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Interactions of the Immune System with Skin and Bone Tissue in Psoriatic Arthritis: A Comprehensive Review

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Abstract Cutaneous psoriasis (e.g., psoriasis vulgaris (PsV)) and psoriatic arthritis (PsA) are complex heterogeneous diseases thought to have similar pathophysiology. The soluble and cellular mediators of these closely related diseases are being elucidated through genetic approaches such as genome-wide association studies (GWAS), as well as animal and molecular models. Novel therapeutics targeting these mediators (IL-12, IL-23, IL-17, IL-17 receptor, TNF) are effective in treating both the skin and joint manifestations of psoriasis, reaffirming the shared pathophysiology of PsV and PsA. However, the molecular and cellular interactions between skin and joint disease have not been well characterized. Clearly, PsV and PsA are highly variable in terms of their clinical manifestations, and this heterogeneity can partially be explained by differences in HLA-associations (HLA-Cw*0602 versus HLA-B*27, for example). In addition, there are numerous other genetic susceptibility loci (*LCE3*, *CARD14*, *NOS2*, *NFKBIA*, *PSMA6*, *ERAP1*, *TRAF3IP2*, *IL12RB2*, *IL23R*, *IL12B*, *TNIP1*, *TNFAIP3*, *TYK2*) and geoepidemiologic factors that contribute to the wide variability seen in psoriasis. Herein, we review the complex interplay between the genetic, cellular, ethnic, and geographic mediators of psoriasis, focusing on the shared mechanisms of PsV and PsA.

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Introduction

Psoriatic arthritis (PsA) is a unique type of inflammatory arthritis that by definition requires the presence of cutaneous psoriasis. Though Moll and Wright were not the first to describe the relationship between cutaneous psoriasis and arthritis, they did provide the epidemiologic, clinical, radiologic, and serologic evidence that defined PsA as a distinct entity, different from other common arthritides like rheumatoid arthritis [1]. Also, they described five clinical patterns of PsA: oligoarticular asymmetrical, polyarticular rheumatoid arthritis-like, distal predominant, spondylitis, and arthritis mutilans. Similar to PsA, cutaneous psoriasis has a variable presentation with different subtypes including guttate, inverse, palmoplantar, pustular, erythrodermic, and the most common, plaque psoriasis. Plaque psoriasis is known as psoriasis vulgaris (PsV), and for the most part PsV predates the onset of arthritis, although this pattern deviates in a small percent of cases [2]. Many aspects of psoriasis pathophysiology remain a mystery despite our new insight into effector cytokines, chemokines, and cell mediators, and the recent advances in psoriasis genetics. This review will discuss the psoriasis genetic susceptibility loci including HLA associations, cell mediators common to both PsV and PsA, and geoepidemiology of psoriasis.

Skin Physiology and Pathology

In broad terms, skin is composed of two layers, the dermis and epidermis, which are separated by a basement

membrane. Basal keratinocytes reside on the basement membrane, generating prodigy that undergo distinct stages of differentiation to ultimately become the stratum corneum, an enucleated, metabolically inactive layer. The layers of the epidermis include the stratum corneum (the outermost layer), stratum granulosum, stratum spinosum, and stratum basale. Each of these layers becomes altered in the setting of PsV (Fig. 1).

Although PsV is usually a clinical diagnosis, challenging presentations sometime require a biopsy. While no consensus guidelines exist for the histologic diagnosis of PsV, "characteristic" histologic features have been well described in the medical literature. The major features include thinned suprapapillary plates, with occasional formation of spongiform pustules of Kogoj; collections of neutrophils in the stratum corneum, termed Munro's microabscesses; psoriasiform epithelial hyperplasia; elongation and edema of dermal papillae; continuous or alternating parakeratosis, retained nuclei in the stratum corneum; a diminished or absent granular layer; and dilated and tortuous capillaries [3, 4]. Given the microscopic diversity of PsV, Trozak created a grading system where histologic features were assigned a number score based on features considered most characteristic of the disease [5]. Nearly pathognomonic histologic findings include Munro's microabscesses and the spongiform pustules of Kojog; thus, these features were given the highest numerical value [6]. Club-shaped rete ridges, suprapapillary plate thinning, total (as opposed to focal) parakeratosis, and absence of a granular layer are considered characteristic of psoriasis, but were given a lesser score as these features can also be seen in other dermatologic conditions [5]. Complicating the histologic diagnosis of PsV further is the finding that early and longstanding lesions can display different features [5].

Genetic Susceptibility Loci

Given the common underlying mechanisms of PsV and PsA, it is somewhat surprising that only 20–30 % of patients with PsV develop joint disease [2, 7]. Heterogeneity in disease presentation is partially reconciled by HLA types, which have been implicated to dictate phenotype, disease onset, and severity. Though the majority of patients ascribe to a typical timeline with arthritis following cutaneous onset, deviations from this stereotype can be explained through HLA genotypes. The major polarizing HLA types, HLA-Cw*0602 and HLA-B*27, are paradigms for primarily cutaneous and joint disease, respectively. These and other genetic susceptibility loci are discussed below, and additional loci are listed in Table 1.

