory disease. While psoriasis is classically associated with psoriatic arthritis, there is mounting evidence for associations with cardiometabolic disease, immune-mediated inflammatory disease, malignancy, and infection. In many cases, whether these associations are evidence of spillover of cutaneous inflammation, shared susceptibility, or pervasive immune dysregulation remains to be determined.

Cardiometabolic disease has been reported in association with psoriasis for over a century (Strauss, 1897). Since 2000, there has been a marked proliferation in publications describing these associations (Gelfand et al., 2006; Neimann et al., 2006; Sommer et al., 2006), with severe psoriasis conferring higher risk. With regard to cardiovascular disease, these studies generally promoted the hypothesis that chronic skin inflammation and the concomitant increase in circulating proinflammatory cytokines favor development of atherosclerosis and that systemic anti-psoriatic therapy may protect against this process and consequent adverse cardiovascular outcomes. Indeed, studies have demonstrated reductions in major adverse cardiovascular events (MACE) in psoriasis patients on TNF-α antagonists (Ahlehoff et al., 2015; Wu et al., 2012).

However, the mechanism may not be so straightforward: circulating inflammatory markers decrease in as little as 4 weeks in psoriasis patients treated with anti-TNF-α therapy (Kim et al., 2018), yet 52 weeks of anti-TNF-α therapy had no effect on vascular inflammation in the ascending aorta and in fact slightly increased vascular inflammation in the carotids (Bissonnette et al., 2017).

More recently, the question of whether obesity promotes psoriasis was tackled using a powerful approach called Mendelian randomization (Budu-Aggrey and Paternoster, 2019) that overcomes challenges of observational epidemiological studies in which reverse causation or confounding factors may obscure causality. The technique uses genetic variants as proxies — termed instruments — for relevant exposures. Allotted randomly at conception, genetic variants are independent from confounders and the outcome itself and thus can be used to estimate the effect of the exposure on the outcome. As psoriasis has long represented a thriving forefront for genome-wide association studies (Elder et al., 2010), a nearly unparalleled amount of genetic data for psoriasis patients has been amassed. Psoriasis is thus particularly well positioned for approaches such as Mendelian randomization. Analyses of these large

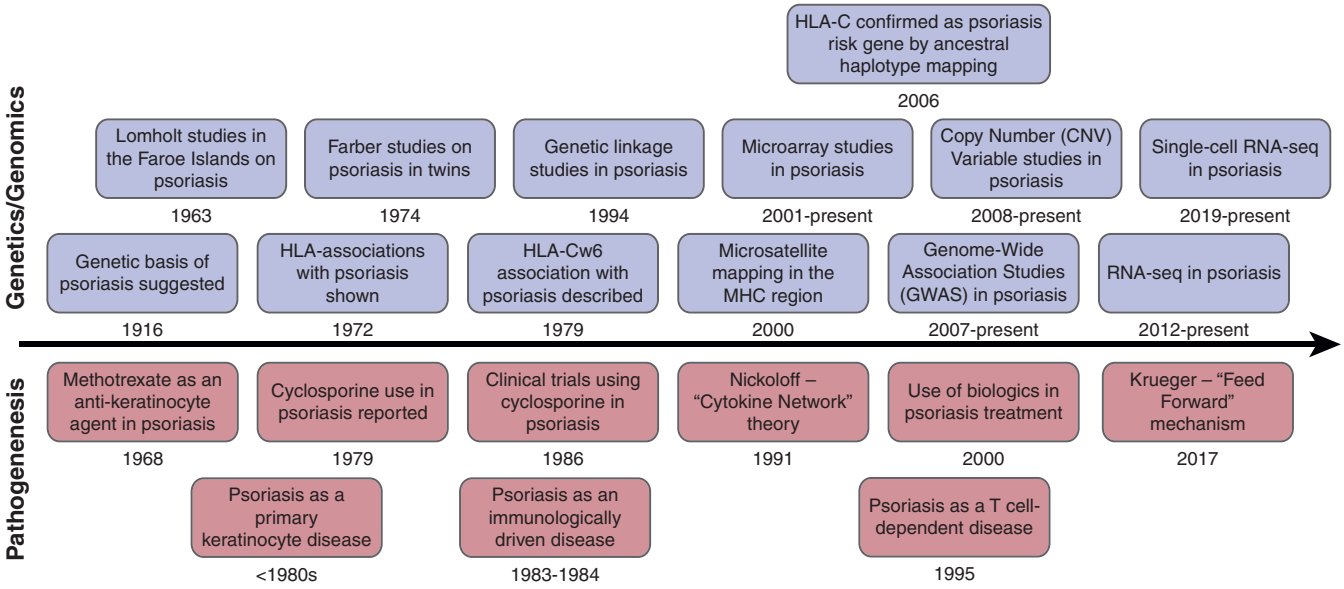

Figure 3. Timeline of discoveries in genetics and (top) genomics of psoriasis and (bottom) pathogenesis of psoriasis.

