# Recent Highlights in Psoriasis Research

Samuel T. Hwang[1], Tamar Nijsten[2] and James T. Elder[3,4]

This article highlights recent advances in the immunology, epidemiology, and genetics/genomics of psoriasis. Advances sometimes generate more questions, and this article makes an attempt to point out where controversies might exist in the literature. Many of the articles mentioned were published in the Journal of Investigative Dermatology, but many articles from the broader scientific literature are also cited, to provide context and to add further validity for some of these key findings. Among the themes we explore are the identification of antigens in psoriasis, the co-morbidities of psoriasis, and novel integrative approaches to genome-wide association studies.

*Journal of Investigative Dermatology* (2017) **137,** 550–556; doi:10.1016/j.jid.2016.11.007

## INTRODUCTION

Advances in psoriasis research continue unabated, even as biologics have revolutionized the way many patients with moderate to severe disease are treated. In this article, we highlight specific advances and findings in psoriasis research related to epidemiology/clinical research, immunology, and genetics. Many of these studies were published in the *Journal of Investigative Dermatology* (*JID*), but others help put these studies in context. Tamar Nijsten focuses on novel, but contradictory, epidemiological data regarding what was thought to be a known comorbidity of psoriasis, as well as on new biomarkers that might improve or "personalize" the way we give therapy in psoriasis. Samuel T. Hwang highlights advances in the role of antimicrobial peptides in terms of how they are regulated and how they might act as antigens in psoriasis and explores the role of skin inflammation as it relates to alterations in adipocyte biology. James T. Elder highlights genetic and genomic advances contributing to our understanding of psoriasis, including novel integrative approaches to genome-wide association studies, bioinformatic tools for transcriptomic comparison of psoriasis versus other skin diseases, and exploration of the contribution of long noncoding RNAs (lncRNAs) to psoriasis pathogenesis.

[1]Department of Dermatology, University of California, Davis, Sacramento, California, USA; [2]Department of Dermatology, Erasmus MC, Burg. 's Jacobplein 51, 3015 CA Rotterdam, The Netherlands; [3]Department of Dermatology, University of Michigan, 1301 East Catherine, Ann Arbor, Michigan, USA; and [4]Department of Dermatology, Ann Arbor Veterans Affairs Hospital, 2215 Fuller Rd, Ann Arbor, Michigan, USA

Correspondence: Samuel T. Hwang, Department of Dermatology, University of California, Davis, 3301 C Street Suite 1300, Sacramento, California 95116, USA. E-mail: sthwang@ucdavis.edu

Abbreviations: CVD, cardiovascular disease; GWAS, genome-wide association study; hBD2, human β-defensin 2; JID, Journal of Investigative Dermatology; lncRNA, long noncoding RNA; miR, microRNA; TNF-α, tumor necrosis factor-α

Received 1 November 2016; accepted 2 November 2016; corrected proof published online 4 January 2017

## EPIDEMIOLOGY AND CLINICAL RESEARCH

### Cardiovascular comorbidities

Since the 2006 landmark study by Gelfand et al. (2006), many, but not all, studies have shown a positive association between metabolic syndrome and cardiovascular disease (CVD) and psoriasis, especially for (young) patients with moderate to severe disease (Armstrong et al., 2013; Gelfand et al., 2006). Most of the observational studies suffered from residual confounding and were not able to assess psoriasis severity, challenging the causality of the observed observation (Nijsten and Wakkee, 2009). The main hypotheses are that the enhanced systemic inflammatory status of psoriasis patients increased their risk or that they share a genetic predisposition to develop these comorbidities. Almost 10 years after Gelfand et al.'s study, the Clinical Practice Research Datalink was reanalyzed by the Manchester team, changing some of the previous assumptions and applied methodology (i.e., incident versus prevalent CVD, varying time of disease severity, including psoriatic arthritis as a covariate, and reclassifying some patients' disease severity on the basis of drug exposure) (Parisi et al., 2015). They confirmed the higher prevalence of CVD risk factors in psoriasis patients but, interestingly, did not find an overall higher risk of myocardial infarction. They concluded that, based on the Clinical Practice Research Datalink data, "Neither psoriasis nor severe psoriasis were associated with the short term risk of major CV events after adjusting for known cardiovascular risk factors" (p. 2189).

In 2015, a German cross-sectional study of 4,185 psoriasis patients showed that severe psoriasis patients were at a slightly increased risk for incident diabetes and myocardial infarction (adjusted relative risk $< 1.15$) (Koch et al., 2015). The uniqueness of this study was that these researchers were the first to compare the genetic architectures in 927 psoriasis patients with almost 4,000 controls. They used the Metabochip (Illumnia Inc., San Diego, CA) custom array to densely genotype and analyze established coronary artery disease risk loci (nearly 200,000 single nucleotide polymorphism markers) showing that only two single nucleotide polymorphisms associated with coronary artery disease were associated with psoriasis and that none of the psoriasis single nucleotide polymorphisms were associated with coronary artery disease. They concluded that "the genetic architecture of psoriasis and cardiometabolic traits is largely distinct" (p. 1283).

