REVIEW ARTICLE

Genetics of Psoriatic Arthritis – an update

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Abstract:

Psoriatic arthritis (PsA) is an inflammatory arthritis that commonly occurs with psoriasis and is attributed to genetic, immunologic and environmental factors. It shares skin involvement with psoriasis, articular involvement particularly with spondyloarthritis, bowel involvement with Crohn's disease and eye involvement with uveitis, suggesting the existence of some common pathways. The Th-17 pathway and the IL-23/IL-17 axis have become prominent players in PsA and have considerably increased our understanding of disease pathogenesis. In this review article, we will focus on the genetic, epigenetic, and pharmacogenetic information with respect to PsA. Prominent genes identified in PsA via GWAS include *HLA-A, HLA-B, HLA-C, IL-12B, IL-23R, IL-23A, TNIP1, TRAF3IP2, CSF2/P4HA2, FBXL19, REL, TYK2, NOS2, PTPN22, TNFAIP3, IFNLR1, IFIH1,* and *NFKBIA*. These genetic markers have also illuminated key signaling pathways involved in PsA pathogenesis which can be broadly classified into those involved in epidermal differentiation, innate immunity, antigen presentation and processing, and acquired/adaptive immunity. With respect to PsA pathogenesis, the most consistent and predominant genetic effect is located on chromosome 6p21.3 within the major histocompatibility complex (MHC) region. The most significant association for increased PsA risk was with asparagine or serine residue at amino acid position 97 of *HLA-B*, where asparagine at position 97 of *HLA-B* represents the *HLA-B*27* allele. Moreover, specific *HLA* alleles have been associated with disease susceptibility, expression and progression in PsA. The prominent emerging role of the Th-17 signaling pathway in PsA pathogenesis will be highlighted. The lack of identified PsA genetic susceptibility loci is largely attributed to the much smaller number of patients, classification criteria used, and the greater clinical heterogeneity of PsA compared with psoriasis.

Keywords: Psoriatic arthritis, genetics, genomics, genome-wide association studies, epigenetics, pharmacogenetics

1.0. Disease phenotype, diagnosis and management of PsA

Psoriatic arthritis (PsA) is an inflammatory arthritis that manifests in 20% to 30% of patients diagnosed with psoriasis.[1] Although the clinical phenotype of PsA is quite heterogeneous, Moll and Wright have described five clinical patterns of PsA based on joint distribution: polyarticular

arthritis (five or more joints), oligoarthritis (one to four joints), distal interphalangeal arthritis, spondyloarthritis and the very destructive, arthritis mutilans.[2] The PsA phenotype also includes extra-articular features, metabolic disease, major advanced cardiac events and depression.[3]

ClASsification criteria for Psoriatic ARthritis (CASPAR) is now widely accepted for classifying PsA.[4] For the management of PsA, the goal is to decrease stiffness, reduce pain, improve function and minimize joint damage. Treatment decisions in PsA are now driven by the extent and severity of the disease and include non-steroidal anti-inflammatory drugs (NSAIDS), disease-modifying anti-rheumatic drugs (DMARDs), and biologic agents. Anti-tumour necrosis factor-alpha (TNF-α) biologic agents (e.g., adalimumab, certolizumab, etanercept, golimumab, and infliximab), anti-interleukin-12/23 agents (e.g., ustekinumab), and anti-IL-17 agents (e.g., secukinumab and ixekizumab) are effective in the management of PsA. A detailed review of the available treatment options for PsA has been recently published.[5] However, there is great variability in patient response with these agents, and there is still no clear method of selecting the preferred therapeutic agent.

2.0. Disease pathogenesis

Disease pathogenesis begins with an initiating event, possibly in the skin or gut where an interaction between genetic and environmental factors can trigger an inflammatory response.[6] PsA can also be understood from the perspective of the synovio-entheseal complex with biomechanical stress or damage representing initiating factors, which can attract inflammatory cells toward the synovium.[7-9] Studies also suggest that some immune responses associated with the transition from innate to adaptive immunity may be altered in PsA.[10]

Originally, the amplification of the immune reaction in PsA was thought to be mediated primarily by the expression of Th-1 and Th-2 mediated cytokines in synovial tissue.[11] Subsequent investigations have revealed a critical role for Th-17 cells and Th-17 mediated cytokines in disease pathology. For example, the enrichment of Th-17 cells and IL-17 levels in peripheral blood and joints in PsA patients is correlated with disease activity.[12, 13] Mast cells have also been identified as a source of IL-17 in synovial tissue.[14] The success of IL-17A inhibitors and IL-12/IL-23 inhibitors in PsA provides further support for a prominent role of Th-17 cells in PsA.[15-19] Likewise, the success of anti-TNF-α strategies in patients with PsA clearly highlights the pivotal role of this cytokine.[20]

The chronic inflammatory nature of PsA culminates in permanent tissue destruction and joint remodeling.[21] In general, upregulation of tissue destructive enzymes has mostly been associated with innate immunity cytokines such as IL-1, and to a lesser extent TNF-α. Bone erosion, caused by osteoclast-mediated destruction of bone, appears to involve the adaptive immune system.[22, 23] Monocyte colony stimulating factor and receptor activator of nuclear factor-κB ligand (RANKL) are involved in osteoclast differentiation and it has been reported that synovial fluid lymphocytes and fibroblasts support osteoclastogenesis with a specific role for RANKL, TNF-α, and IL-7.[22, 24] Importantly, Th-17 cells represent a source of RANKL under inflammatory conditions.[25] PsA is also characterized by new bone formation apparent as enthesophytes or syndesmophytes, eventually leading to joint ankyloses.[8] Links between new bone formation and innate or adaptive immune mechanisms have been suggested by the TNF-α and IL-1 mediated signaling

involving bone morphogenetic proteins and the Wnt signaling cascade.[26-28] However, information regarding the contribution of T-cells to osteoneogenesis is lacking. Moreover, there are currently no validated serological or biomarkers that will help predict the development of inflammatory arthritis in psoriasis patients.