HLA Associations

*HLA-Cw*0602*

PsV is strongly associated with the human leukocyte-associated antigen (HLA), Cw6. HLA-C, a type of MHC class I molecule, is expressed on all human nucleated cells. Like other class I molecules, it functions to present endogenously processed antigens to the immune system [8, 9]. Patients with the HLA-Cw*0602 allele have a 10–20-fold increased risk of developing PsV [10]. Gudjonsson et al. demonstrated that heterozygotes have a relative risk of developing psoriasis of 8.9, whereas homozygotes have a relative risk of 23.1, with earlier disease onset being more common in this group [11]. Cibulova et al. found HLA-Cw*0602 to be the most prominent HLA in Type I PsV, correlating well with an earlier disease onset and a family history of psoriasis [12]. This finding was echoed in siblings discordant for HLA-Cw*0602, where the positive HLA-Cw*0602 sibling had significantly early disease onset [13]. Interestingly, there is mixed data regarding the effect of HLA-Cw*0602 on disease severity and phenotype. Some have reported that HLA-Cw*0602 does not dictate severity or phenotype, while others have reported that HLA-Cw*0602 patients develop more extensive disease and guttate-like psoriatic lesions [11, 13–15].

While the data regarding the association with PsV is solid, the relationship between HLA-Cw*0602 and PsA is not as strong. Several studies failed to show a statistically significant relationship between HLA-Cw*0602 and PsA [14, 16]. In one said study, arthritis was more common in the HLA-Cw*0602-negative group, though this difference was not significant [17]. Interestingly, when patients were stratified by onset of skin and joint disease, HLA-Cw*0602 patients had more time-dependent development of musculoskeletal disease [18]. Also, this cohort of patients had a lower percentage of HLA-Cw*0602, thought to be due to more stringent criteria, excluding patients with non-psoriatic musculoskeletal syndromes [18]. Indeed, the complex, heterogeneous presentation of PsA makes gene studies challenging [16].

*HLA-B*27*

While HLA-B27 is widely associated with seronegative spondarthritides such as ankylosing spondylitis, it has also been found to play an important role in PsA. As stated by Winchester et al., the HLA-B*27 allele encodes for a MHC class I molecule with electronegative "B pockets," which bind endogenously processed peptides with positively charged arginine anchor motifs at position P2 [18]. This is a proposed mechanism in ankylosing spondylitis, which might also be related to HLA-B*27's ability to cause PsA [19–22]. HLA-B*27 has been suggested as the strongest risk allele for PsA. In cases of HLA-B*27 positivity, patients had nearly