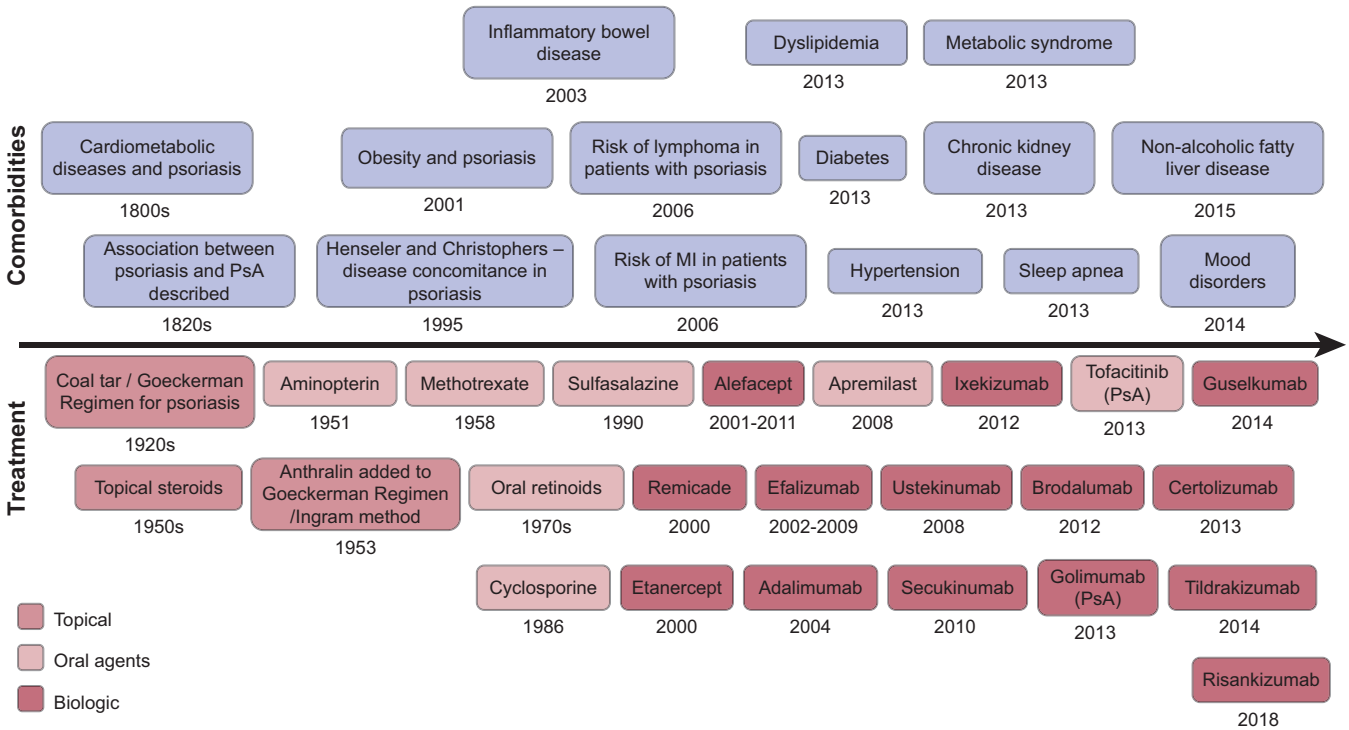

Figure 4. Timeline of discoveries of psoriasis (top) comorbidities and (bottom) treatment. MI, myocardial infarction.

datasets using obesity-associated genetic variants as a proxy for actual measured body mass index (BMI) strongly suggested that higher BMI causally increases risk of psoriasis; the converse analyses showed little to no causal effect of psoriasis genetic risk on BMI (Budu-Aggrey et al., 2019; Ogawa et al., 2019). Additional comorbid conditions will likely benefit from similar analysis to help deconvolute the complex relationships between psoriasis and cardiometabolic diseases.