2.1. Genetic contribution

Although the pathogenesis of PsA involves a complex interplay between genetic, immunological and environmental factors, this review will focus primarily on the current genetic knowledge. PsA predominantly exhibits a multifactorial pattern of inheritance.[29] Epidemiologic studies suggest a strong genetic basis to PsA. The genetic contribution to PsA is estimated between 80% to 100% with a recurrence rate in siblings and first-degree relatives between 30 and 55.[30-33]

Initial genetic investigations in PsA were centred around the interrogation of human leukocyte antigen (HLA) alleles located in the major histocompatibility complex (MHC) region. Next, multiple genome-wide linkage studies were performed using either large multiplex families or sibling pairs, followed by candidate gene investigations. With the availability of high throughput SNP-based technology, large-scale associated based studies emerged. Genome-wide association (GWA) studies and meta-analyses followed, which have identified numerous signals in genes reaching genome-wide significance including *HLA-A*[34], *HLA-B*,[34-37] *HLA-C*,[34-37] *IL-12B*,[34, 36, 37] *IL-23R*,[34] *IL-23A*,[34] *TNIP1*,[34, 36] *TRAF3IP2*,[34, 37, 38] *CSF2/P4HA2*,[34] *HCP5*,[35] *FBXL19*,[39] *REL*,[40] *TYK2*,[34] *NOS2*,[41] *PTPN22*,[41] *TNFAIP3*,[42] *IFNLR1*[42], *IFIH1*[42], and *NFKBIA*[42] (**Table 1**). Genetic variants weighted for or specific to PsA have also been identified (**Table 2**). These genetic markers have illuminated key signaling pathways involved in PsA pathogenesis which can be broadly classified into those involved in epidermal differentiation, innate immunity, antigen presentation and processing, and acquired/adaptive immunity. The prominent emerging role of the Th-17 signaling pathway in PsA pathogenesis will be highlighted. Newer technologies are being used to investigate the genetic basis of PsA using next-generation sequencing, copy number variation (CNV) analysis, and epigenetics.

Table 1. Genetic variations associated with psoriatic arthritis (PsA) susceptibility from genome-wide association studies or consistently identified in targeted analysis studies.

Chr.	Gene/Locus	dbSNP ID	Ethnicity	Function	Immune Response
1p36.11	***IFNLR1***	rs7540214	European	Interferon signaling	Innate
1p36	*RUNX3*	rs7536201	European	Antigen presentation	Acquired
1p31.3	***IL-23R***	rs11209026 rs12044149	European European	Th-17 signaling	Acquired
1p13.2	***PTPN22***	rs2476601	European	T-cell signaling Macrophage polarization Interferon signaling	Acquired Innate Innate
2p16.1	***REL***	rs13017599	European	NFkB signaling	Innate
2q24.2	***IFIH1***	rs35667974 rs1990760	European European	Interferon signaling	Innate
2q32.2-	*STAT4*	rs10181656	European	Th-17 signaling	Acquired

q32.3				Th-1 signaling	Acquired
3p14.1	*ADAMTS9/MAGI1*	deletion	European	ER-golgi transport	Innate
5q15	*ERAP-1*	rs30187 rs27524	European Asian	Antigen presentation	Acquired
5q15	*ERAP2*	rs2248374	European	Antigen presentation	Acquired
5q31	***CSF2/P4HA2***	rs715285	European	Macrophage production, function, differentiation	Innate
5q33.1	***TNIP1***	rs17728338 rs17728338	European Asian	NFkB signaling	Innate
5q33.3	***IL-12B***	rs7709212 rs2082412 rs6887695 rs12188300 rs3212227 (rs918520	European European European European European European	Th-17 signaling	Acquired
5q33.3	*PTTG1*	rs2431697	Asian	Cell cycle regulation Angiogenic activity	Other
6p22.1	***HLA-A*0201***	N/A	European	Antigen presentation	Acquired
6p21.33	***HLA-B*27***	rs36058333	European	Antigen presentation	Acquired
6p21.33	***HLA-C*0602***	rs12191877 rs13191343 rs12212594 rs10484554	European European European European	Antigen presentation	Acquired
6p21.33	*HCP5*	rs2395029	European	Autoimmunity	Acquired
6p21.33	*TNF-α -238*	rs361525	European	NFkB signaling	Innate
6p21.33	*TNF-α -308*	rs1800629	European	NFkB signaling	Innate
6p21.33	*TNF-α -857*	rs1799724	European	NFkB signaling	Innate
6p21.33	*TNF-α +489*	rs80267959	European	NFkB signaling	Innate
6p21.32	*C6orf10*	rs2073048	European	NFkB signaling	Innate
6q21	***TRAF3IP2***	rs33980500 rs13190932	European European	Th-17 signaling	Acquired
6q23.3	***TNFAIP3***	rs9321623	European	NFkB signaling	Innate
9q33.1	*TLR4*	rs4986790	European	Antigen presentation	Acquired
12q13.3	***IL-23A***	rs2020854	European	Th-17 signaling	Acquired
13q12.11	*GJB2*	rs3751385	Asian	Gap junctions	Skin barrier
14q13.2	***NFKBIA***	rs12586317 rs12883343	European European	NFkB signaling	Innate
16p11.2	***FBXL19***	rs10782001	European	NFkB signaling	Innate
17q11.2	***NOS2***	rs4795067	European	NFkB signaling	Innate
17q21.2	*STAT3*	rs744166	European	T-17 signaling	Acquired
18q22.2	*CD226*	rs763361			
19p13.2	***TYK2***	rs34536443 rs35251378 rs34725611	European European	NFkB signaling Interferon signaling T-17 signaling	Innate Innate Acquired
22q11.23	*MIF-173*	rs755622	European	Macrophage activation	Innate
22q11.23	*MIF*	rs5844572	Latino	Macrophage activation	Innate