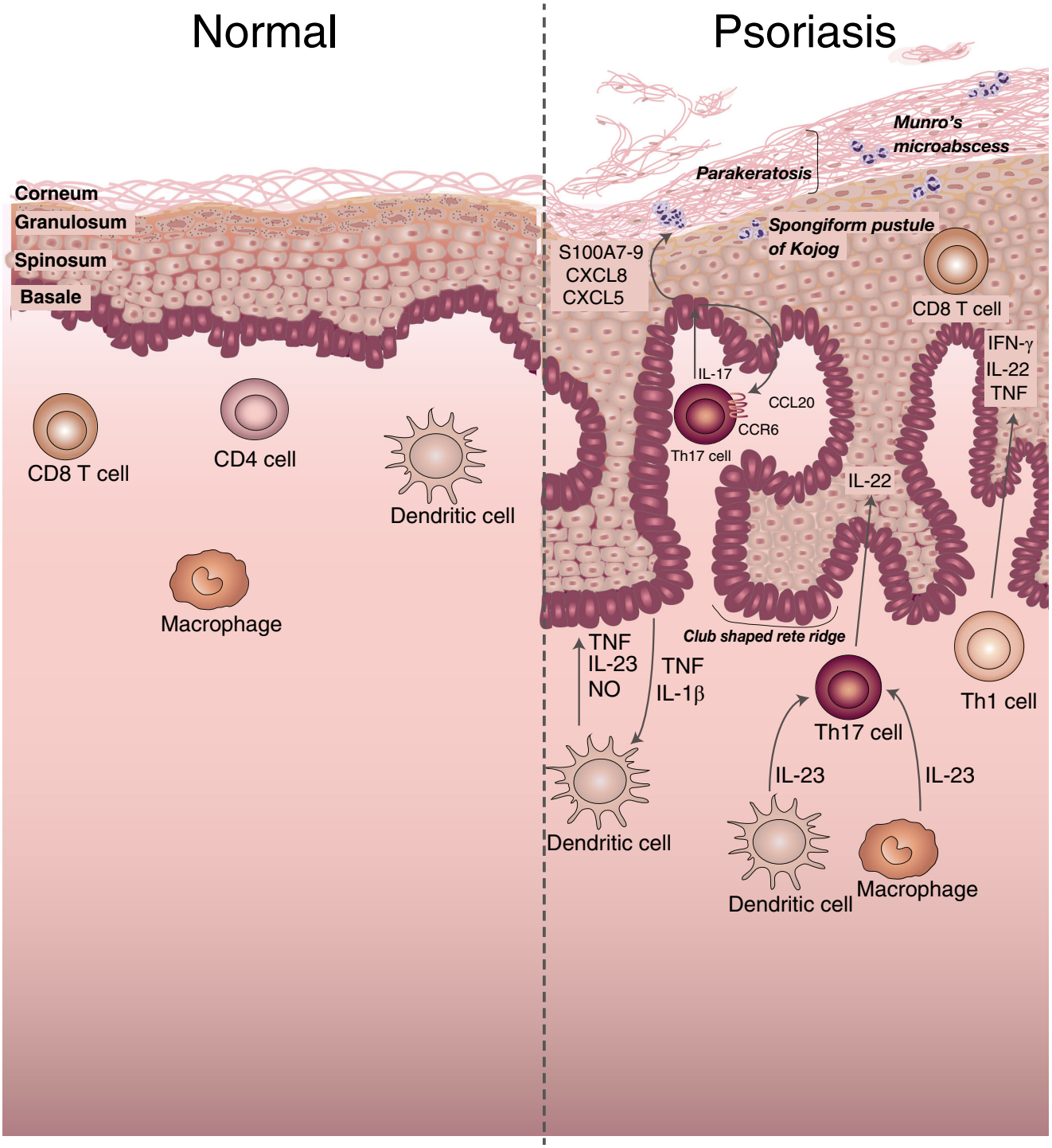

Fig. 1 Normal skin and psoriatic plaque histology. This figure juxtaposes normal and lesional skin to highlight the characteristic histologic changes of cutaneous psoriasis. In comparison to normal skin, psoriatic plaques have: a compact, thickened stratum corneum with retained nuclei (parakeratosis), an absent granular layer, expansion of the stratum spinosum to create club-shaped rete ridges, and neutrophilic collections in the stratum corneum (Munro's microabscesses) and stratum spinosum (spongiform pustules of Kojog). Cellular features common to both cutaneous psoriasis and psoriatic arthritis are shown. Cutaneous psoriasis features dendritic cells and macrophages, which promote the differentiation of T helper 17 (Th17) cells and T helper 1 (Th1) cells. In addition, dendritic cells release TNF, IL-23 and nitric oxide (NO), which stimulate keratinocyte production of TNF and IL-1β. Products of Th17 cells include IL-22, which induces keratinocyte proliferation; IL-17, which stimulates keratinocytes to release neutrophilic chemotactic factors; IL-12 and TNF. In response to IL-17, keratinocytes release CCL20, which attracts additional $CCR6^{+}$ Th17 cells to the skin. Th1 cells release the inflammatory factors IL-22, IFNγ and TNF

Table 1 Genetic susceptibility loci

Antigen presentation		References
*HLA-Cw*0602*	Strongly associated with PsV, earlier disease onset and a positive family history.	[12, 13]
*HLA-B*27*	One of the strongest risk alleles for axial joint disease in PsA.	[23–25]
*HLA-B*39*	Similar to HLA-B*27, this allele encodes electronegative B pockets, and is associated with ankylosing spondylitis and PsA.	[18]
*HLA-B*40*	This allele is protective against PsA, and encodes electropositive B pockets.	[18]
ERAP1	Variants of *ERAP1* have decreased aminopeptidase activity involved in antigen processing, and is associated with HLA-Cw*0602 and HLA-B*27 alleles.	[47]
PSMA6	*PSMA6* encodes a subunit involved in MHC class I antigen processing.	[38]
Skin barrier function		
LCE3	The *LCE3C_LCEB-del* is thought to increase susceptibility to exogenous substances due to impaired barrier function in PsV.	[28, 30, 31]
Innate immune response		
CARD14	*CARD14* activates NF-κB which upregulates IL-8 and CCL20 in skin, and controls early osteoclast differentiation in bone.	[34–36]
NOS2	*NOS2* encodes inducible nitric oxide synthase, which has increased expression in psoriatic plaques and synovium.	[39–42]
TNIP1, *TNFAIP3*	These genes control the ubiquination and degradation of IκB-a, which inhibits NF-κB transcription by retaining it in the cytoplasm.	[44, 45]
NFKBIA	*NFKBIA* encodes IκB-a, which is an inhibitor of NF-κB signaling.	[38]
Adaptive immune response		
IL12B	Significantly increased levels of *IL12B* gene expression have been identified in psoriatic plaques. *IL12B* encodes the common subunit of IL-12 and IL-23.	[28, 62]
IL23R, *IL23A*	*IL23R* encodes the receptor for IL-23, which is a cytokine critical for the survival and stabilization of Th17 cells. *IL23A* encodes the p40 subunit of IL-23.	[28, 48, 59]
IL12RB2, *TYK2*	*IL12RB2* encodes the IL-12 receptor, and is critical in controlling Th1 lineage differentiation and responsiveness to IL-12. *TYK2* is required for IL-12B1 signaling.	[28, 48, 59, 60]
TRAF3IP2	*TRAF3IP2* encodes adaptor protein CIKS (Act1), which is recruited to IL-17RA, a significant step required for the expression of IL-17 mediated inflammatory genes.	[56, 57]