A recent 2016 study in *Circulation Research* showed that GlycA, which is a novel biomarker for systemic inflammation, was associated with psoriasis severity and subclinical CVD in a cross-sectional study in two cohorts (Joshi et al., 2016). Altogether, the two cohorts included more than 300 psoriasis patients, and in one of the cohorts (151 psoriasis

patients and 30 control subjects) the subclinical CVD was assessed by VI by 18-fludeoxyglucose positron emission tomography/computed tomography scan and coronary CT angiography. GlycA was significantly, but modestly, correlated with several inflammatory cytokines (correlation coefficients between 0.73 and 0.12) and cardiometabolic traits (correlation coefficients varied mostly between 0.20 and 0.40). Adding GlycA to the base model that included conventional CVD risk variables further increased the area under the receiver operating characteristic curve for VI from 0.86 to 0.93 and for coronary artery disease from 0.89 to 0.92, suggesting that this biomarker added some value in predicting subclinical CVD in psoriasis patients. Altogether, this comprehensive study suggests that at a subclinical CVD level, psoriasis patients differ from control subjects.

### Access to care and drug survival

Although the management of psoriasis has changed dramatically with the introduction of multiple biologics and a new oral drug, relatively little was known about the level of access to care in different countries. In the US Medicare population, it was estimated that approximately 1% of the elderly had sought care for their psoriasis (Takeshita et al., 2015). Of the total Medicare psoriasis sample, about a quarter had used phototherapy or oral systemic or biologic therapies; of these, 37.2% had used biologics (10.1% of total psoriasis sample). Elderly black psoriasis patients and those without a low-income subsidy were 70% less likely to have received biologics for their psoriasis. Patients living in an urban county with higher levels of dermatology and primary care provider density, as well as those with concomitant inflammatory conditions, were more likely to have used biologics. In a follow-up study in the same population, it was shown that about 80% of patients used adalimumab or etanercept and that both infliximab and ustekinumab were used in approximately 10% of patients between 2009 and 2012. In the 12 months after having started an antipsoriatic biologic, 38% of patients using biologics were adherent, 46% discontinued, 8% switched, and 9% restarted the therapy (Doshi et al., 2016). Female patients and those without a low-income subsidy were at increased odds of decreased adherence.

The use pattern of biologics in the UK differed from the United States in that adalimumab (56.2%) was more commonly used, followed by etanercept (33.4%) and ustekinumab (10.4%) in a national registry of predominantly biologic-naïve patients between 2007 and 2014 (Iskandar et al., 2016). In a 12-month period, 77.4% of the 2,980 UK patients continued the biologic, and more than 85% used the recommended dose. However, a quarter of patients combined conventional drugs, which was most often methotrexate, with the biologic it was initiated on. Although there are clear distinctions with respect to data source and study population between the US and UK in the study, there seem to be real geographic differences in real-world care of psoriasis. The same research group investigated drug survival of biologic therapies in the prospective UK registry. Among 3,523 patients, the overall drug survival rate in the first year was 77%, falling to 53% in the third year. Compared with adalimumab users, patients on etanercept and infliximab were 60% more likely to discontinue therapy, and those on ustekinumab were 50% more likely to continue therapy. In contrast with the US Medicare study, this study had more detailed patient information to assess risk factors associated with discontinuation and showed that female sex, current smoker, and higher quality-of-life impairment were predictors of stopping treatment, whereas the presence of psoriatic arthritis increased the likelihood of continuation by 60% (hazard ratio = 1.63, 95% confidence interval = 1.45−1.84).

### Advances in personalized medicine for psoriatic patients

The abovementioned observational studies investigating the predictors of drug survival are small steps toward the highly desirable concept of personalized medicine. Another approach toward personalized treatment is measuring trough levels of the biologics, which might also explain why more obese patients seem to respond less to biologics (Zweegers et al., 2016). A Dutch and Belgian research group estimated a therapeutic range of adalimumab trough levels between 3.5 and 7.0 mg/L to be associated with a more optimal clinical effect (Menting et al., 2015a). They also suggested that about a third of psoriasis patients using adalimumab exceeded the therapeutic window, allowing a rationale for extending the treatment intervals. However, the diagnostic properties (sensitivity and specificity were less than 80%) of the therapeutic range require improvement, and the concept should be validated in a larger prospective psoriasis cohort. The same research group observed no correlation between trough levels of ustekinumab and treatment response (Menting et al., 2015b).

In 2016, an interesting large pharmacogenetics study was published using well-defined psoriasis patients taking ustekinumab derived from three randomized clinical trials (Li et al., 2016). The HLA-C*06:02 allele is known to substantially increase the risk of psoriasis and is associated with earlier onset and more severe disease. The overall HLA-C*06:02 prevalence was 44.6% in the psoriasis cohort. Both the HLA-C*06:02-positive and -negative psoriasis patients responded well to ustekinumab (86% and 76%, respectively, achieved 75% reduction in psoriasis area severity index at week 24). According to different sensitivity analyses, a possible modest differential response to ustekinumab in HLA-C*06:02-positive patients achieving higher response rates for getting (almost) clear at later time points was shown. Although the effect of HLA-C*06:02 is limited, the robust assessment of pharmacogenetic biomarkers is definitely the way forward to optimize care in the most cost-effective manner.