Bold indicates genome-wide level of significance ($P<5.0x10^{-8}$).

Table 2. Genetic variants weighted for or specific to psoriatic arthritis (PsA) susceptibility.

Chr.	Gene/Locus	dbSNP ID	Ethnicity	Function	Immune Response
1p31.3	*IL-23R*	rs12044149	European	Th-17 signaling	Acquired
1p13.2	*PTPN22*	rs2476601	European	T-cell signaling Macrophage polarization Interferon signaling	Acquired Innate
5q31	*CSF2/P4HA2*	rs715285	European	Macrophage production, function, differentiation	Innate
6p21.33	*HLA-B*08*	N/A	European	Antigen presentation	Acquired
6p21.33	*HLA-B*27*	N/A	European	Antigen presentation	Acquired
6p21.33	*HLA-B*38*	N/A	European	Antigen presentation	Acquired
6p21.33	*HLA-B*39*	N/A	European	Antigen presentation	Acquired
6q23.3	*TNFAIP3*	rs9321623	European	NFkB signaling	Innate

2.1.1. Innate immunity

Activation of the innate immune response may represent the initial physiological trigger, which sets in motion an inflammatory cascade initiating PsA pathogenesis. An important cellular regulator of the innate immune response is the immediate–early response transcription factor NF-kB, which transcribes numerous target genes including pro-inflammatory cytokines, contributing to the pathogenesis of PsA. The resultant inflammatory milieu and related downstream cellular signaling tip the immune balance towards autoimmunity. TNF-α and IFNs appear to represent the predominant cytokines involved in triggering the innate immune response in PsA.[43, 44]

2.1.1.1. NF-kB signaling

An important cellular regulator of the innate response is the immediate–early response transcription factor NF-kB. Genes that have achieved a genome-wide level of significance involved in NF-kB signaling include *TNIP1*,[34, 36] *FBXL19*,[39] *REL*,[40] *NFKBIA*[42], *TNFAIP3*,[42] and *NOS2*,[41]. *TNIP1* encodes for a protein that inhibits NF-kB activation and was upregulated in synovial tissues in rheumatoid arthritis patients,[45] suggesting that it may play a role in the pathogenesis of PsA. *FBXL19* is a member of the F-box family and the encoded protein was reported to reversibly inhibit NF-kB signaling. *REL* genes encode a subunit of the NF-kB complex that is essential for proper signaling and the product of *NFKBIA* interferes with nuclear localization signals by inhibiting the activity of dimeric NF-kB-Rel complexes.[46] TNF-α-inducible protein 3 (*TNFAIP3*) encodes the inducible zinc finger protein A20, a critical protein in the inhibition of NF-kB signaling.[47] Importantly, the PsA-specific variant for *TNFAIP3* (rs9321623) was independent of the previously identified psoriasis variants near *TNFAIP3*.[42] *NOS2* encodes inducible nitric oxide synthase (iNOS), an enzyme responsible for producing pro-inflammatory nitric oxide and under transcriptional control of NFkB.[48] Collectively, the genetic loci revealed by GWA or targeted genotyping studies strongly support a role of NF-kB in the pathogenesis of PsA.

2.1.1.2. TNF-α signaling

TNF-α induces the production of inflammatory chemokines resulting in the

accumulation of pro-inflammatory leukocytes, including neutrophils, monocytes, and activated T cells.[49] Although *TNF-α* is localized within the MHC region, and that *HLA* alleles are also located in the MHC region and strongly associated with PsA, variants within *TNF-α* have failed to reach a genome-wide level of significance in GWA studies. Meta-analyses of PsA and healthy controls revealed a significant association between *TNF-α -238A/G* (rs361525) and *TNF-α -857T/C* (rs1799724) and disease susceptibility.[50, 51] Associations have also been reported with *TNF-α -308* promotor region variant (rs1800629) and PsA.[52, 53] The *TNF-α +489* variant (rs80267959) was significantly associated with PsA susceptibility and severity of clinical and laboratory parameters PsA patients.[54] A variant located within c6orf10 (rs2073048), a potential downstream effecter of TNF-α, was also associated with PsA.[55] TNF-α plays an important role in the pathogenesis PsA by triggering and recruiting multiple cytokines, activating the inflammatory process in the skin and joints and inducing osteoclastogenesis.[56, 57] TNF-α inhibitors are widely used in PsA considerably decreasing inflammation in the skin and synovial tissue of patients with PsA,[58-60] achieving clinical improvement in approximately 70% of patients.[61]