For some psoriasis comorbidities, however, there is direct evidence that the association is due not to unidirectional causality but rather to shared susceptibility. This is best exemplified by the overlap of genetic risk variants — many of which affect immune regulatory genes — between psoriasis and certain associated conditions. Chief among these is Crohn's disease, but shared risk loci have also been identified for diseases such as type II diabetes mellitus that are not classically considered to be autoinflammatory (Capon et al., 2007; Cargill et al., 2007; Wolf et al., 2008). As might be anticipated for conditions with shared susceptibility, incident Crohn's disease is more common among psoriasis patients (Li et al., 2013), and incident psoriasis is more common among patients with Crohn's disease (Egeberg et al., 2019). Also not unexpectedly, these conditions share many therapies, and investigations into their immunopathogenesis have revealed considerable similarities.

For psoriatic arthritis (PsA), the best-known psoriasis comorbidity, both shared genetic susceptibility and spillover of cutaneous inflammation likely contribute to the association. PsA and psoriasis susceptibility genes are largely overlapping, yet variants have been identified that are more strongly associated with PsA than psoriasis (Ellinghaus et al., 2012; Stuart et al., 2015), suggesting the possibility of independent genetic drivers for PsA. However, PsA is generally diagnosed after the appearance of cutaneous psoriasis and seldom occurs in the absence of cutaneous psoriasis, and data indicate that cutaneous inflammation of psoriasis may exacerbate or even directly drive PsA: development of joint disease in a genetic mouse model of autoimmune arthritis is dramatically accelerated in the presence of psoriasis-like skin inflammation due to hyperactivation of Stat3 in the epidermis (Yamamoto et al., 2015). Furthermore, epidermally restricted hyperactivation (Winge et al., 2016) or deletion (Zenz et al., 2005) of genes implicated in human psoriasis can promote spontaneous development of PsA-like joint disease. Thus, controlling cutaneous psoriasis may be of benefit in preventing or limiting joint disease, lending credence to the concept of PsA as a 'disease within a disease' (Eder et al., 2011).

While not entirely distinct from the above mechanisms, a third possible explanation for psoriasis comorbidities is pervasive immune dysregulation. This mechanism is often invoked for associations of psoriasis with malignancy and infection. In one nationwide study, malignancy carried the highest absolute and excess risks of death in psoriasis (Lee et al., 2017). In larger cohort and meta-analysis studies, patients with psoriasis show higher risks for multiple cancers, particularly lymphohematopoietic malignancy, that persist even when controlling for confounders such as increased smoking and alcohol consumption among psoriasis patients and use of potentially malignancy-promoting anti-psoriatic therapies (Brauchli et al., 2009; Lee et al., 2017; Pouplard et al., 2013).