## PSORIASIS IMMUNOLOGY

### Antimicrobial peptides in psoriasis: from passive bystanders to active antigens

Antimicrobial peptides, including the β-defensins and LL-37, have long been known to be overexpressed in psoriatic lesions. Given the known antibacterial properties of most of these small proteins, this might explain the relatively low presence of bacterial and bacterial infections in psoriatic lesions. But what roles, if any, do these highly conserved small proteins play in psoriasis pathogenesis? The recent publications described below provide new insights into the complex regulatory mechanisms that regulate their

expression; indicate a potential role for one of them with respect to the induction of IL-23 in Langerhans cells, skin dendritic cells with a controversial role in psoriasis; and finally, introduce novel structural and in silico-based methods for understanding how LL-37 could act as an autoantigen in psoriasis.

First, human β-defensin 2 (hBD2), an antimicrobial protein encoded by the *DEFB4* gene, along with other antimicrobial peptides, is up-regulated by keratinocytes in psoriasis skin. In keratinocytes, *DEFB4* mRNA and hBD2 protein are known to be synergistically up-regulated by two key cytokines, IL-17A and tumor necrosis factor (TNF)-α, that are signature psoriatic cytokines (Chiricozzi et al., 2011), but the mechanism by which this synergism occurs is unknown. Johansen et al. (2016) use classical biochemical approaches that combined pharmacologic inhibitors of key signaling pathways, such as p38 mitogen-activated protein kinase and c-Jun N-terminal kinase, and a small interfering RNA approach to show that three specific transcription factors (OCT-1, NF-κB, and AP-1) are responsible for integrating the signals that control this synergism. The regulation of hBD2 may have other implications, because of fact that hBD2 also acts as a ligand of CCR6 (Rohrl et al., 2010), a chemokine receptor that is used in the recruitment of pathogenic T helper type 17 cells to psoriatic skin (Homey et al., 2000; Mabuchi et al., 2013). The other known chemokine ligand for CCR6 is CCL20, but Johansen et al. showed that IL-17/TNF-α—mediated synergistic enhancement of CCL20 expression is not regulated by OCT-1. That three different transcription factors "fine-tune" the expression of hBD2 and CCL20 shows the complexity of the positive feedback loops that are present in psoriatic skin. Although the antimicrobial functions of hBD2 may or may not contribute to psoriasis inflammation, the chemotactic function of hBD2 through CCR6 certainly may play a critical role. Targeting the downstream effector proteins of these transcription factors may also provide new targets for more effective treatment of psoriasis.

The role of β-defensins in psoriatic inflammation was also explored in work by Sweeney et al. (2016). Human β-defensin 3 (the ortholog of murine β-defensin 14) is also highly up-regulated in psoriatic skin. These authors found that murine β-defensin 14 stimulated Langerhans cells to produce IL-23, whose importance in psoriatic inflammation is well known. Alone, murine β-defensin 14 stimulated only mild psoriatic inflammation, however, compared with imiquimod. Although the role of Langerhans cells in murine psoriasis-like inflammation is controversial (some studies show that they are critical, but others do not) and difficult to conclude in humans, these authors speculate that hBD3 in humans may exacerbate or maintain disease through enhanced IL-23 production by Langerhans cells, thus providing another mechanism by which defensins may contribute to psoriatic inflammation.

Finally, LL-37 (also known as cathelicidin) may be the most interesting of the antimicrobial peptides in psoriasis pathogenesis. Earlier reports (Lande et al., 2007) found that LL-37 complexes with self-DNA to enhance plasmacytoid dendritic cell production of interferon-α that could contribute to the development of psoriasis. Of even greater interest, this group later reported that LL37 may be a T-cell autoantigen in psoriasis (Lande et al., 2014). HLA-C*06:02 is known to be the strongest major histocompatibility complex risk factor for psoriasis. Mabuchi and Hirayama (2016) used in silico computer simulation of predicted HLA-*C06:02 with all nine possible contiguous amino acid sequences of LL-37 (39 amino acids long) to identify potential peptide sequences with high binding affinity to this HLA allele. Of note, several of the highest predicted binding sequences matched LL-37 9-mer peptides that were experimentally determined to bind with HLA-*C06:02 (Lande et al., 2014). The peptides that bound best had several common amino acid features, such as the presence of a basic or hydrophobic amino acid, at key locations in the sequence, and the researchers were able to illustrate the binding of several high binding affinity peptides to the proposed structure of HLA-C*06-02, which has not yet been determined by crystallography but was modeled on the basis of other known HLA structures. These in silico methods potentially allow identification of peptides that would have high binding affinity to HLA-C*06-02 but low affinity to the TCR, thus acting as inhibitors of TCR-HLA interaction. This work is theoretical in nature and based on computer models, but it describes a sophisticated approach to designing a new class of TCR-MHC peptide-based antipsoriasis agents.