HLA human leukocyte antigen, *PsV* psoriasis vulgaris (plaque psoriasis), *PsA* psoriatic arthritis, *LCE* late cornified envelope, *ERAP1* endoplasmic reticulum aminopeptidase 1, *CARD14* caspase recruitment domain family member 14, *TNFAIP3* TNF alpha-induced protein 3, *TNIP1* TNKAIP3 interacting protein 1, *IL* interleukin, *TRAF3IP2* TRAF 3 interacting protein 2

contemporaneous onset of cutaneous and musculoskeletal disease, with less extensive skin disease [18]. This phenomenon was found in other studies showing decreased time between skin and joint disease in patients with HLA-B*27, as well as earlier disease onset of both PsV and PsA [16]. Winchester postulated that self peptides presented by HLA-B*27 give rise to autoreactive T cells, specific to skin and joints, whereas HLA-Cw*0602-presented autoantigens might primarily be of cutaneous origin [18].

With regard to arthritis, HLA-B*27 is strongly associated with axial disease [23–25]. McHugh et al. found that the association with HLA-B*27, and spondylitis became weaker as more peripheral joints were involved [26]. Others have found an increased risk of HLA-B*27-positive individuals developing enthesitis, dactylitis, and uveitis [27]. Given the presence of similar extra-articular features (mucous membrane lesions, iritis, urethritis, diarrhea, and aortic root dilatation), rheumatoid factor seronegativity, and spondarthritis, PsA makes for a natural member of HLA-B*27-associated spondyloarthritides [2]. For other HLA associations and skin and joint affiliations, see Table 1.

Genes of Skin Barrier Function

LCE3

In addition to HLA alleles, genes involved in skin barrier function, the innate system, and the adaptive immune system have known ties to PsV and PsA pathophysiology. Of the genes involved in skin barrier function, only *LCE3* has been associated with both PsV and PsA [28]. The late cornified envelope gene cluster 3 (*LCE3*) is part of the *epidermal differentiation complex* (*EDC*) that encodes stratum corneum proteins in the cornified envelope that have potential functions in epidermal terminal differentiation [29]. LCE3 proteins encompass five genes (*LCE3A*, *LCE3B*, *LCE3C*, *LCE3D*, *LCE3E*), each with a unique structure and function [30]. Of these genes, deletions of *LCE3B* and *LCE3C (LCE3C_LCE3B-del)* are significantly associated with the risk of PsV and PsA [30]. One possibility is that a breach of the skin barrier function allows for a cross-reactive skin/joint immune response to develop. An alternative hypothesis is that *LCE3* deletions affect tissues

other than the skin, promoting autoimmunity at multiple sites.

With regard to skin barrier function, *LCE3C* promotes hyperproliferation and keratinocyte differentiation in normal individuals following tape stripping [31]. This response was not seen in patients homozygous for *LCE3C_LCE3B-del*. De Cid et al. suggested that this deletion could result in impaired epidermal repair after barrier disruption, causing increased susceptibility to exogenous antigens, resulting in inflammation. The latter mechanism supports the Koebner phenomenon, whereby non-lesional skin develops inflammatory lesions in response to traumatic exfoliation [31].

Genes of the Innate Immune Response

CARD14

Whereas *LCE3* encodes skin barrier function, caspase recruitment domain family member 14 (*CARD14*) is closely tied to the innate (and adaptive) immune system via NF-κB. The psoriasis susceptibility locus 2 (PSORS2) is due to a gain of function mutation in *CARD14* that affect epithelial and stromal cells [32, 33]. In addition, localization of *CARD14* is different in psoriatic plaques compared to normal skin. Jordan et al. found psoriatic plaques had reduced expression of *CARD14* in basal layers and mild upregulation in suprabasal layers [32]. In the skin, *CARD14* induces activation of NF-κB that in turn upregulates a variety of factors including keratinocyte IL-8, which is a strong neutrophilic chemotactic factor, and CCL20 [34, 35]. In the joint, *CARD14* induces inflammation through NF-κB-mediated processes, triggering early osteoclast differentiation via RANKL and TNF [36]. The requirement of NF-κB activation in bone resorption has previously been demonstrated in NF-κB deficient mice that develop osteopetrosis due to an absence of bone resorbing osteoclasts [37].