2.1.1.3. Interferon signaling

IFN signaling is an important early pro-inflammatory mediator producing cytokines and regulating effector cells involved in innate immunity.[62] Genes that have achieved a genome-wide level of significance involved in interferon signaling include *TYK2*,[34] *IFNLR1*[42], *IFIH1*,[42, 63] and *PTPN22*.[41] *TYK2* encodes a tyrosine kinase involved in the initiation of IFN-α signaling.[64] *IFNLR1* encodes the interferon lambda receptor 1, a protein that forms a receptor complex with IL-10RB and interacts with three closely related cytokines, including IL-28A, IL-28B and IL-29.[65] *IFIH1* encodes a cytoplasmic RNA helicase that recognises viral RNA and mediates an immune response on viral infection.[66] The protective effect of the rare *IFIH1* allele observed with PsA suggests that the variant results in a loss of function phenotype, where the production or activity of *IFIH1* is decreased.[63] A variant located within *PTPN22* (rs2476601) reached a genome-wide level of significance for PsA and may represent another marker specific for PsA.[41] *PTPN22* encodes a tyrosine phosphatase that is expressed by haematopoietic cells and functions as a key regulator of immune homeostasis by inhibiting T-cell receptor signalling and by selectively promoting type I interferon responses after activation of myeloid-cell pattern-recognition receptors.[67] Collectively, the genetic loci revealed by GWASs support a role of IFNs in the pathogenesis of PsA.

2.1.1.4. Macrophage activation and tissue degradation

A macrophage is a cell responsible for detecting, engulfing and destroying pathogens and apoptotic cells, and synovial macrophages are a major source of pro-inflammatory cytokines.[68] GWA and targeted genotyping studies have identified variants in *MIF*,[69] *PTPN22*[70] and *CSF2/P4HA2*[34] associated with PsA. The *MIF* variant (CATT5-8; rs5844572) was associated with protection to PsA whereas the *MIF-173G>C* (rs755622) was associated with susceptibility to PsA.[69] The cytokine macrophage migration inhibitory factor (MIF) sustains pro-inflammatory activation co-stimulates T and B lymphocytes and upregulates the production of IL-6, interferon γ and TNFα by a positive feedback loop.[71, 72] A novel PsA-specific association was detected at chromosome 5q31 (rs715285) flanked by *CSF2* and

P4HA2.[34] *CSF2* encodes a cytokine that controls the production, differentiation, and function of granulocytes and macrophages, and phosphorylation of NF-kB and Rel resulted in an increase in *CSF2* expression.[34] Subsequent functional annotation identified a candidate genetic variant (rs100657871) located within *SLC22A5* that may represent the causative event at 5q31 that is associated with PsA pathogenesis.[34] As previously mentioned, a variant located within *PTPN22* (rs2476601) reached a genome-wide level of significance for PsA and may represent another marker specific for PsA.[41] In addition to an effect on IFN signaling, PTPN22 is involved in the polarization of macrophages, and loss of PTPN22 may render monocytes and macrophages more reactive towards bacterial antigens enhancing antigen-presentation and secretion of pro-inflammatory cytokines.[70]

A highly significant association of an intergenic deletion between *ADAMTS9* and *MAGI1* genes on chromosome 3p14.1 has been reported.[73] Interestingly, this deletion occurred at a higher frequency in PsA than psoriasis, suggesting a more prominent role in PsA pathogenesis. ADAM metallopeptidase with thrombospondin type 1 motif 9 (*ADAMTS9*) gene is involved in the degradation of the extracellular matrix and is associated with cartilage degradation in PsA.[74, 75] Membrane-associated guanylate kinase, WW and PDZ domain containing 1 (*MAG1*) is involved in cell-to-cell contact, including epithelial and endothelial tight junctions.[76]

2.1.2. Acquired immunity

Antigen presentation by MHC proteins is essential for adaptive immunity. Activated T cells reacting to skin or synovial antigens presented by macrophages or dendritic cells activate the acquired immune response in PsA.[77] The disease had been considered a 'Th-1' disease; however, IL-17-producing Th-17 cells have emerged as a critical signaling pathway contributing to PsA pathogenesis.[78] Indeed, the discovery of the Th-17 subset has considerably advanced our understanding of disease pathogenesis. In this section, we focus on the genetics involved in antigen presentation and processing as well as Th-17 differentiation and downstream Th-17-mediated signaling (e.g., IL-17, IL-21, and IL-22).

2.1.2.1. Antigen presentation

Antigen presentation to the adaptive immune system is an important event driving PsA and its disruption can result in inappropriate targeting and destruction of cells, contributing to PsA pathogenesis. Association signals have been identified for *HLA* and non-*HLA* genes within the MHC region. With respect to PsA pathogenesis, the most consistent and predominant genetic effect is located on chromosome 6p21.3 within the major histocompatibility complex (MHC) region, accounting for one-third of the genetic contribution.[79]

2.1.2.2. MHC region

HLA alleles have been associated with disease susceptibility, expression and prognosis in PsA. Several candidate *HLA* genes have been identified that are associated with PsA pathogenesis including *HLA-A*0201*,[34] *HLA-B*07*,[80] *HLA-B*1302*,[81-83] *HLA-B*2705*,[34, 80, 84-86] *HLA-B*3801*,[84-86] *HLA-B*3901*,[84-86] *HLA-B*5701*,[81-85, 87] *HLA-C*0602*,[34, 81-83] and *HLA-DRB1*04*.[84, 85, 87] With respect to haplotypes, *HLA-C*12/B*38*, *HLA-B*27*, and *HLA-C*06/B*57* are associated with PsA.[83] The most significant association for increased PsA risk was with asparagine or serine residue at amino acid position 97 of *HLA-B*, where asparagine at position 97 of *HLA-B* represents the *HLA-B*27* allele.[80] The position is located within the peptide

binding groove of the HLA-B molecule and highlights the importance of antigen presentation in disease aetiology.[80]