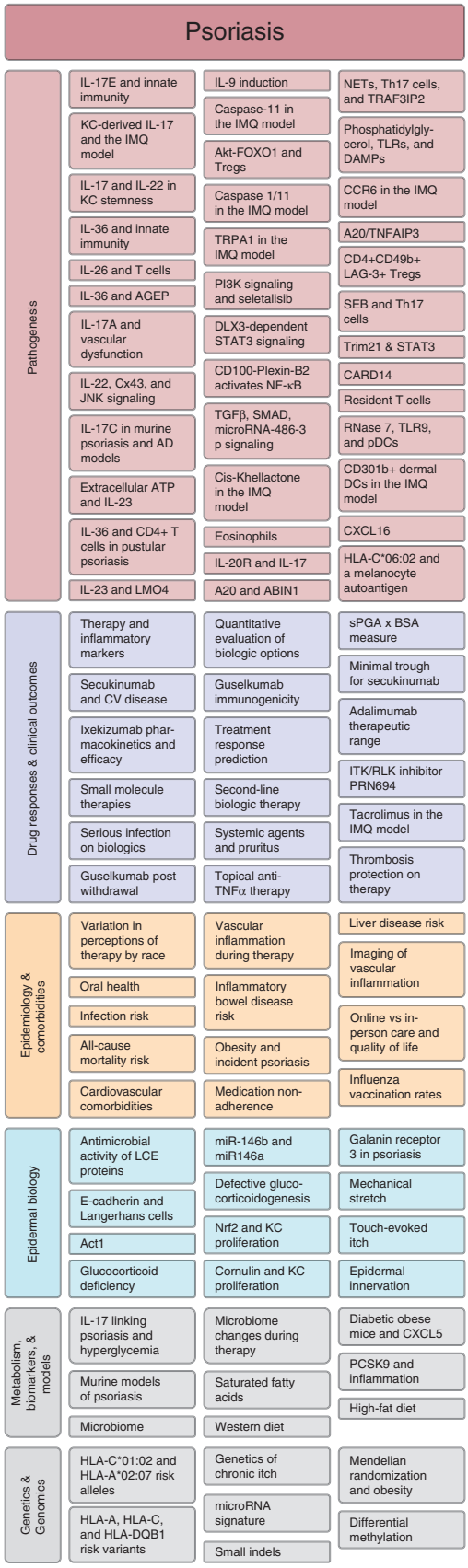

Figure 5. Areas of research focus for psoriasis publications in the *Journal of Investigative Dermatology* (*JID*) in the preceding 2 years. Subcategorization reveals predominant focus on pathogenesis, drug responses, and clinical outcomes but also a strong emphasis on epidemiology and comorbidities. Literature search includes JID publications from July 2017 through June 2019 containing the search term "psoria*" with direct relevance to psoriasis. Some topics are common to multiple publications but represented only once in the figure. Many publications could be appropriately classified in multiple ways; the figure is intended to provide an overall impression of distribution of scientific focus. AD, atopic dermatitis; AGEP, acute generalized exanthematous pustulosis; BSA, body surface area; CV, cardiovascular; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; IMQ, imiquimod; KC, keratinocyte; LCE, late cornified envelope; NETs, neutrophil extracellular traps; sPGA, static physician global assessment; TLRs, toll-like receptors.

In the case of lymphoma, many have posited that the chronically dysregulated immune state of psoriasis drives increased risk. Now in the era of immunotherapy, as our understanding of the critical role of the immune system in limiting malignancy increases, it is tempting to speculate that immune dysregulation and associated impairment of antineoplastic immune surveillance underlies all excess malignancy risk among psoriasis patients. However, this will be challenging to ever prove. Chronic immune dysfunction also likely contributes to the increased risk of serious infections that is observed in patients with psoriasis, even when excluding those on immunosuppressive therapies (Takeshita et al., 2018).

While the true natures of the relationships between psoriasis and associated conditions have proven difficult to define, investigations of their intersection continue to advance understanding of psoriasis immunopathogenesis and guide therapeutic pursuits. Accordingly, publications addressing epidemiology and comorbidities are now well represented research in the *JID* psoriasis literature (Figure 5).

Modeling of psoriasis – mouse models and beyond

With two reported exceptions, a rhesus monkey and a cynomolgus monkey, psoriasis is not observed in animals other than humans (Gudjonsson et al., 2007). However, over the past three decades, numerous mouse models of psoriasis have been described, created through genetic modifications, topical application, or intradermal cytokine injection. Furthermore, various non-animal *in vitro* models such as the epidermal raft system (Barker et al.,

2004; Gordon et al., 2013) have been developed; these have become more frequently used in recent years, and many of these landmark advances in psoriasis have been published in the *JID*.

The first mouse model of psoriasis described was a xenograft model in which lesional psoriatic skin was grafted onto congenitally athymic (nude) mice (Krueger et al., 1975). These mice lack a thymus and are therefore unable to mount an immune response against the grafted skin, enabling maintenance of the skin graft for up to 11 weeks.

A major step forward was made in 2004 when spontaneous development of psoriasis was described in a novel xenograft model where non-lesional psoriatic skin spontaneously developed histologic hallmarks of psoriasis after grafting (Boyman et al., 2004). This model is uniquely dependent upon the recipient mouse, which is deficient in type I and type II interferon receptors along with being deficient in the recombination activating gene 2 (*Rag2*), as this spontaneous development of psoriasis-like disease is not observed with skin grafting onto other immunodeficient mouse strains. This model has been used to show the importance of plasmacytoid dendritic cells in initiation of psoriasis (Nestle et al., 2005), role of epidermal T cells (Conrad et al., 2007), and role of CD8+ T cells (Di Meglio et al., 2016).