**Where do the inflammatory pathways in the skin intersect adipocyte dysfunction?**

Obesity is one of several comorbidities associated with psoriasis, but it is unclear which inflammatory or regulatory pathways connect the two processes. MicroRNAs (miRs) control gene expression in a global fashion with many miRs affecting many genes. Cheung et al. (2016) examined the differential expression of mRNAs in subcutaneous adipose tissue directly beneath psoriatic lesions and compared that miR signature to adipose tissue beneath noninflamed skin. Several miRs, including miR-26b, that were known to be involved in adipogenesis were altered in lesional versus nonlesional adipose tissue. miR-26b was of particular interest because it was previously shown to be required for adipogenesis (Karbiener et al., 2014). Cheung et al. showed that miR-26b targets *NCEH1,* a gene known to be required for efficient cholesterol transport. When *NCEH1* is impaired, cholesterol becomes trapped intracellularly, which can lead to so-called foam cells in macrophages that are commonly found in atherosclerotic lesions (Igarashi et al., 2010). Hence, this work provides a plausible link between inflammation at specific skin sites, which then influences adipocyte tissue-specific expression of miRs that affect further adipocyte development and proliferation. That *NCEH1* was found to be down-regulated in adipocytes and macrophages in lesional adipose tissue suggests that inflammatory processes in the skin clearly affect the adipose tissue as well as the overlying dermis and epidermis, leading to outcomes that enhance fat cell development and macrophage dysfunction. This work and other recent publications provide a clearer understanding of skin inflammation and the systemic comorbidities found in psoriatic patients.

**Which skin antigens drive autoimmunity in psoriasis?**

Current dogma is that psoriasis is an autoimmune disease, but the supposed antigen(s) that triggers autoimmunity has been elusive. As mentioned, recent reports (Lande et al., 2014;

Mabuchi and Hirayama, 2016) have proposed that peptides derived from LL-37, a well-known antimicrobial peptide that is overexpressed in psoriatic epidermis, may act as autoantigens for T cells in an HLA-*C06:02-dependent manner. Clues to an autoimmune process in psoriasis include the findings that the Vα3S1/Vβ113S1 T-cell receptor rearrangement is preferentially found in some patients with psoriasis (Chang et al., 1994) and that some HLA alleles (e.g., HLA-C*06:02) confer much greater risk of psoriasis than others (Gudjonsson et al., 2003), but identifying the actual antigen in the disease tissue is challenging for many technical reasons. Knowing this, Arakawa et al. (2015) created an unique T-cell hybridoma that carried a reconstituted Vα3S1/Vβ113S1 TCR from an HLA-C*06:02 patient. The hybridoma also was engineered with an activation-induced fluorescent marker, which allowed it to be used in screening an unbiased peptide library in conjunction with a cell line that expressed the HLA-C*06:02 MHC to bind the peptide. This screen showed that a peptide sequence from a melanocyte-specific protein called ADAMTSL5 activated the hybridoma. The researchers further observed $CD8^+$ T cells in close proximity to melanocytes in psoriatic lesions and that, in vitro, $CD8^+$ T cells from psoriatic patients, but not healthy volunteers, produced IL-17A, a key signature cytokine of psoriasis when exposed to ADAMTSL5. Although this work is intriguing, psoriasis patients generally do not develop total loss of melanocytes—otherwise, they would develop vitiligo. The researchers rightfully caution that the identification of ADAMTSL5 as an autoreactive antigen does not exclude other proteins as also being autoantigens. Thus, the validity of ADAMTSL5 being the only psoriatic autoantigen may be questionable, but the unique screening approach that takes advantage of HLA-C*0602 as a known genetic marker of psoriasis provides a powerful tool to search for other antigens that may ultimately bear more relevance in most psoriatic patients.

## GENETIC AND GENOMIC ADVANCES IN PSORIASIS

Two research strategies addressing these knowledge gaps have advanced rapidly in the 21st century are: genetics and genomics. These "big data" approaches can be daunting because they entail a good deal of technical parlance and complex bioinformatic and statistical analysis. This challenge begins with their names. Although "genetics" and "genomics" both refer to genome-wide interrogation of high-throughput data as a function of disease status across multiple individuals, these terms are not interchangeable: "genetics" refers to the effects of DNA sequence variation, whereas "genomics" refers to the measurement of expression levels. Genomic studies often focus on RNA (transcriptomics) because of our current technical capabilities but increasingly involve protein, carbohydrates, lipids, and others, each with its corresponding "-omic" name.

### Advances in genetics

Initial searches for psoriasis genes involved genetic linkage studies, which measure transmission of alleles through generations or sharing of alleles between affected family members. Earlier linkage studies reported 18 psoriasis susceptibility loci including the MHC (Sagoo et al., 2004). However, with certain exceptions, including *PSORS2* spanning the *CARD14* gene, PSORS4 in the epidermal differentiation complex, *PSORS7* spanning the *IL23R* gene, and *PSORS6* spanning the *TYK2* gene, most of these early linkage signals have not been replicated. With the rise of array-based genotyping technologies, many genetic studies of psoriasis and other "complex" (i.e., polygenic) diseases pivoted from family-based designs to genome-wide association studies (GWAS) performed in patients and control subjects, as reviewed in *JID* (Ray-Jones et al., 2016). As of today (some results not yet published), GWASs in European-origin and Chinese populations have identified loci in 86 genomic regions that are associated with psoriasis at genome-wide significance. Eleven of these are shared by European-origin and Chinese populations, 55 loci have been established for Europeans only, and 20 loci have been established for Chinese only. Sixteen of these loci have been established as susceptibility loci for psoriatic arthritis, and 12 for purely cutaneous psoriasis. The strength of association of psoriatic arthritis versus cutaneous psoriasis is approximately equal for most of the analyzed psoriasis loci, but there were significant differences in relative strength of psoriatic arthritis and cutaneous psoriasis association for variants near *TNFAIP3*, *IL23R*, *TNFRSF9,* and *LCE3C/B* (Stuart et al., 2015).