With respect to disease susceptibility, the most consistently reported *HLA-B* alleles that are specific to PsA are *HLA-B*08*, *HLA-B*27*, *HLA-B*38* and *HLA-B*39* (**Table 3**).[84-86] Although the association magnitude of *HLA-B*27* is not as strong as in ankylosing spondylitis,[85] it represents the most discriminative allele separating PsA from psoriasis. A more refined analysis revealed that the presence of glutamine in position 45 of the HLA-B antigen conferred the strongest risk for PsA and interestingly, the PsA-specific alleles (*HLA-B*27*, *HLA-B*38*, *HLA-B*39*) all encode proteins at that position.[86] Given that psoriasis often precedes PsA combined with an enhanced understanding the genetic factors that differentiate PsA from psoriasis, genetic variants that identify patients with psoriasis at an elevated risk of developing PsA would represent a major advancement in healthcare delivery for those patients.

Table 3. Genetic variations associated with disease expression in psoriatic arthritis (PsA).

Chr.	Gene/Locus	Associated sub-phenotype	
		Positive correlation	**Negative correlation**
6p21.33	*HLA-B*08*	Joint fusion and deformities Asymmetrical sacroiliitis Dactylitis Nail disease	
6p21.33	*HLA-B*18*	Nail disease	
6p21.33	*HLA-B*27*	Axial involvement Enthesitis Dactylitis Symmetric sacroiliitis Uveitis	
6p21.33	*HLA-B*38*	Asymmetric sacroiliitis Peripheral polyarthritis	
6p21.33	*HLA-B*39*	Peripheral polyarthritis	Nail disease
6p21.33	*HLA-B*55*	Asymmetric sacroiliitis	
6p21.33	*HLA-C*06*	Delayed onset of PsA	Asymmetric sacroiliitis Nail disease

Numerous *HLA* alleles have been associated with disease expression in PsA (**Table 3**). *HLA-B*27* was strongly associated with axial disease; however, the association weakened as more peripheral joints were involved.[81, 82, 88, 89] Specifically, *HLA-B*27:05* was positively associated with enthesitis, dactylitis, uveitis and symmetric sacroiliitis.[88, 90-92] Peripheral polyarthritis was associated with *HLA-B*38* and *HLA-B*39*.[88, 90, 91] *HLA-C*06* was associated with PsA; however, psoriasis patients who carried the *HLA-C*06* allele had a delayed onset of or were less likely to develop PsA.[84, 85, 87]. In contrast, asymmetric sacroiliitis was associated with *HLA-B*08:01*, *HLA-B*38:01* and *HLA-B*55:01*.[89, 93] Specifically, *HLA-B*08:01-HLA-C*07:01* and its component alleles were positively associated with joint fusion and deformities, asymmetrical sacroiliitis, and dactylitis,[91] whereas *HLA-C*06:01* was negatively associated with asymmetrical sacroiliitis.[91] Nail disease was positively associated with *HLA-B*08:01* and *HLA-B*18:01*, and negatively associated with

*HLA-B*39:01*, and *HLA-C*06:02*.[93] With respect to haplotypes, *HLA-B*27:05-HLA-C*02:02*, *HLA-B*08:01-HLA-C*07:01* and *HLA-B*37:01-HLA-C*06:02*, but not the *HLA-B*27:05-HLA-C*01:01* or *HLA-B*57:01-HLA-C*06:02* haplotypes were associated with severe PsA.[91] In contrast, *HLA-B*44* haplotypes were associated with presence of milder disease with a decreased frequency of enthesitis, joint fusion, deformities and dactylitis.[91] With respect to disease prognosis, *HLA-B*39* alone, *HLA-B*27* with *HLA-DR*7*, and *HLA-DQ*3* without *HLA-DR*7* and *HLA-C*06* were associated with advanced rate of disease progression.[91] Although *HLA* alleles have been associated with disease expression and prognosis in PsA, effect sizes have been modest limiting clinical utility.

2.1.2.2. Outside MHC region

Several association studies in PsA have identified non-*HLA* genes involved in antigen presentation and processing. Specifically, GWA and targeted studies have identified *MICA, KIR2DS2, ERAP-1, ERAP-2, RUNX3, HCP5* and *TLR4* as being associated with PsA susceptibility.

MICA (MHC class I polypeptide-related sequence A) functions as a stress-inducible antigen and plays a key role in innate and adaptive immune responses by interacting with the natural killer group 2 member D (NKG2D)-activating receptor of natural killer (NK) cells and CD8 T cells.[94] *MICA*, located within the MHC region, resides in close proximity to the *HLA-B* locus, and *MICA*002* (trinucleotide repeat polymorphism, *MICA-A9*) and appeared to represent an independent association signal for PsA susceptability.[55, 95-97] Moreover, *MICA-A9* was associated with peripheral symmetric poly-arthritis/spondylitis in PsA patients.[98] Independently of HLA, only homozygosity for *MICA*008:01* appeared to increase the risk of developing PsA.[99] The *MICA-129* methionine (Met) allele was also associated with PsA independently of *HLA-B* and *HLA-C*.[100] However, a more recent large fine mapping of the MHC region failed to find an independent association with PsA within the *MICA* locus after controlling for *HLA* candidate genes.[86]