The majority of the spontaneous and transgenic mouse models of psoriasis were developed and described in the mid-1990s to mid-to-late 2000s (Gudjonsson et al., 2007; Hawkes et al., 2018). Over 40 unique mouse models have been described (Hawkes et al., 2018). With the initial description of the imiquimod (IMQ) inducible model of psoriasis (van der Fits et al., 2009) and cytokine injection models (Zheng et al., 2007), acute or inducible models have rapidly become one of the most widely used systems for studying human psoriasis (Hawkes et al., 2018). Recent examples of the utilization of this model include the demonstration of IL-1β/IL-1R signaling pathway in skin inflammation (Cai et al., 2019); therapeutic intervention to determine the response to topical tacrolimus (Pischon et al., 2018); link between skin inflammation and hyperglycemia (Ikumi et al., 2019); role of IL-20 receptor signaling (Ha et al., 2019) and IL-17E (Senra et al., 2019) in psoriasis pathogenesis; and to elucidate the function of Trim32 in psoriasis and atopic dermatitis (Liu et al., 2017). However, some concerns have been raised about the overutilization of this model and its variability depending on the mouse strain used (Swindell et al., 2017). Nonetheless, since the first report of this model in 2009, the IMQ psoriasis-like model has been used in over 200 publications (Hawkes et al., 2017).

Other models entail intradermal injection of pro-inflammatory cytokines, with the first instance of this reported in 2003 with IL-23 (Kopp et al., 2003), and later with injections of IL-22 (Zheng et al., 2007), IL-21 (Caruso et al., 2009), and most recently IL-36A (Campbell et al., 2019). Other publications in the *JID* exploiting these models have explored the role of IL-6 (Lindroos et al., 2011), superoxide dismutase (Lee et al., 2013), and the toll-like-receptors (TLRs) 7, 8, and 9 in psoriasis (Jiang et al., 2013). The raft models have also been used to explore specific mechanisms in psoriasis including glucocorticoid deficiency in lesional psoriatic skin (Sarkar et al., 2017) and biology of Ephrin-A signaling (Gordon et al., 2013).

Complex diseases such as psoriasis create a formidable challenge for attempts to model pathogenesis. However, while no model can capture the entirety of psoriasis pathogenesis, these models are indispensable and help us understand the roles of specific mediators and signaling pathways.

Future directions in psoriasis

Despite dramatic advances in understanding of psoriasis immunopathogenesis and treatment over the last several decades, psoriasis remains a vibrant field of investigation. This is perhaps because psoriasis serves as a readily accessible — although deeply complex — immune-mediated inflammatory disease paradigm for exploration of forefronts such as the role of tissue-resident memory T cells and the interplay between metabolism and autoinflammation. These and several other emerging entities are reviewed in brief below.

Tissue-resident memory T cells (TRMs) and the psoriasis autoantigen. Psoriasis patients are frequently frustrated by the propensity for their psoriasis to recur at sites of previous lesions upon cessation of therapy. Early investigation of this phenomenon revealed a 'residual disease genomic profile' including expression of cytokines and T cell-specific transcripts in skin previously affected by psoriasis, suggesting the presence of persistent and likely disease-perpetuating memory T cells residing in resolved lesions between flares (Suarez-Farinas et al., 2011). Shortly thereafter, these TRMs were found to include IL-22-producing CD4+ T cells and IL-17-producing CD8+ T cells (Cheuk et al., 2014), providing a cytokine source for the instigation of recurrent lesions.

In 2017, however, high-throughput T cell receptor (TCR) screening revealed that resolved psoriasis lesions contain oligoclonal IL-17A-producing T cell populations; some of the expressed TCR sequences were found to be identical across multiple patients but absent in skin from healthy controls and patients with other cutaneous inflammatory diseases (Matos et al., 2017). Interestingly, while γδ T cells represent the primary source of IL-17 in the IMQ psoriasis-like mouse model (Laggner et al., 2011; Pantelyushin et al., 2012), all of the most frequent putatively pathogenic T cell clones were αβ T cells. This is concordant with the findings of another high-throughput examination of T cell repertoires in psoriasis that reported that γδ T cells constitute a very small population of cutaneous psoriatic T cells and do not correlate with IL-17A expression in humans (Merleev et al., 2018).