Genetic studies of psoriasis published this year in *JID* addressed genome-wide DNA methylation (Zhou et al., 2016) and sequence variation associated with psoriasis risk at the pathway level (Aterido et al., 2016). DNA methylation is an epigenetic modification that often correlates with gene inactivation by stabilizing a closed chromatin configuration. However, some DNA methylation events correlate with increased gene expression. Using three independent datasets, Zhou et al. identified nine genomic regions that were consistently differentially methylated in skin biopsy samples of psoriasis patients versus control subjects. Although none of the differentially methylated regions mapped to sites of significant psoriasis-associated DNA sequence variation, genes mapping to five of the differentially methylated sites manifested decreased mRNA expression correlating with increased DNA methylation, whereas the remaining four did not. A major role of DNA methylation, and of epigenetic regulation in general, is to enforce different patterns of gene expression in different cell types. For this reason, epigenetic studies differ from genetic studies in that they are critically dependent on the cell type being analyzed. Besides skin biopsy samples, Zhou et al. analyzed the nine replicated CpG methylation sites in peripheral blood mononuclear cells. They found that blood and skin methylation values differed significantly for three of the nine sites examined, which would be consistent with the fact that keratinocytes are by far the predominant cell type in skin but are not present in peripheral blood mononuclear cells.

One of the mysteries of GWASs is that they consistently fail to account for all of the heritability predicted by twin and family studies (Manolio et al., 2009). Although there are many possible explanations, a likely one is that there exist many small effects that even large GWASs are unable to detect because of limited sample size. Scientists from Spain and the UK tackled this problem by analyzing their GWAS data in terms of biological pathways (Aterido et al., 2016). They began by imposing a relaxed threshold ($P < 0.05$) to

declare disease association, thereby allowing the hypothesized small effects to be noted. Although this approach will undoubtedly yield some false positive results, the concept is that the true positive results will aggregate into discrete biological pathways. Beginning with a discovery cohort of 2,281 Spanish patients and control subjects, the researchers found 14 genetic pathways to be significantly associated with psoriasis risk after multiple testing correction, and six of these were confirmed in an independent validation cohort of 7,353 individuals from the UK. This "genome-wide pathway analysis" identified single nucleotide polymorphisms near 37 "small effect" genes, which mapped to functional pathways. Besides "inflammatory response," "natural killer T cell," and "DNA repair," this analysis identified three pathways that had not been previously associated with psoriasis, including "retinol metabolism," "transport of inorganic ions and amino acids," and "posttranslational protein modification." Although promising, this study is limited not only by the inclusion of disease associations that may ultimately prove to be false positive but also the inherent limitations of pathway annotation and the proximity of some genetic signals to genes belonging to different biological pathways (for example, *REV3L* and *TRAF3IP2*). Nevertheless, the results merit further confirmation, whether by means of even larger GWASs or through functional studies.

**Advances in genomics**

Over the past 15 years, several studies of the psoriatic skin transcriptome have been carried out, initially by microarray analysis and subsequently by high-throughput cDNA sequencing (RNA-seq). More recently, these studies have expanded to include proteomics and metabolomics (Jiang et al., 2015). Each of these techniques provides complementary molecular information, but they all are limited to the extent that skin is a complex, multicellular tissue, and the "-omics" results must be interpreted in that light. Techniques such as laser capture microdissection (Lovendorf et al., 2015) and single cell transcriptomic analysis (Joost et al., 2016) are beginning to provide higher levels of cellular detail in transcriptomic data.

Two recent publications used microarray-based transcriptomics to define the spectrum of mild to severe psoriasis: one comparing Asian- versus European-origin psoriatics (Kim et al., 2016b), and another comparing European-origin psoriatics with mild versus severe disease (Kim et al., 2016a). The prevalence of psoriasis is lower in Asian individuals compared with European-origin individuals. Asians also tend to have less severe psoriasis, leading some authors to describe a distinct phenotype called "small plaque psoriasis" in many (but not all) Asian individuals. Because comparison of Asian and European-origin individuals does not control for many possible genetic confounders, the follow-up study focused only on Europeans. Using microarrays and quantitative PCR, both studies found higher expression of negative regulatory immune genes in lesional skin of patients with milder disease, including CTLA4, CD69, Fas, and PL-L1. These findings suggest that psoriatic inflammation is under dynamic counterregulation and that the balance between positive and negative immune regulators is likely to be a key determinant of disease severity.