The killer-cell immunoglobulin-like receptors (KIR) are located on natural killer cells and interact with class I HLA antigens.[101] HLA-B27 free heavy chains have been shown to bind KIR3DL2 receptors with greater affinity causing proliferation and survival of IL-17-producing T cells.[102-104] The frequency of *KIR2DS2* was increased in PsA compared with unaffected controls and may represent another PsA specific genetic marker.[105]

Endoplasmic reticulum aminopeptidases-1 and -2 (ERAP-1 and ERAP-2) recognize and process a vast variety of antigenic peptides to generate epitopes for presentation by MHC class I molecules.[106] ERAP-1 is also involved in angiogenesis and in pro-inflammatory cytokine receptor shedding.[107] PsA first showed a significant association with *ERAP-1* (rs27524) in a Chinese population.[108] *ERAP-1* (rs30187) was subsequently demonstrated to be associated with *HLAB*27* positive disease in a European population.[109] In that same study, *ERAP-2* (rs2248374) was associated *HLA-B*27* negative PsA.[109] The rs2248374 variant truncates *ERAP-2* mRNA decreasing the levels of MHC class I expressed on the surface of B cells and the immune response.[110] Interestingly, *ERAP-1* and *ERAP-2* have also been associated with ankylosing spondylitis.[111, 112]

Associations to key genes involved in the differentiation of CD8+ cells, such as *RUNX3*, have also been identified in PsA.[113] *HCP5* was also strongly associated with PsA susceptibility and is expressed primarily in cells of the immune system such as spleen, blood and thymus,

consistent with a potential role in autoimmunity.[35] *TLR-4* (toll-like receptor-4) variants may also be a risk factor for PsA as suggested by a significant association between *TLR-4* (rs4986790) and with PsA.[114, 115] Toll-like receptors in the immune system have a significant role in antigen recognition and initiation of an immune cascade.[116] However, further studies are required to explore this association with PsA.

2.1.2.2. Th-17 pathway

The discovery and subsequent importance of the Th-17 signaling pathway, also known as the IL-23/IL-17 axis, has greatly advanced our understanding of the pathogenesis of PsA. Th-17 cells produce IL-17, which induces pro-inflammatory cytokines and commits naive T cells to the Th-17 lineage contributing to the adaptive immune response.[78] The Th-17 pathway, through its intermediaries, also contributes to the innate immune response by interacting with TNF-α and NF-kB.[117, 118]

The Th-17 signaling pathway is of great importance to PsA pathology as evidenced by the upregulation of elements of this pathway in skin, peripheral blood, synovial fluid and tissue. Virtually all elements of the Th-17 signaling pathway were elevated in peripheral blood cells, synovial fluid and biopsies of PsA patients.[119-123] Nine genes (*MMP3, CCL1, IL-17C, CCL20, IL-17F, IL-3, CXCL5, IL-6* and *CX3CL1*) had concordant expression in synovial fluid cells and in peripheral blood cells of PsA compared with controls.[124] Moreover, there were increased numbers of GM-CSF-producing CD4+ and CD8+ lymphocytes in the blood and joints of PsA patients, and increased numbers of IL-17A+GM-CSF+ double-producing CD4+, CD8+, γδ and NK cells.[125] CCL20, a chemotactic factor, was also correlated with PsA disease activity.[126] IL-23 promotes erosive bone disease by stimulating Th-17 cells to produce RANKL and IL-17, IL-23 and IL-17 induces osteoclast formation.[127-129] In an animal model of IL-23 over-expression, enthesitis, pannus formation, and bone erosion have been reported.[130, 131] Given that anti-IL-23/IL-17 agents inhibit Th-17 differentiation and IL-17 production, an anti-IL-23 agent, ustekinumab, was effective in treatment of PsA with symptomatic and radiographic improvement in dactylitis and enthesitis,[132] and IL-17A inhibitors, like secukinumab and ixekizumab, were also effective in treating PsA.[16, 133] It has become apparent that disruption of this key signaling pathway by genetic variation can contribute to PsA pathology.

IL-17-promoting cytokines, including TGF-β, IL-6, IL-1β, and IL-23, trigger Th-17 cell differentiation. Only genes with variants associated with PsA will be discussed. GWA studies in PsA have failed to detect an association of variants in *TGF-β, IL-6,* and *IL-1β* genes. IL-6 and IL-1β cytokines are needed for the differentiation of Th-17 cells.[134] IL-6 promotes synovitis and induces bone resorption and an increase in synovial membrane and fluid of IL-6 associated to inflammatory disease activity has been demonstrated in PsA.[135, 136] However, studies on the possible association of *IL-6* variants with disease activity, the presence of erosions, or clinical patterns of PsA are lacking. A higher concentration of IL-1β was also found both in the synovial membrane and in the synovial fluid of PsA patients compared with patients with osteoarthritis.[58] Targeted analysis of *IL-1β* as a susceptibility locus for PsA has produced conflicting results.[137-140] The *IL-1B* variant (rs16944) might be associated with higher peripheral joint disease activity and the presence of clinical inflammation.[140]