The presence of oligoclonal TRM populations in psoriasis has also breathed new life into a longstanding question: What is the psoriasis autoantigen? The most strongly associated psoriasis susceptibility loci correspond to specific human leukocyte antigen (HLA) alleles, particularly HLA-Cw6 (Nair et al., 2006), consistent with the existence of autoantigen presentation to pathogenic CD8+ T cells. Multiple studies have identified candidate epidermal autoantigens, including keratinocyte proteins with similarity to streptococcal antigens (Besgen et al., 2010; Valdimarsson et al., 2009), the antimicrobial peptide LL37 (Lande et al., 2014), neolipid antigens (Cheung

et al., 2016; Kim et al., 2016), and an HLA-C*06:02—presented melanocytic protein, ADAMTSL5, recognized by IL-17A-producing CD8+ T cells of the Vα3S1/Vβ13S1 TCR (Arakawa et al., 2015; Prinz, 2017). The autoantigen presentation by HLA-Cw*06:02 in psoriasis has been characterized, and compared to other HLA-C alleles, HLA-Cw*06:02 has the greatest accessible contact area for the bound antigen, which might promote binding to greater number of T-cell receptors (Wei et al., 2017). Notably, LL-37 and M-protein antigens of streptococci were all predicted to be able to be presented by HLA*06:02 (Wei et al., 2017). Intriguingly, Vβ13 is among the putative pathogenic T cell clones identified by the high-throughput TCR screening approach above (Matos et al., 2017), suggesting that deeper investigation into the antigen recognition of TRMs in psoriasis may serve to definitively establish psoriasis as a primary autoimmune condition.

Influence of metabolism on psoriasis and inflammation. A shift in focus toward metabolism and inflammation has recently occurred. As mentioned above, obesity and the metabolic syndrome are closely linked with psoriasis, and obesity was recently shown to have a causal link to psoriasis (Budu-Aggrey et al., 2019; Ogawa et al., 2019). High-fat diet has been shown to exacerbate psoriatic skin inflammation in a mouse model of psoriasis (Herbert et al., 2018; Shimoura et al., 2018). Some of this effect may be mediated by fatty acids, which have been shown to shift immune responses in dendritic cells towards IL-23 and exacerbate psoriasis-like skin inflammation (Mogilenko et al., 2019).

Psoriasis subtypes and related insights. While chronic plaque psoriasis, or psoriasis vulgaris, is the most common subtype of psoriasis, representing approximately 90% of all cases, research on other clinical subtypes of cutaneous psoriasis, such as inverse, erythrodermic, guttate, and pustular forms, have greatly increased in recent years. The common thread among all subtypes of psoriasis is the prominence of IL-17 responses (Xing et al., 2016), although these appear to be present on a gradient and are less dominant in pustular forms of psoriasis, in which IL-36 activity has greater prominence (Johnston et al., 2017). In contrast, IL-36 activity is less prominent in chronic plaque psoriasis (Johnston et al., 2011). Mutation in *IL36RN*, encoding the IL-36 receptor antagonist, has been associated with a spectrum of psoriasis-associated pustular phenotypes (Setta-Kaffetzi et al., 2013), and in particular generalized pustular psoriasis without psoriasis vulgaris (Sugiura et al., 2013), reiterating the role of the IL-36 inflammatory axis in pustular subtypes of psoriasis. Interestingly, IL-36 may contribute to and promote IL-17/Th17 responses (Arakawa et al., 2018), providing a link between these two inflammatory responses beyond the role of IL-17A as one of the major inducers of IL-36 expression (Carrier et al., 2011).

Furthermore, other presentations of psoriasis may be related to imbalances in the cytokine network. One example of this is the balance between TNF and type I interferon responses. A recent publication has shown that TNF blockade induces a dysregulated type I interferon response without autoimmunity in "paradoxical" psoriasis (Conrad et al., 2018). Furthermore, IL-6 blockade can induce new-onset psoriasis-like disease (Blauvelt, 2017), a phenomenon that has been explored in mouse models of psoriasis (Fritz et al., 2017) and clinically can present like chronic plaque psoriasis with guttate-like lesions (Laurent et al., 2010). Taken together, these data suggest that variation in the cytokine network may be a key factor in shaping different clinical manifestations of psoriasis.

Conclusion

The historical perspective of the field of psoriasis provides many intriguing connections between past and present. Recurring characters such as the PDE inhibitors highlight how a long-lived and thriving field can shed new light on old players. Nevertheless, our understanding of psoriasis pathogenesis continues to grow deeper and our therapeutics ever more effective, and the rise of psoriasis as an archetypal systemic immune-mediated disease assures a vibrant future for psoriasis research.

CONFLICT OF INTEREST

JEG serves on the Advisory Boards for Novartis, AbbVie, Almirall, and MiRagen. Research support was received from AbbVie, Novartis, AnaptysBio, and Celgene. ACB and JJV state no conflict of interest.

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