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Review article

Genetic and inflammatory factors associated with psoriatic arthritis: Relevance to diagnosis and management

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ABSTRACT

Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory musculoskeletal condition with complex pathophysiology. In recent years, understanding of the pathogenesis of PsA has improved substantially. Several genetic and inflammatory factors have been identified and studied as targets for new biologic disease-modifying therapies. This review presents findings from a detailed literature assessment conducted to identify genes and biomarkers associated with PsA and its most common comorbidities. This literature assessment identifies genes and biomarkers that may be predictive of the onset and severity of PsA, places them in the context of our understanding of PsA pathogenesis, and explores potential connections between the pathways involved in PsA and current biologic therapeutics used to treat PsA. Knowledge of the genetics and inflammatory factors associated with disease pathogenesis can support the targeted development of new biologic therapies and biomarkers for PsA.

1. Introduction

Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory musculoskeletal condition that occurs with cutaneous psoriasis (PsC) and presents with diverse clinical and radiographic manifestations [1–3]. Indeed, PsC commonly presents with erythematous plaques encircled with silver scales (vulgaris), in a droplet form (guttate), only in the intertriginous regions (inverse), with sterile pustules in the palms and soles (palmoplantar pustulosis), as the more serious generalized pustular form, or the rare erythodermic form [4]. The musculoskeletal features of PsA present with diverse combinations of musculoskeletal manifestations, including enthesitis, tendonitis, synovitis, dactylitis, osteitis, sacroiliitis, and/or peripheral joint and axial deformities that can result in dramatic osteolysis and/or joint fusion [2,3,5,6].

PsA is considered one of the spondyloarthropathies (SpAs), a group of diseases that includes ankylosing spondylitis (AS) and reactive arthritis, and is associated with other systemic inflammatory conditions such as inflammatory bowel disease (IBD) and uveitis [7]. Almost all patients with PsA develop PsC during the course of their disease; in most cases, PsC precedes or occurs simultaneously with PsA [3,8,9]. Although the scalp, nails, and intertriginous regions are commonly affected areas in plaque PsC, the severity and distribution of PsC at a specific time does not predict or correlate with any of the musculoskeletal manifestations of PsA [10,11]. Furthermore, the diverse mechanisms of continuous inflammation in patients with PsC and PsA are associated with a broad range of comorbidities, including cardiovascular disease, osteoporosis, depression, and cancer [12–14]. Thus, the multifarious presentations of both skin and musculoskeletal features suggest several pathogenetic mechanisms, which are induced by multiple genetic, epigenetic, and environmental influences operative in different cellular locations.

Genetic susceptibility was initially estimated to be a contributing factor in about 50% of patients with PsA who had a family history of SpA or PsC [3]. Furthermore, both PsC and PsA showed a greater tendency to be inherited from affected fathers rather than affected mothers [15]. More recently, genome-wide association studies (GWAS) have

Abbreviations: ACR, American College of Rheumatology; AS, ankylosing spondylitis; cAMP, cyclic adenosine monophosphate; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; DC-STAMP, dendritic cell specific transmembrane protein; GWAS, genome-wide association studies; ILC3, group 3 innate lymphoid cells; IL, interleukin; HLA, human leukocyte antigen; *HLA-C*, human leukocyte antigen-C; IBD, inflammatory bowel disease; IFN, interferon; JAK, Janus kinase; MHC, major histocompatibility; MMP, matrix metalloproteinase; NK, natural killer; NF-kB, nuclear factor-kappa B; OCP, osteoclast precursor; PASI, Psoriasis Area and Severity Index; PDE, phosphodiesterase; PsA, psoriatic arthritis; PsC, cutaneous psoriasis; RANKL, receptor activator of nuclear factor-κB ligand; SNP, single-nucleotide polymorphism; SpA, spondyloarthropathy; STAT, signal transducers and activators of transcription; TNF, tumor necrosis factor