IL-23 promotes the expansion and survival of Th-17 cells through its receptor and

signaling pathway.[141] IL-23 is a heterodimeric cytokine that binds IL-23R and IL-12Rβ1, promotes the expansion and survival of Th-17 cells.[142] GWA studies in PsA have only identified variants located within *IL-12B*,[34, 36, 37] *IL-23R*,[34] *IL-23A*,[34] and *TYK2*.[34] The *IL-23R* (rs11209026) variant may also be associated with disease severity.[143] A distinct PsA-specific variant has been identified at the *IL-23R* locus (rs12044149), which remained highly significant after conditioning on the psoriasis SNP (rs9988642), providing compelling evidence for a distinct PsA risk variant.[34] This finding has been subsequently confirmed in an independent cohort.[144] Results from candidate gene studies have revealed an association with *STAT3*[145] and *STAT4*.[146] IL-12B, IL-23A, and IL-23R are involved in IL-23 receptor activation and downstream signaling.[147, 148] IL-12 has been shown to play a protective role against the development of PsA.[35, 149] *TYK2* encodes Tyk2, which binds directly to IL-12Rb1 and is essential for IL-23-mediated signaling and Th-17 cell differentiation. *STAT3* encodes for Stat3 required for the differentiation of Th-17 cells, whereas *STAT4* encodes Stat4 essential for mediating responses to IL-12 in lymphocytes, and regulating the differentiation of T helper cells.[150]

Th-17 effector signaling involves IL-17, IL-21, and IL-22, that contributes to the development of PsA. The relevance of the IL-17 in psoriatic disease is supported by the elevation of IL-17/IL-17R in psoriatic skin and synovial fluid from PsA patients.[119, 151, 152] Only effectors with genetic information available will be discussed in this section. GWA studies in PsA have identified a single variant located within *TRAF3IP2*,[34, 37, 38] which encodes the TRAF3 interacting protein 2 (TRAF3IP2) required for Th-17-mediated inflammatory responses,[118] and the TRAF3IP2 variant associated with PsA (rs33980500) nearly abolished the interaction with TRAF6.[37] No genetic variants in IL-17, IL-21 or IL-22 have been associated with PsA pathogenesis.

There was a distinct gene expression pattern in skin and synovium in PsA evidenced by an enhanced IL-17 gene signature in skin compared with in synovium and more equivalent TNF-α and INF gene signatures in both tissues.[153] These results are in keeping with clinical trial data showing that PsA skin and joint disease are similarly responsive to TNF-α inhibitors, while IL-17 inhibitors have better results in PsA skin than in PsA joints.[153]

2.1.2.3. Other pathways

Associations with variants in genes encoding proteins involved in skin barrier function and epidermal differentiation have been reported in PsA. This is not surprising given that a breach of the skin barrier could result in impaired epidermal repair after barrier disruption, causing increased susceptibility to exogenous antigens, resulting in inflammation.[154] The *LCE* gene cluster encodes the cornified envelope proteins that are important for epidermal cell differentiation. The *LCE3C_LCE3B-del* has been tested in PsA patients with conflicting results. Some studies noted a significant association[155, 156] while others failed to detect any such association.[157, 158] PsA also showed a significant association with *GJB2* (rs3751385) when compared with the control group in a Chinese population[108].

PsA showed a significant association with *PTTG1* (rs2431697) in a Chinese population[108]. *PTTG1* (the pituitary tumour transforming gene) encodes a multifunctional protein that is involved in cell cycle regulation. Interestingly, it also possesses angiogenic activity,[159] which appears to be important in PsA pathology, as an increase in the number of synovial

membrane blood vessels has been reported in PsA.[160]

Cytokines such as TNF-α, IL-12, IFN-γ, IL-23 and, more recently, IL-9, have been implicated in the initiation/maintenance of inflammation in PsA. Peripheral and synovial expansion of Th-9 cells, increased expression of IL-9 and IL-9R, and an expansion of γδ T cells was observed in patients with PsA.[161, 162]

2.2. Epigenetics/omics

Epigenetics, which refers to the molecular mechanisms that regulate gene expression without changing the DNA sequence, is comprised largely of methylation of the DNA sequence and histone proteins. Importantly, epigenetics can be altered by environmental factors such as infections, psychological stress, cigarette smoking, and obesity.

With respect to PsA, epigenetics offer an explanation for disease discordance in genetically identical monozygotic twins with PsA[163] and a parent-of-origin effect.[164, 165] Although PsA predominantly exhibits a multifactorial pattern of inheritance,[29] genomic imprinting, an epigenetic effect that causes differential expression of a gene depending on the sex of the transmitting parent, may also play a role in the inheritance.[164] A meta-analysis showed a significant excess of paternal transmissions overall in psoriasis[166] and PsA.[164, 165]

Numerous epigenetic studies have been conducted in psoriasis as summarized in an excellent recent review.[167] Epigenetic investigations have identified a region on chromosome 16q near *NOD2* (*CARD15*),[168] *HLA-B*08* and *MICA-129Met/Val* in PsA patients as genetic associations that are specific to paternally transmitted disease.[165] Although epigenetic studies in psoriasis have identified differentially methylated regions between cases and controls, there is a lack of such studies including genome-wide investigations in PsA. The data that does exist suggests that epigenetic phenomena may play a role in PsA.