Another exciting advance, highlighted in two *JID* articles, is the ability to obtain transcriptomic data from RNA extracted from formalin-fixed, paraffin-embedded tissues (Rittié et al., 2016; Xing et al., 2016). One of these followed up on the observation of coordinately expressed lipid biosynthetic genes, the expression of which is decreased in lesional psoriatic compared with normal skin (Li et al., 2014). Using three-dimensional reconstructions of horizontally sectioned biopsy samples, Rittié et al. showed that sebaceous glands were markedly atrophic in psoriatic lesions (Rittié et al., 2016). Using RNA extracted from formalin-fixed, paraffin-embedded–preserved lesions of sebaceous hyperplasia compared with normal skin, they identified a set of genes more than 4-fold increased in sebaceous hyperplasia and more than 4-fold decreased in psoriasis. All genes in this signature belonged to the same co-expressed module in normal skin, which they related to IL-17 signaling by identifying an inverse relationship of the sebaceous gland and keratinocyte responses to IL-17. The second article used RNA from formalin-fixed, paraffin-embedded skin biopsy samples to compare the transcriptomes of chronic plaque, inverse, and erythrodermic psoriasis (Xing et al., 2016). Both subtype-specific and shared expression signatures were identified, with the highest proportion of subtype-specific genes belonging to chronic plaque psoriasis. The most enriched canonical pathway from the group of genes shared among plaque, inverse, and erythrodermic psoriasis was IL-17 signaling, followed by p38 mitogen-activated protein kinase signaling and communication between innate and adaptive immune cells. Thus, this study also identified a central role for IL-17 responsiveness in multiple subtypes of psoriasis.

Two other articles (Inkeles et al., 2015; Swindell et al., 2016) described further development of bioinformatic tools allowing the transcriptomic comparison of psoriasis with other skin diseases using data deposited in the Gene Expression Omnibus and other publicly available databases. Both studies also incorporated data on keratinocyte responses to various cytokines, also deposited in Gene Expression Omnibus. The 2015 study used disease-specific signatures to generate a multidisease classifier, which predicted the clinical diagnosis with 93% accuracy. This study also identified a significant inverse correlation between IFN-β– and IFN-γ–induced gene expression programs, which extended across all conditions studied. The 2016 study used RNA-seq–based meta-analysis to distinguish psoriasis-specific differentially expressed genes from nonspecific differentially expressed genes similarly altered in many other skin conditions. Psoriasis-specific differentially expressed genes were expressed by keratinocytes and induced by IL-17A, whereas nonspecific differentially expressed genes were expressed by inflammatory cells and induced by IFN-γ and tumor necrosis factor. These studies further emphasize the distinctive importance of IL-17 signaling to keratinocytes in the pathogenesis of psoriasis, which is occurring in the context of a less specific background signature produced largely but not solely by inflammatory cells.

lncRNAs are defined as sequences longer than 200 nucleotides, which do not encode proteins. lncRNAs are emerging as major regulators of development and differentiation, acting at multiple levels including chromatin

organization. A 2016 *JID* study by Gupta et al. (2016) described the landscape of lncRNAs in psoriatic versus healthy skin. This study expanded on an earlier study of lncRNAs in psoriasis (Tsoi et al., 2015) by using ribosomal RNA-depleted rather than polyadenylated RNA as the starting point for the construction of RNA-seq libraries. Comparisons of differentially expressed lncRNAs in lesional and normal skin identified an lncRNA signature capable of distinguishing the two and showed improvement after anti-TNF treatment. The study also used a "guilt by association" approach similar to that used by Tsoi et al. (2015) to gain insight into the function of the identified lncRNAs. There was strong agreement with respect to differentially expressed lncRNAs between the two datasets. The Tsoi et al. study found that the up-regulated lncRNAs in psoriatic skin were significantly enriched (over 2-fold) for lncRNAs induced by IL17+TNF in keratinocytes (Tsoi et al., 2015), further emphasizing the importance of IL-17 signaling, in concert with other cytokines, in the pathogenesis of psoriasis.

## SUMMARY

We apologize to the many authors whose outstanding work in psoriasis research could not be highlighted in this article. Other comprehensive reviews of the field may acknowledge the many recent advances beyond those highlighted in this article. The immunology and genetics of psoriasis are, as we have long suspected, indeed complex, but in our drive to understand the heterogeneity and regulatory pathways that govern psoriasis, we begin to personalize care toward our patients based on biogenetic markers and identify new avenues for treatment based on a more complete understanding of the immunological mechanisms at play.

## CONFLICT OF INTEREST

The authors state no conflict of interest.

## REFERENCES

Arakawa A, Siewert K, Stohr J, Besgen P, Kim SM, Ruhl G, et al. Melanocyte antigen triggers autoimmunity in human psoriasis. J Exp Med 2015;212:2203–12.

Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc 2013;2(2):e000062.

Aterido A, Julia A, Ferrandiz C, Puig L, Fonseca E, Fernandez-Lopez E, et al. Genome-wide pathway analysis identifies genetic pathways associated with psoriasis. J Invest Dermatol 2016;136:593–602.

Chang JC, Smith LR, Froning KJ, Schwabe BJ, Laxer JA, Caralli LL, et al. CD8+ T cells in psoriatic lesions preferentially use T-cell receptor V beta 3 and/or V beta 13.1 genes. Proc Natl Acad Sci USA 1994;91:9282–6.