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identified that the genetic contributions of psoriatic disease accounts for less than 25% of heritability [16]. The thorough GWAS technology identifies single-nucleotide polymorphisms (SNPs) within the DNA of increasing numbers of affected individuals compared with control populations and attributes SNP's predictive association to nearby described genes active in the current and related diseases [16]. Of course, the selection of patients utilizes various clinical criteria in different ethnic groups. In addition, the heritability of PsA may be due, in part, to epigenetic factors, which result in alterations in gene expression or post-translational protein modifications without alterations in the DNA sequence [16,17]. Epigenetic factors that induce molecular mechanisms such as DNA methylation, acetylation, phosphorylation and sumoylation, histone modifications of proteins, and micro-RNAs that degrade target mRNAs can inhibit gene expression and are possibly induced by environmental triggers such as an infection, a chemical, a drug, physical trauma, psychological stress, and a rubella vaccination [9,16,18].

An understanding of genetic, epigenetic, and inflammatory factors that contribute to PsA pathogenesis is a strategy to develop more-targeted therapies. Although many different therapies have been approved for the treatment of PsA, most were originally developed to treat other inflammatory conditions, such as rheumatoid arthritis (RA) and PsC, and a significant proportion of patients with PsA fail to respond to many of these agents [19]. With the identification of key innate and immune pathways associated with PsC and PsA, particularly the interleukin [IL]-23/Th17 axis and the Janus kinase [JAK]/signal transducer and activator of transcription [STAT] axis, development of new therapies has focused on targeting specific proinflammatory cytokines associated with disease pathogenesis [20–22].

This review presents findings from a literature analysis to identify genes associated with PsA and associated comorbidities. The expression of proinflammatory and anti-inflammatory molecular targets that may be affected by biologic therapies for PsC and PsA are also discussed.

2. Methods

Targeted PubMed literature searches were conducted to identify articles discussing inflammatory pathways and genes involved in the development of PsA. Searches were conducted using combinations of search terms, including psoriatic arthritis, inflammation, pathway, pathogenesis, gene, biomarker, polymorphism, bone formation, bone loss, comorbidities, IL-6, IL-12, IL-17, IL-23, TNF/tumor necrosis factor, CTLA-4/cytotoxic T lymphocyte antigen-4, PDE4/phosphodiesterase 4, and JAK/Janus kinase. Search results were supplemented based on the reference citations in articles identified in initial searches.

3. Genes associated with PsA

The association of genetics with PsA was reported as early as 1973, when Moll and Wright described a 49-fold increase in PsA prevalence among people with at least one first-degree relative who had PsA [23]. In 1973, two research groups independently reported increased specificity for the human leukocyte antigen *(HLA)-B*27* allele in patients with AS [24,25]. These seminal discoveries were the first steps in proposing the importance of genes that may generate "arthritogenic" peptides in SpA pathogenesis [26]. Since then, PsA heritability has become well established, with more recent studies confirming that people with a first-degree relative with PsA have a 40-fold increased risk of developing the disease and those with a second-degree relative with PsA have a 12-fold increased risk [27].

PsC and PsA are closely related diseases with certain genetic similarities; however, each disease and their respective clinical subsets are associated with certain unique immunologic and genetic characteristics [2,22]. Genes and gene products identified by our literature assessment are provided in Table 1.