3.0. Pharmacogenetics/pharmacogenomics

Significant inter-individual variability in drug efficacy and adverse events is well recognized and challenges remain regarding treating PsA patients. The most common pharmacogenetic approach utilized to assess the variability in the efficacy and toxicity of PsA treatments has been the evaluation of single nucleotide variants present in genes encoding drug-metabolizing enzymes, drug transporters and receptors. Generally, genome-wide investigations in PsA are lacking. For a more detailed assessment on the role of pharmacogenetics and pharmacogenomics in psoriatic disease, please refer to an excellent recent review.[5]

3.1. Non-biological agents

Individual variation in therapeutic efficacy and adverse events such as gastrointestinal bleeding exists in PsA patients treated with NSAIDS. Alleles such as *CYP2C9*2* and *CYP2C9*3* have been correlated with decreased metabolic clearance of NSAIDs when compared with individuals with the *CYP2C9*1* allele (wildtype).[169]

In PsA, systemic agents used to modify the immune response or spare corticosteroids include methotrexate, leflunomide and sulphasalazine. Response to these treatments is variable as are the adverse events experienced. Variants associated with response to methotrexate in PsA impact the transport of methotrexate across the cell membrane or impact enzymes in the methotrexate pathway. Variants in *DHFR* were associated with an increase in methotrexate response (rs1232027) and an increased risk of hepatotoxicity

(rs1801133).[170] Methotrexate responders also have up-regulated expression of 12 genes and down-regulated expression of 33 genes when compared with untreated PsA controls.[171] Pharmacogenetic studies on sulphasalazine and leflunomide in PsA patients are lacking.

3.2. Biological agents

Biologic agents are increasingly being used to treat moderate-to-severe PsA, especially in patients that have failed systemic therapy. That biologic agents are very expensive and appear to be effective in about 50% to 60% of patients emphasizes the importance of being able to identify treatment responders *a priori*.

The three most established and commonly used anti-TNF-α agents for PsA are etanercept, infliximab, and adalimumab, with newer agents including golimumab and certolizumab.[172] Anti-TNF-α agents have revolutionized the management of PsA as evidenced by their ability to inhibit radiographic progression of arthritis.[18, 172-174] Several studies have investigated the effect of genetic variations on response to TNF-α inhibitors in PsA patients. The *TNF-α* variants (rs1799724, rs80267959) were a predictor of good response to TNF-α inhibitors,[54, 175] whereas a male-specific association with reduced response was identified with the *SLO1C1* variant (rs3794271).[176] PsA patients with the high affinity *FCGR2A* genotype (His/His, or His/Arg) displayed an increased response to TNF-α inhibitors compared with those with low the affinity genotype (Arg/Arg).[177] Infliximab was significantly associated with response in patients with *TNFRSF10A* (rs20575) and *TNFRSF1A* (rs767455) variants.[178] Although several pharmacogenomics studies have been performed in psoriasis as previously reviewed,[5] only a couple of TNF-α pharmacogenetics investigations in PsA have been completed. Using an expression microarray, 161 genes were down-regulated and 27 genes were up-regulated in PsA patients treated with etanercept as compared with untreated controls.[171] A divergent pattern of altered gene expression in the blood and target organs (i.e., lesional skin and synovial tissue) was reported following treatment of infliximab in both psoriasis and PsA patients.[179]

Ustekinumab has demonstrated high efficacy and safety in treatment of psoriatic disease by inhibiting IL-12/IL-23 signaling pathways.[15, 180-182] No pharmacogenetics studies using IL-12/IL-23 inhibitors have been performed in PsA. In psoriasis patients, response to ustekinumab was significantly increased and occurred faster in *HLA-Cw6*-positive patients and those carrying an *IL-17F* variant (rs763780).[183, 184] A lack of significance was found between variant in *IL-12B*, *IL-23R*, and *IL-6* and response to ustekinumab in psoriasis patients.[185]

Collectively, these pharmacogenetic and pharmacogenomic studies suggest that genetic variants located within TNF-α IL-12/IL-23 or other genes involved in its signalling and Th-17 signalling cascades might influence response to anti-TNFα and anti-IL-12/IL-23 therapies; however, additional studies, including genome-wide investigations are needed.

4.0. Summary and future direction

The remarkable accumulation of knowledge gained in recent years from genetic and genomic studies of PsA has fundamentally changed and advanced our understanding disease pathogenesis. Key signaling pathways involved in PsA pathogenesis have been discovered, specifically with respect to innate immunity, antigen presentation and processing, and acquired/adaptive immunity. Most notable

was the emergence of the importance of the Th-17 signaling pathway in PsA pathogenesis.

Although much knowledge has been gleaned from such investigation in PsA, challenges still remain. Despite the number of genes identified in PsA, only a small fraction of the heritability has been explained coining the term "missing heritability". The relative lack of significant and reproducible genetic and genomic findings in PsA as compared with psoriasis is likely attributed to the much smaller number of PsA patients who have been studied, the prevailing diagnostic criteria for PsA, the greater clinical heterogeneity of PsA.

While genetic and genomic investigations have yielded great insights into the genes that contribute to the pathogenesis of PsA, replication of findings in large independent cohorts, loci fine-mapping, and resequencing efforts, combined with functional studies are warranted to advance our knowledge of disease pathogenesis. It is now well accepted that searching simply for common variants (e.g., GWA studies) will identify only a fraction of the entire genetic burden of disease, and that applying next-generation sequencing technologies with and without additional -omics (e.g., genome-wide copy number variations, transcriptome, methylome) may culminate in additional genetic discoveries of high-effect size and possible clinical utility. Furthermore, careful evaluation of gene-gene and gene-environment interactions should also be performed. Moreover, global genotype relative risk scores for disease susceptibility, expression, and prognosis should also be developed, and their clinical utility evaluated.

Pharmacogenetic and pharmacogenomic studies in PsA need to be adequately powered to better assist with discovery variants of modest effect sizes. Importantly, *a priori* knowledge of pharmacogenetic mechanisms associated with PsA treatment has the potential to stratify patients into clinically important treatment categories.

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