NOS2

Like *CARD14*, *NOS2* encodes a protein involved in the innate immune system. SNP rs4795067 maps to the intron of the *NOS2* gene, which encodes inducible nitric oxide synthase (iNOS), an enzyme responsible for producing the proinflammatory signaling molecule, nitric oxide. While this SNP was significant only in subphenotye analysis for PsV, it was strongly associated with PsA [38]. Melchiorri et al. demonstrated that iNOS is markedly overexpressed in the synovium, either by synovial fibroblasts or infiltrating dendritic cells in the setting of PsA [39]. Increased iNOS leads to activation of metalloproteinases and inhibits the production of the matrix elements [39, 40]. The importance of iNOS in the pathophysiology of PsV has also been well highlighted in the literature. Within psoriatic skin, Zaba et al. described a 30-fold increase of TNF-producing CD11c-positive ($CD11c^+$), CD1c-negative dendritic cells expressing iNOS [41, 42]. Through anti-$CD11c^+$ therapy, Lowes et al. demonstrated that PsV disease activity correlates less to T cell infiltrates and more to dendritic cell infiltration and iNOS expression [42]. This study suggests that dendritic cells accumulate in psoriatic lesions and perpetuate inflammation though production of iNOS and TNF.

Genes of the Adaptive Immune System

NFKBIA, PSMA6, and ERAP1

NFKBIA, *PSMA6*, and *ERAP1* are genes involved in the adaptive immune system thought to be important in PsA and PsV pathophysiology. An SNP (rs12586317) in the region of the genes *KIAA0391*, *PSMA6*, and *NFKBIA* was found to be significantly associated with PsV and PsA [38]. Of the three genes, *NFKBIA* and *PSMA6* are considered most significant in PsV susceptibility. IκB-a, which is an inhibitor of NF-κB signaling, is encoded by *NFKBIA* [38]. IκB-a retains NF-κB in the cytoplasm by sterically blocking the NF-κB nuclear localizing sequence [43]. Many activating agents of NF-κB, like TNF and IL-1, disrupt the IκB-a /NF-κB interaction by phosphorylation-induced degradation of IκB-a, allowing NF-κB to translocate to the nucleus [43]. Transcriptional products of NF-κB include chemokines (CXCL1, CXCL2, CXCL10), cytokines (TNF, IL-6, IL1β), negative cell regulators (A20, NFKBIA), and the cell survival factors (BCL2L1 and PAI2). Additional genetic susceptibility loci involving the NF-κB pathway include TNF alpha-induced protein 3 (*TNFAIP3*) and TNKAIP3 interacting protein 1 (*TNIP1*) that activate NF-κB through ubiquitination and degradation of IκB-a [44, 45].

In contrast, *ERAP1* and *PSMA6* encode protein involved in MHC class I antigen processing [38]. Endoplasmic reticulum aminopeptidase 1 (ERAP1) processes peptides within the endoplasmic reticulum that are presented by HLA molecules on antigen-presenting cells [46]. Molecular models of an *ERAP1* gene variant showed decreased aminopeptidase activity in the enzyme pocket [47]. Given its role of antigen processing, it is thought that ERAP1 could process autoantigens, which are then presented by HLA-Cw6 [48]. This theory is strengthened by the finding that PsV susceptibility was only influenced in patients carrying the *ERAP1* gene variant in the presence of HLA-Cw*0602 [49]. *ERAP1* has been associated with the PsA subtype resembling ankylosing spondylitis, which is not surprising considering *ERAP1* has been shown to affect HL-B27 expression [50]. Chen et al. demonstrated that an *ERAP1* variant increased HLA-B27 free heavy chain expression in HeLa.B27 and ERAAP $^{-/-}$ cells compared to protective *ERAP1* variants [50]. HLA-B27 free heavy chains are cell membrane-

bound remnants of the HLA-B27 molecule after dissociation of the β2-microglobulin and peptide. Traditionally, heavy chains are thought to translocate to the cell surface as part of a fully functional HLA molecule, though free heavy chains have been shown to reach the cell surface independently of β2-microglobulin and peptide [51, 52]. HLA-B27 free heavy chains have been shown to bind immunoregulatory receptors killer cell immunoglobulin-like receptor 3DL2 (KIR3DL2) with greater affinity, ultimately causing proliferation and survival of IL-17-producing T cells [50, 53, 54].

Similar to *ERAP1*, *PSMA6* is involved in encoding protein involved in MHC class I antigen processing, and it is likely that the disruption of PSMA6's normal function generates autoantigens or other proinflammatory antigens for presentation to pathogenic $CD8^+$ T cells. *PSMA6* is known to be overexpressed in psoriatic lesions [38]. Though the mechanism of *PSMA6* in PsA is not fully understood, *PSMA6* has been significantly associated with ankylosing spondylitis, which suggests a similar etiology for both arthritides [55]. Moreover, polymorphisms of this SNP are associated with other autoimmune diseases such as Graves' disease and inflammatory bowel disease [38].

Cytokines, Chemokines, and Effector Cells

Many of the other genes identified in GWAS encode proteins that overlap with the soluble mediators identified in animal, immunologic, and molecular models of psoriasis. The concept of an altered cytokine network being central to the pathophysiology of PsV and PsA was popularized by the Th1/Th2 hypothesis, with psoriasis being originally labeled as a prototypic Th1 disease [56]. Now, the IL-23/Th17 axis is more at the forefront of current theories, though many cytokines are likely involved in psoriasis pathophysiology. Some of the mechanisms for the major cytokines linked to PSV and PsA are explained below.