Not surprisingly, the most consistent and dominant genetic effects in PsA are found on chromosome 6p21.3 within the major histocompatibility (MHC) region, particularly genetic variants involving class I *HLA* alleles and other non-*HLA* genes [18,28]. HLA class I genes (*HLA-A, B, C*) normally function by presenting peptides generated from intracellular cytosolic proteins and from invasive viruses to CD 8+ T cells and natural killer cells [29]. HLA class II genes (*HLA-DRA* or *HLA-DRB*) generate peptides endocytosed from external sources to present to CD 4+ T cells [29]. The *HLA-B* genes are associated with PsA and other SpA diseases, contributing to the musculoskeletal manifestations of PsA, while the human leukocyte antigen-C (*HLA-C*) contributes primarily to skin manifestations in PsA [30,31]. Specifically, *HLA-B*27*, initially described in 90% of patients with AS, occurs as a genetic marker for PsA but not for PsC [19,32]. Patients who have positive test findings for the *HLA-B*27* allele are significantly more likely to develop bilateral axial sacroiliitis even before PsC, while those who have *HLA-C*06* are more likely to develop PsC several years before PsA [30,33]. Furthermore, other *HLA-B* alleles such as *HLA-B*38* and *HLA-B*8* alleles are reported with more prominent musculoskeletal features in patients with PsC [18]. In addition, Okada and colleagues observed that amino acid polymorphisms at position Glu45 in HLA-B significantly increased susceptibility to PsA but not to PsC [31]. This site is contained within the binding groove of HLA-B and affects cell-surface expression of HLA class I, peptide binding, and presentation of exogenous and endogenous peptides [34]. Glu45 is also present in HLA-B*27, HLA-B*08, HLA-B*38, and HLA-B*39 [31,35,36].

Specific *HLA* allele combinations in PsA have also been associated with differing clinical manifestations and small effects on prognosis according to the affected allele [3,28,30]. For example, the *B*27:05-C*01:02* haplotype is preferentially associated with enthesitis (inflammation at sites of ligament, tendon, and joint capsule attachments to bone), an early hallmark that distinguishes PsA and other SpA from RA, which is characterized primarily by inflammation in the synovium [3,37]. Interestingly, in a study evaluating validated PsA susceptibility alleles (*HLA-B*27*, *HLA-B*38:01*, *HLA-B*39:01*, *HLA-B*44:02/44:03*, *HLA-B*08:01*, and *HLA-C*06:02*), only *HLA-B*27* was independently associated with more severe enthesitis [38]. In 282 patients with PsA, the *HLA-B*08:01:01-C*07:01:01* susceptibility haplotype is associated with synovitis, joint deformity, and fusion. In addition, when *HLA-B*27:05* is associated with *HLA-B*08:01*, dactylitis occurs [3]. The *HLA-B*27:05-C*01:02* haplotype is also associated with dactylitis; however, dactylitis is also positively associated with the *HLA-B*08:01-C*07:01* haplotype, which is considered to be associated with synovial-based pathophysiology in PsA [3]. Clinically, dactylitis occurs with inflammation in the enthesis, synovium, and bone. These findings highlight possible heterogeneity in mechanisms underlying different phenotypes with *HLA-B*08:01* associating with synovitis and *HLA-B*27* associating with enthesitis [3,38].

Other genes located near or within the MHC region shown to be associated with PsA include *MICA-TM*, *HLA-E*, and *SEEK1* [39–41]. The MHC class I chain-related gene, *MICA*, which regulates natural killer (NK)- and T-cell activation in innate and adaptive immune responses, was associated with PsA in European and other mostly white populations [40,42–46] and with PsC in Asian populations [40] Additionally, certain *MICA* alleles and polymorphisms are linked to *HLA-B*38* and *B*39* [43,47]. Increased frequency of the killer immunoglobulin-like receptor gene, *KIR2DS1*, has been observed in patients with PsA compared to patients with PsC alone [48]. This gene encodes a transmembrane glycoprotein expressed by NK cells that recognize HLA-C as its ligand [48].

Epigenetic mechanisms can also play a role in the development of PsA. For example, global hypomethylation is observed in patients with PsA not receiving methotrexate compared with control patients and patients receiving methotrexate [49]. Research has also identified specific gene loci that are hypermethylated (*MICA*, *IRIF1*, *PSORS1C3*, and *TNFSF4*) or hypomethylated (*PSORS1C1*) in patients with heritable PsA [50]. Additionally, histone regulatory genes (*HAT1*, *SETD2*) have been proposed as biomarkers for PsA [15].

Table 1
Results of literature searches for genes associated with psoriatic arthritis.