Cheung L, Fisher RM, Kuzmina N, Li D, Li X, Werngren O, et al. Psoriasis skin inflammation-induced microRNA-26b targets NCEH1 in underlying subcutaneous adipose tissue. J Invest Dermatol 2016;136:640–8.

Chiricozzi A, Guttman-Yassky E, Suarez-Farinas M, Nograles KE, Tian S, Cardinale I, et al. Integrative responses to IL-17 and TNF-alpha in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. J Invest Dermatol 2011;131:677–87.

Doshi JA, Takeshita J, Pinto L, Li P, Yu X, Rao P, et al. Biologic therapy adherence, discontinuation, switching, and restarting among patients with psoriasis in the US Medicare population. J Am Acad Dermatol 2016;74:1057–65.

Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA 2006;296:1735–41.

Gudjonsson JE, Karason A, Antonsdottir A, Runarsdottir EH, Hauksson VB, Upmanyu R, et al. Psoriasis patients who are homozygous for the HLA-Cw*0602 allele have a 2.5-fold increased risk of developing psoriasis compared with Cw6 heterozygotes. Br J Dermatol 2003;148:233–5.

Gupta R, Ahn R, Lai K, Mullins E, Debbaneh M, Dimon M, et al. Landscape of long noncoding RNAs in psoriatic and healthy skin. J Invest Dermatol 2016;136:603–9.

Homey B, Dieu-Nosjean MC, Wiesenborn A, Massacrier C, Pin JJ, Oldham E, et al. Up-regulation of macrophage inflammatory protein-3 alpha/CCL20 and CC chemokine receptor 6 in psoriasis. J Immunol 2000;164:6621–32.

Igarashi M, Osuga J, Uozaki H, Sekiya M, Nagashima S, Takahashi M, et al. The critical role of neutral cholesterol ester hydrolase 1 in cholesterol removal from human macrophages. Circ Res 2010;107:1387–95.

Inkeles MS, Scumpia PO, Swindell WR, Lopez D, Teles RM, Graeber TG, et al. Comparison of molecular signatures from multiple skin diseases identifies mechanisms of immunopathogenesis. J Invest Dermatol 2015;135:151–9.

Iskandar IY, Ashcroft DM, Warren RB, Evans I, McElhone K, Owen CM, et al. Patterns of biologic therapy use in the management of psoriasis: cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR) [e-pub ahead of print]. Br J Dermatol 2016; http://dx.doi.org/10.1111/bjd.15027.

Jiang S, Hinchliffe TE, Wu T. Biomarkers of an autoimmune skin disease–psoriasis. Genomics Proteomics Bioinformatics 2015;13:224–33.

Johansen C, Bertelsen T, Ljungberg C, Mose M, Iversen L. Characterization of TNF-alpha- and IL-17A-mediated synergistic induction of DEFB4 gene expression in human keratinocytes through IκBζ. J Invest Dermatol 2016;136:1608–16.

Joost S, Zeisel A, Jacob T, Sun X, La Manno G, Lonnerberg P, et al. Single-cell transcriptomics reveals that differentiation and spatial signatures shape epidermal and hair follicle heterogeneity. Cell Syst 2016;3(3):221–37.

Joshi AA, Lerman JB, Aberra TM, Afshar M, Teague HL, Rodante JA, et al. GlycA is a novel biomarker of inflammation and subclinical cardiovascular disease in psoriasis [e-pub ahead of print]. Circ Res 2016; http://dx.doi.org/10.1161/CIRCRESAHA.116.309637.

Karbiener M, Pisani DF, Frontini A, Oberreiter LM, Lang E, Vegiopoulos A, et al. MicroRNA-26 family is required for human adipogenesis and drives characteristics of brown adipocytes. Stem Cells 2014;32:1578–90.

Kim J, Bissonnette R, Lee J, Correa da Rosa J, Suarez-Farinas M, Lowes MA, et al. The spectrum of mild to severe psoriasis vulgaris is defined by a common activation of IL-17 pathway genes, but with key differences in immune regulatory genes. J Invest Dermatol 2016a;136:2173–82.

Kim J, Oh CH, Jeon J, Baek Y, Ahn J, Kim DJ, et al. Molecular phenotyping small (Asian) versus large (Western) plaque psoriasis shows common activation of IL-17 pathway genes but different regulatory gene sets. J Invest Dermatol 2016b;136:161–72.

Koch M, Baurecht H, Ried JS, Rodriguez E, Schlesinger S, Volks N, et al. Psoriasis and cardiometabolic traits: modest association but distinct genetic architectures. J Invest Dermatol 2015;135:1283–93.

Lande R, Botti E, Jandus C, Dojcinovic D, Fanelli G, Conrad C, et al. The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis. Nat Commun 2014;5:5621.

Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B, et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Nature 2007;449(7162):564–9.

Li B, Tsoi LC, Swindell WR, Gudjonsson JE, Tejasvi T, Johnston A, et al. Transcriptome analysis of psoriasis in a large case-control sample: RNA-Seq rovides insights into disease mechanisms. J Invest Dermatol 2014;134:1828–38.

Li K, Huang CC, Randazzo B, Li S, Szapary P, Curran M, et al. HLA-C*06:02 allele and response to IL-12/23 inhibition: results from the ustekinumab phase 3 psoriasis program. J Invest Dermatol 2016;136:2364–71.