IL-23/Th17 Axis

The IL-23/Th17 axis is a major pathway in the pathogenesis of multiple autoimmune diseases, including PsV and PsA. Virtually all elements of the IL-23/Th17 axis (Th17 cells, IL-17, IL-17R, IL-22 and IL-23p19, IL-23R) have been shown to be elevated in psoriatic plaques and synovial fluid of PsA patients [57–62]. Differentiation of Th17 cells occurs after exposure to IL-1β, IL-6, and TGF-β [63–65]. Of these, TGF-β increases responsiveness to IL-23, which is necessary for stabilization, survival, and proliferation of Th17 cells [66, 67]. This may be an oversimplification of the Th17 pathway given the discovery of unique subtypes of Th17 cells, which are described in detail elsewhere [68].

The IL-23/Th17 axis has been shown to evoke the various features of psoriatic plaques. We have found that systemic expression of IL-17A in murine models resulted in neutrophilia and histologic features consistent with plaque psoriasis including epidermal hyperplasia, parakeratosis, and hypertrophy of the spinous layer [69]. Others have shown that IL-17 stimulated keratinocytes to release chemotactic factors IL-8/CXCL8, CXCL3, CXCL5, and CXCL8, causing neutrophil migration, resulting in the formation of Munro's microabscesses [61]. While IL-17 is largely considered the primary proinflammatory cytokine that induces cell trafficking of neutrophils (also dendritic cells and T cells), another Th17-related cytokine, IL-22, is responsible for epidermal hyperplasia by downregulating keratinocyte differentiation genes suggesting that IL-17 and IL-22 mediate distinct pathways that contribute to psoriasis [61]. In addition, IL-23, which partly regulates the Th17 cell population, also seems to stimulate epidermal hyperplasia via other mechanisms involving TNF and IL-20R2 [70]. It is noteworthy that in an animal model of IL-23 overexpression, mixed features of psoriasis and arthritis occur such as enthesitis, pannus formation, and bone erosion has been observed [71, 72] and unpublished data. The mechanism by which the IL-23/Th17 axis induces joint disease is a field of active investigation. Although IL-23 promotes erosive bone disease by stimulating Th17 cells to produce RANKL and IL-17, IL-23 and IL-17 independently induce myeloid cells to undergo osteoclast formation [73–75].

Medications targeting elements of the IL-23/Th17 axis have proven effective in the treatment of both PsA and PsV, further substantiating this axis in psoriasis pathophysiology. Ustekinumab is a cytokine-neutralizing human monoclonal antibody directed against the common p40 subunit shared between IL-12 and IL-23 [76]. By blocking IL-23, ustekinumab inhibits Th17 differentiation and survival thereby decreasing levels of IL-17 [76]. Phase III, randomized, double blind, and placebo-controlled trials of ustekinumab proved successful in treatment of PsV [77, 78]. Similarly, ustekinumab was effective in treatment of PsA with symptomatic and radiographic improvement in dactylitis and enthesitis [79]. IL-17A inhibitors, like secukinumab and ixekizumab, have also proven effective in the treatment of PsV and PsA.

The CLEAR trial demonstrated that secukinumab was superior to ustekinumab in inducing PASI 100 (44.3 % of patients receiving secukinumab versus 28.4 % of patients receiving ustekinumab0 [80]). However in this trial, the dose of secukinumab was markedly higher compared to ustekinumab (300 mg weekly for the first 4 weeks, then every 4 weeks thereafter versus 90 mg on weeks 1 and 4, then every 12 weeks thereafter). Similar to the efficacy in treating PsV, IL-17A inhibitors showed improvement in patients with PsA, demonstrated in the FUTURE 2, FIXTURE, and ERASURE trials [81, 82]. Brodalumab, a monoclonal antibody specific to the

IL-17 receptor, has been shown to be effective in treating PsV; however, due to concern for increased suicide risk, it is unclear if it will make it to market [83]. These trials underscore the shared pathophysiology of the IL-23/Th17 axis in PsA and PsV.

CCL20 and CCR6

Though Th17 cells express a variety of receptors (CCR2, CCR4, CCR5, CXCR3), their hallmark receptor CCR6 distinguishes them from Th1 and Th2 cells [84]. CCR6 is a CC chemokine G protein-coupled receptor. Th17 cells also produce the ligand for CCR6, chemokine (C-C motif) ligand 20 (CCL20), which is a cytokine of the CC chemokine family [84]. While keratinocytes produce low levels of CCL20 at baseline, proinflammatory cytokines, namely IL-17, TNF, IL-1, IFNγ, enhance CCL20 expression [85]. Also, Harper et al. demonstrated that human keratinocytes upregulate CCL20 expression in a dose-dependent manner when exposed to IL-17A, IL-22, and TNF [86].