Gene	Name of encoded protein and associated pathway or function	Association with comorbidities of PsA or other arthropathies
Antigen presentation and binding		
HLA-B [3,30,31,140–142]	Major histocompatibility complex, class I, B; important in immune system regulation; numerous polymorphisms have been identified in PsA	Spondyloarthropathy, PsC
HLA-C [3,30,31,39,140–150]	Human leukocyte antigen; important in immune system regulation; HLA-Cw*06 allele identified in early-onset PsC	PsC
HLA-E [39]	Major histocompatibility complex, class I, E; plays a role in NK cell recognition/inhibition	PsC, RA
KIR2DS1 [48,151]	Killer cell immunoglobulin-like receptor; on natural killer cells, interacts with HLA-C ligands	Guttate PsC
Skin barrier		
LCE3B, 3C (PSORS4) [152,153]	Late cornified envelope protein; forms skin barrier	PsC
NF-κB activation and signaling		
ADIPOQ (*APMI*) [154–156]	Adiponectin, adipocyte hormone, which supresses TNF-α, VCAM-1, ICAM-1, and NF-κB signaling; associated with use of anti-TNFα therapy	Metabolic syndrome
TNF-α (*cachectin*) [144,157]	Tumor necrosis factor-α; cytokine secreted by macrophages that regulate cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation; regulator of inflammation and bone remodeling in PsA	
TNFAIP3 (*A20*) [64]	Tumor necrosis factor α-induced protein 3; zinc finger protein and ubiquitin-editing enzyme that inhibits NF-κB activation and TNF-α mediated cell death	PsC, Crohn's disease, RA
TRAF3IP2 (*PSORS13*) [158–160]	Tumor necrosis factor receptor-associated factor 3 interacting protein 2; encodes for Act1, a signaling molecule that regulates adaptive immune pathways; downstream of IL-17 receptor and link between IL-17-mediated adaptive immune responses and NF-κB in innate immune responses	PsC, candidiasis
Th17 differentiation and signaling		
IL-6 [60]	Interleukin-6; proinflammatory cytokine that regulates inflammation and B-cell activation; required for generation of Th17 cells	Systemic juvenile idiopathic arthritis
IL-12B [146,161–163]	Interleukin-12B (p40 subunit); acts on T cells and NK cells; important in innate and adaptive immunity; associates with IL-23A to form the heterodimeric cytokine IL-23	Immunodeficiencies, mycobacteriosis, PsC
IL-17A [16,164]	Interleukin-17A; proinflammatory cytokine produced by activated T cells; also involved in osteoclastogenesis and bone erosion	RA, PsC
IL-23A [16,165–168]	Interleukin-23A; promotes production of proinflammatory cytokines and stimulates memory T cells; associates with IL-12B to form IL-23; also involved in osteoclastogenesis and bone erosion	Colitis, autoimmune inflammatory diseases, PsC
IL-23R [66,146,162,163,167,169,170]	Interleukin-23 receptor subunit; associates with IL-12RB1 to form the IL-23 receptor; binds IL-23 and mediates T-cell and NK-cell function; associates with JAK2 and binds STAT3	Inflammatory bowel disease, PsC, ankylosing spondylitis
TYK2 [16]	Tyrosine kinase 2; protein in the Janus kinase family important in interferon and IL-12/23 signaling pathways, Th17 cell differentiation, and NF-κB activation	Immunodeficiency, mycobacteriosis, PsC
Bone formation		
BMPR2 [60]	Bone morphogenetic protein receptor, type II, in the TGFβ family, is a serine/threonine kinase involved in regulation of endochondral bone formation and embryogenesis	
COL2A1 [60]	Collagen type II, α 1; cartilage collagen from chondrocytes, essential for skeletal growth and development	
BSP [60]	Integrin-binding sialoprotein or cell-binding bone sialoprotein; major structural protein of bone matrix	
STAT3 [171,172]	Signal transducer and activator of transcription 3; acute phase response factor that is activated through phosphorylation in response to various cytokines and growth factors; mediator of apoptosis and cell growth; involved in osteoblast-mediated bone remodeling	PsC
TGFBR1 [60]	Transforming growth factor beta receptor 1; transmembrane serine/threonine protein kinase that regulates epithelial and hematopoietic cell-cycle arrest, mesenchymal cell proliferation and differentiation, wound healing, extracellular matrix production, immunosuppression, and carcinogenesis	
WNT3A [60]	Wingless-type MMTV integration-site family member 3A; ligand for frizzled family transmembrane receptors; associated with osteoblast function and bone development	
WISP1 [60]	WNT1 inducible signaling pathway protein 1; part of the connective tissue growth factor family; downstream regulator of the Wnt/frizzled signaling pathway	
CYTL1 [60]	Cytokine-like 1; synovium-specific protein-coding gene, which regulates cartilage homeostasis and chondrocyte differentiation via collagen IIB	
Bone loss		
IL-1A [173,174]	Interleukin-1α; endogenous pyrogen involved in inflammatory responses; produced by activated macrophages during inflammatory responses; also produced by keratinocytes and fibroblasts; stimulates osteoclast activity and bone/cartilage resorption	Dermatologic disorders, RA
IL-1B [173,174]	Interleukin-1β; produced by activated macrophages during inflammatory responses; also produced by keratinocytes and fibroblasts; stimulates osteoclast activity and bone/cartilage resorption	Systemic juvenile idiopathic arthritis