Lovendorf MB, Mitsui H, Zibert JR, Ropke MA, Hafner M, Dyring-Andersen B, et al. Laser capture microdissection followed by next-generation sequencing identifies disease-related microRNAs in psoriatic skin that reflect systemic microRNA changes in psoriasis. Exp Dermatol 2015;24:187–93.

Mabuchi T, Hirayama N. Binding affinity and interaction of LL-37 with HLA-C*06:02 in psoriasis. J Invest Dermatol 2016;136:1901–3.

Mabuchi T, Singh TP, Takekoshi T, Jia GF, Wu X, Kao MC, et al. CCR6 is required for epidermal trafficking of gammadelta-T cells in an IL-23-induced model of psoriasiform dermatitis. J Invest Dermatol 2013;133:164–71.

Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, et al. Finding the missing heritability of complex diseases. Nature 2009;461(7265):747–53.

Menting SP, Coussens E, Pouw MF, van den Reek JM, Temmerman L, Boonen H, et al. Developing a therapeutic range of adalimumab serum concentrations in management of psoriasis: a step toward personalized treatment. JAMA Dermatol 2015a;151:616–22.

Menting SP, van den Reek JM, Baerveldt EM, de Jong EM, Prens EP, Lecluse LL, et al. The correlation of clinical efficacy, serum trough levels and antidrug antibodies in ustekinumab-treated patients with psoriasis in a clinical-practice setting. Br J Dermatol 2015b;173:855–7.

Nijsten T, Wakkee M. Complexity of the association between psoriasis and comorbidities. J Invest Dermatol 2009;129:1601–3.

Parisi R, Rutter MK, Lunt M, Young HS, Symmons DP, Griffiths CE, et al. Psoriasis and the risk of major cardiovascular events: cohort study using the clinical practice research datalink. J Invest Dermatol 2015;135:2189–97.

Ray-Jones H, Eyre S, Barton A, Warren RB. One SNP at a time: moving beyond GWAS in psoriasis. J Invest Dermatol 2016;136:567–73.

Rittié L, Tejasvi T, Harms PW, Xing X, Nair RP, Gudjonsson JE, et al. Sebaceous gland atrophy in psoriasis: an explanation for psoriatic alopecia? J Invest Dermatol 2016;136:1792–800.

Rohrl J, Yang D, Oppenheim JJ, Hehlgans T. Specific binding and chemotactic activity of mBD4 and its functional orthologue hBD2 to CCR6-expressing cells. J Biol Chem 2010;285:7028–34.

Sagoo GS, Tazi-Ahnini R, Barker JW, Elder JT, Nair RP, Samuelsson L, et al. Meta-analysis of genome-wide studies of psoriasis susceptibility reveals linkage to chromosomes 6p21 and 4q28-q31 in Caucasian and Chinese Hans population. J Invest Dermatol 2004;122:1401–5.

Stuart PE, Nair RP, Tsoi LC, Tejasvi T, Das S, Kang HM, et al. Genome-wide aAssociation analysis of psoriatic arthritis and cutaneous psoriasis reveals cifferences in their genetic architecture. Am J Hum Genet 2015;97:816–36.

Sweeney CM, Russell SE, Malara A, Kelly G, Hughes R, Tobin AM, et al. Human ss-defensin 3 and its mouse ortholog murine ss-defensin 14 activate Langerhans cells and exacerbate psoriasis-like skin inflammation in mice. J Invest Dermatol 2016;136:723–7.

Swindell WR, Sarkar MK, Liang Y, Xing X, Gudjonsson JE. Cross-disease transcriptomics: unique IL-17A signaling in psoriasis lesions and an autoimmune PBMC signature. J Invest Dermatol 2016;136:1820–30.

Takeshita J, Gelfand JM, Li P, Pinto L, Yu X, Rao P, et al. Psoriasis in the US Medicare population: prevalence, treatment, and factors associated with biologic use. J Invest Dermatol 2015;135:2955–63.

Tsoi LC, Iyer MK, Stuart PE, Swindell WR, Gudjonsson JE, Tejasvi T, et al. Analysis of long non-coding RNAs highlights tissue-specific expression patterns and epigenetic profiles in normal and psoriatic skin. Genome Biol 2015;16:24.

Xing X, Liang Y, Sarkar MK, Wolterink L, Swindell WR, Voorhees JJ, et al. IL-17 responses are the dominant inflammatory signal linking inverse, erythrodermic, and chronic plaque psoriasis. J Invest Dermatol 2016;136:2498–501.

Zhou F, Wang W, Shen C, Li H, Zuo X, Zheng X, et al. Epigenome-wide association analysis identified nine skin DNA methylation loci for psoriasis. J Invest Dermatol 2016;136:779–87.

Zweegers J, van den Reek JM, van de Kerkhof PC, Otero ME, Kuijpers AL, Koetsier MI, et al. Body mass index predicts discontinuation due to ineffectiveness and female sex predicts discontinuation due to side-effects in patients with psoriasis treated with adalimumab, etanercept or ustekinumab in daily practice: a prospective, comparative, long-term drug-survival study from the BioCAPTURE registry. Br J Dermatol 2016;175:340–7.