CCL20 is a chemotactic factor for CCR6+ T cells, immature dendritic cells, and resident epidermal dendritic cells, also known as Langerhan cells [41, 84]. $CCR6^{+}$ T cells include memory T cells and Th17 effector cells, which infiltrate psoriatic lesions in response to CCL20 [61]. Hendrick et al. showed that CCR6 is essential to the psoriasiform phenotype in an animal psoriasis model. Specifically following IL-23 injection, mice that did not express CCR6 failed to develop the IL-23-inducible psoriatic features seen in control animals [87, 88]. Though literature on CCL20 in PsA is not as extensive, CCL20 also strongly correlates with PsA disease activity [89]. Celis et al. have shown that CCL20 in PsA synovial fluid correlates with known markers of inflammation. In addition, CCL20 serum levels strongly correlate with CCL20 synovial fluid levels [89, 90]. Thus, CCL20 fits well into the IL-23/Th17 paradigm, as it acts as a major Th17-attracting chemokine and is elevated in both the blood and synovial fluid of PsA patients.

IL-22

IL-22 is an alpha-helical cytokine belonging to the IL-10 superfamily. It is believed to be involved in psoriasis pathophysiology and is produced by Th17 cells, Th1 cells, and natural killer cells [91]. In the skin, IL-22 modulates keratinocyte mobility, induces acute phase reactants, and promotes antimicrobial defense [91]. Levels of IL-22 are massively overexpressed in psoriatic lesions and increased in serum of PsV patients, the later strongly correlating with disease severity [92, 93]. IL-22 contributes to the PsV phenotype by promoting keratinocyte hyperproliferation and preventing their terminal differentiation [94]. IL-20 and STAT3 amplify the actions of IL-22 by creating a positive feedback loop [95–97]. Similar to the induced hyperproliferation of keratinocytes, IL-22 promotes hyperproliferation leading to entheseal and periosteal bone formation in PsA. Specifically, Mitra et al. found elevated levels of IL-22 in synovial fluid of PsA patients and demonstrated the ability of IL-22 to induce proliferation of fibroblast-like synoviocytes [62]. This effect was magnified in the presence of TNF [62]. Likewise, in a PsA animal model, $IL\text{-}22^{-/-}$ mice had reduced arthritis and pannus formation compared to control animals [98].

TNF

As a prototypic Th1 cytokine and one of the products induced by IL-17 stimulation, it is not surprising that TNF plays a central role in psoriasis pathophysiology [70, 99]. TNF blockade was initially being developed as therapy for sepsis, but its coincidental success in treating PsV revolutionized psoriasis therapy [100]. TNF expression is upregulated in psoriatic skin and is essential to the development of the psoriatic plaque [70]. Boyman et al. demonstrated that mice failed to develop psoriatic plaques when exposed to TNF-neutralizing monoclonal antibodies or receptor fusion proteins [101]. Today, the most commonly prescribed biologics for psoriasis are the TNF inhibitors including etanercept, infliximab, and adalimumab [76]. Although all of these medications neutralize soluble TNF, each have unique properties that tie into their mechanism of action [76]. For a comprehensive review of their differences, see Sivamani et al. (2013). TNF is also implicated in PsA pathophysiology by inducing osteoclastogenesis, and anti-TNF therapy is widely used in PsA with clinical improvement in approximately 70 % of patients [102–104]. TNF is responsible for a stimulating inflammation through a variety of processes, some of which include the production of IL-1, prostaglandin E2, and acute phase reactants, as well as promoting the expression of adhesion molecules in endothelial cells.

IL-12

IL-12 is a heterodimeric inflammatory cytokine made of four alpha helices encoded by *IL-12A* and *IL-12B*. It shares a common subunit (p40) and receptor (IL12RB1) with IL-23. In PsV pathophysiology, IL-12 promotes the differentiation of naïve $CD4^{+}$ T cells into mature IFNγ-producing T-helper type 1 (Th1) effector cells. In addition, it is a potent stimulus of natural killer cells and induces CD8+ T cells to produce IFNγ [56]. High levels of IFNγ transcripts originating from $IFN\gamma^{+}$-secreting T cells are enriched in psoriatic plaques, and multiple studies have shown synergy between Th1 and Th17 pathways in PsV pathophysiology [57, 105–107]. Kryczek et al. demonstrated that IFNγ-stimulated myeloid antigen presenting cells induce differentiation of IL-17-secreting T cells through a mechanism involving IL-1β and IL-23 [57]. In addition,

IFNγ induces CCL20 expression, which promotes homing of Th17 cells to lesional skin [57]. Therefore, both Th1 and Th17 cells play important roles in PsV pathophysiology.