(*continued on next page*)

Table 1 (*continued*)

Gene	Name of encoded protein and associated pathway or function	Association with comorbidities of PsA or other arthropathies
MMP1 [60,175]	Matrix metalloproteinase 1; fibroblast collagenase that breaks down interstitial collagen I, II, III in the extracellular matrix	RA, epidermolysis bullosa
RANKL (TNFSF11) [61]	Receptor activator of NF-κB; ligand for osteoprotegerin; key regulator of osteoclast differentiation and activation, and of T-cell-dependent immune responses	Osteopetrosis
Immune response/host defense		
CCL20 (*MIP3A*) [110]	Chemokine that binds CCR6 and attracts immune cells	PsC
CRP [176]	C-reactive protein; member of the pentaxin family; involved in host defense mechanisms, including acute phase responses to tissue injury, infection, and inflammatory stimuli	Cardiovascular disease
CXCL2 (*MIP2*) [60]	Chemokine (C-X-C motif) ligand 2; chemotactic for polymorphonuclear leukocytes, part of a chemokine superfamily of proteins involved in immunoregulatory and inflammatory processes	
IL-13 [177–180]	Proinflammatory cytokine made by activated T cells to induce IgG4 and IgE from B cells and transforming growth factor from macrophages. In PsA peripheral blood and synovial fluid	
IL-22 [181–183]	Interleukin-22; activates STAT 1, 3, 5	Colitis, PsC
MICA [40,42–46,184,185]	Major histocompatibility complex class I polypeptide-repeated sequence A; related to major histocompatibility complex class I, protein that recognizes intracellular antigens from NK cells and cytotoxic intestinal epithelial γδT cells	Behcet's disease
MIF [186]	Macrophage migration inhibitory factor; proinflammatory cytokine involved in cell-mediated immunity and immunoregulation of macrophage function in host defense; suppresses the anti-inflammatory effects of glucocorticoids	Systemic juvenile idiopathic arthritis
NOS2 [187]	Inducible nitric oxide synthase; expressed by TNF-α-producing inflammatory macrophages, dendritic cells, and chondrocytes	PsC
TLR4 [176]	Toll-like receptor 4; involved in pathogen recognition and activation of innate immune pathways via bacterial lipopolysaccharide	
Cell proliferation/intracellular signaling		
FZD8 [60]	Frizzled family receptor 8; synovium-specific receptor for Wnt proteins, via β-catenin and JNK	
PDE4 [188]	cAMP-specific phosphodiesterase 4B and 4D isoforms; involved in signal transduction mechanisms, upregulated by TNF-α	RA, inflammatory bowel disease, osteoporosis
Uncharacterized		
SEEK1 (PSORS1C1) [41]	Psoriasis susceptibility 1 candidate gene 1; confers susceptibility to PsC; located on chromosome 6 near the MHC class I region	PsC