While elements of the IL-12 pathway including *IL12B* and *IL12RB2* are significant to PsV and PsA in GWAS, IL-12 has been shown to play a protective role against the development of PsA [28, 49]. IL-12 has an anti-inflammatory effect on joints, with IL-12 deficient mice experiencing more joint inflammation than control mice [108]. In addition, animal models have shown the absence of IL-12 results in the elevation of IL-1β, IL-6 IL-17, and TNF expression, thus favoring an inflammatory environment [108]. Experimental autoimmune encephalitis (EAE) serves as a model of multiple sclerosis and has supported the anti-inflammatory affects of IL-12. Animals lacking IL-12 were highly susceptible to EAE compared to controls and cited IL-23 as the critical end stage effector cytokine [109, 110]. In fact, the p40 heterodimer shared by IL-12 and IL-23 played a central role in EAE pathogenesis, whereas the p35 subunit (unique to IL-12) conferred a protective effect against EAE [110]. This is in agreement with GWAS where *IL12B*, the gene-encoding p40, is significant to PsA [28]. *IL12RB2* codes for the subunit unique to IL-12 and lies adjacent to IL23R on chromosome 1, whereby inactivation of this gene could result in autoimmunity [111]. Therefore, IL-12 is significant to PsA development through its own inactivation, or its association with the p40 subunit.

RANK/RANKL

Receptor activator of nuclear factor κB (RANK) is widely associated with bone metabolism and plays a pathogenic role in PsV as well. RANK (the receptor for RANKL) is found on epidermal dendritic cells [112]. Keratinocytes residing in all epidermal layers within lesional psoriatic skin strongly express RANKL. Interestingly, Loser et al. demonstrated that RANK expression does not change epidermal dendritic cell behavior or number, but when stimulated by RANKL, causes increased proliferation of $CD4^+CD25^+$ T cells [112]. This compliments the finding whereby psoriatic plaques have a proliferation of regulatory T cells [113]. In addition, Sugiyama et al. found that dermal $CD4^+CD25^+$ T cells demonstrated decreased suppression of effector T cells, though this finding was not replicated by Loser et al. [113, 114]. Perhaps increased RANKL expression in psoriatic plaques leads to the expansion of non-functional regulatory T cells, resulting in the increased activity of effector T cells. Though much still needs to be explored in the RANK/RANKL pathway in PsV, the pathophysiology of RANKL in arthritis has been well described. RANKL is critical to osteoclastogenesis whereby RANKL-RANK binding results in recruitment of adaptor molecules to induce NF-κB and mitogen-activated kinases [36]. RANKL-induced transcription factors ultimately lead to the differentiation of functional osteoclasts whereby secretion of bone matrix degradation enzymes, including tartrate resistant acid phosphatase (TRAP), matrix metalloproteinase 9 (MMP9), and cathepsin K (CatK) resorb mineralized bone [115].

Geoepidemiology

Psoriatic disease, while common worldwide, demonstrates patterns of skin and joint involvement with similar ethnic and geographic variation. Though challenging to precisely measure, the presence of PsA has been shown to mirror PsV in distinct ethnic groups. For example, Norway has the highest prevalence of PsV and arthritis in PsV patients compared to other Nordic regions (Denmark, Finland, Iceland, and Faroe Islands) [116, 117]. Similarly, Europe and the USA have a similar prevalence of PsV and incidence of PsA [117–120]. The annual incidence of PsA is 6.59 per 100,00 in the USA, and 6 per 100,000 in Europe [121, 122]. This pattern is upheld in countries with warmer climates. Japan has one of the lowest prevalences of PsV, estimated to be 0.34 % [123]. Similarly, the incidence of PsA among Japanese PsV patients is extremely low at 0.1 per 100,000 [124]. American Samoa and natives in the Andes of South America were reported to have no cases of PsV or PsA [125, 126]. Thus, not only does PsV and PsA show similar ethnic patterns but also exhibit geographic variation, increasing in prevalence from tropical environments to colder, northern regions [127].

Genetic susceptibility loci demonstrate interesting trends, as well. HLA-Cw*0602 is a high-risk PsV allele, though its frequency does not necessarily correlate to skin disease. Psoriasis is less common in Africans, with a prevalence as low as 0.3 % in West Africa [117]. However, Africans (all black populations tested by Gudjonsson et al.) are known to have the highest prevalence of the HLA-Cw*0602 allele, at 15.09 % [20, 117]. Similarly, the *LCE3C_LCE3B-del* has been associated with PsA in Italian and Spanish populations, but no similar association was shown in German and Tunisian populations [128–130]. Thus, genetic susceptibility loci must be considered alongside population-specific effects and environmental exposures, which can vary dramatically.

Conclusion

Although the pathophysiology of psoriasis is broad, we have attempted to highlight the important factors shared by PsV and PsA. GWAS, animal models, and a variety of immunology and molecular biology approaches have given us critical insight into the pathophysiology of psoriasis. Despite our knowledge of these mechanisms, there is great variability in the clinical presentation of PsA and PsV. In addition, there is regional and ethnic diversity, which suggests mediating

factors that have yet to be thoroughly described. Hopefully, future research endeavors will elucidate the mechanisms of these underlying factors, allowing for the development of more effective, targeted therapies for these debilitating diseases.

Compliance with Ethical Standards

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Conflict of Interest The authors declare that they have no competing interests.

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