Categories listed for groupings of genes denote only their primary function and are not exhaustive of all effects of individual genes.
IL, interleukin; IFN, interferon; JAK, Janus kinase; HLA, human leukocyte antigen; ICAM, intercellular adhesion molecule; Ig, immunoglobulin; MHC, major histocompatibility complex; NF-κB, nuclear factor κB; NK, natural killer; PsA, psoriatic arthritis; PsC, cutaneous psoriasis; RA, rheumatoid arthritis; STAT, signal transducer and activator of transcription; Th, T helper; TNF-α, tumor necrosis factor-α; VCAM, vascular cell adhesion molecule.

Non-MHC susceptibility genes associated with PsA, PsC, and AS include those genetic loci that associate with the IL-23/IL-17 pathway, antigen presentation and binding, and T cell activation and differentiation (Table 1). In various animal models of PsA and in human PsA tissue, activation of IL-23 and IL-12 receptors cause Th17 cells, γδ T cells, and neutrophils to secrete pro-inflammatory cytokines, including IL-17, IL-21, IL-22, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and chemokines that attract inflammatory cells [51]. In addition, IL-23 induces proliferation of keratinocytes, hyperplasia, and skin inflammation and IL-23 binding to monocytes/macrophages generates production of macrophage colony stimulating factor, tartrate resistant acid phosphatase, cathepsin K, and MMPs in osteoclasts that facilitate bone resorption [51]. Yamamoto and colleagues found that in the K5.Stat3C:F759 mouse model of psoriatic inflammation and arthritis, keratinocytes express active STAT3 and the mice develop PsC-like skin changes, as well as joint swelling and nail deformities characteristic of PsA. Histopathology showed upregulation of proinflammatory cytokines associated with the IL-23/Th17 pathway [52].

Periarticular cartilage and bone loss and new bone formation are also characteristic features of SpA, including PsA (Fig. 1) [53]. As the disease progresses, trabecular bone mineral density decreases and bone microstructure deteriorates, with development of bony spurs and syndesmophytes at cortical bone sites [54–56]. Changes in bone structure and new bone formation occur when production of proinflammatory cytokines (eg, IL-23, IL-17A, transforming growth factor-β, and IL-6) increase in association with chronic enthesitis and synovitis [56–59].

As shown in Table 1, a substantial proportion of the gene loci identified in our search are associated with regulation of bone, cartilage, and/or collagen formation and breakdown; evaluation of these factors may help identify patients with PsC who will develop PsA. In a recent study profiling the genes associated with PsA joint and skin inflammatory pathways, the most frequent changes in synovial tissue gene expression were associated with upstream regulators of cartilage and bone breakdown and formation, including *MMP1*, *COL2A1*, *WISP1*, *HAS1*, *IBSP*, *FZD8*, *BMPR2*, and *WNT3A* [60].

In addition, upregulation of receptor activator of nuclear factor-κB ligand (RANKL), a key cytokine-triggered regulator of osteoclast differentiation and activation, is observed in the synovial lining of patients with PsA. When peripheral blood monocytes/osteoclast precursors (OCPs) are exposed to RANKL and TNF-α, osteoclastogenesis increases, resulting in erosion at the bone-pannus junction and subchondral bone [61]. In an analysis of blood samples from patients with PsA, synovial fibroblastoid cells from psoriatic hip and knee joint samples expressed high levels of RANKL, and that RANKL receptor and dendritic cell specific transmembrane protein (DC-STAMP) expression was increased on the surface of OCP cells, promoting cell-to-cell fusion of monocytes to form osteoclasts and giant cells [61,62]. OCP levels are higher in patients with PsA compared to healthy controls and may be predictive of bone erosions in patients with PsA [61]. Indeed, following treatment with a TNF-α inhibitor, levels of OCP significantly decreased in patients with erosive PsA [63].

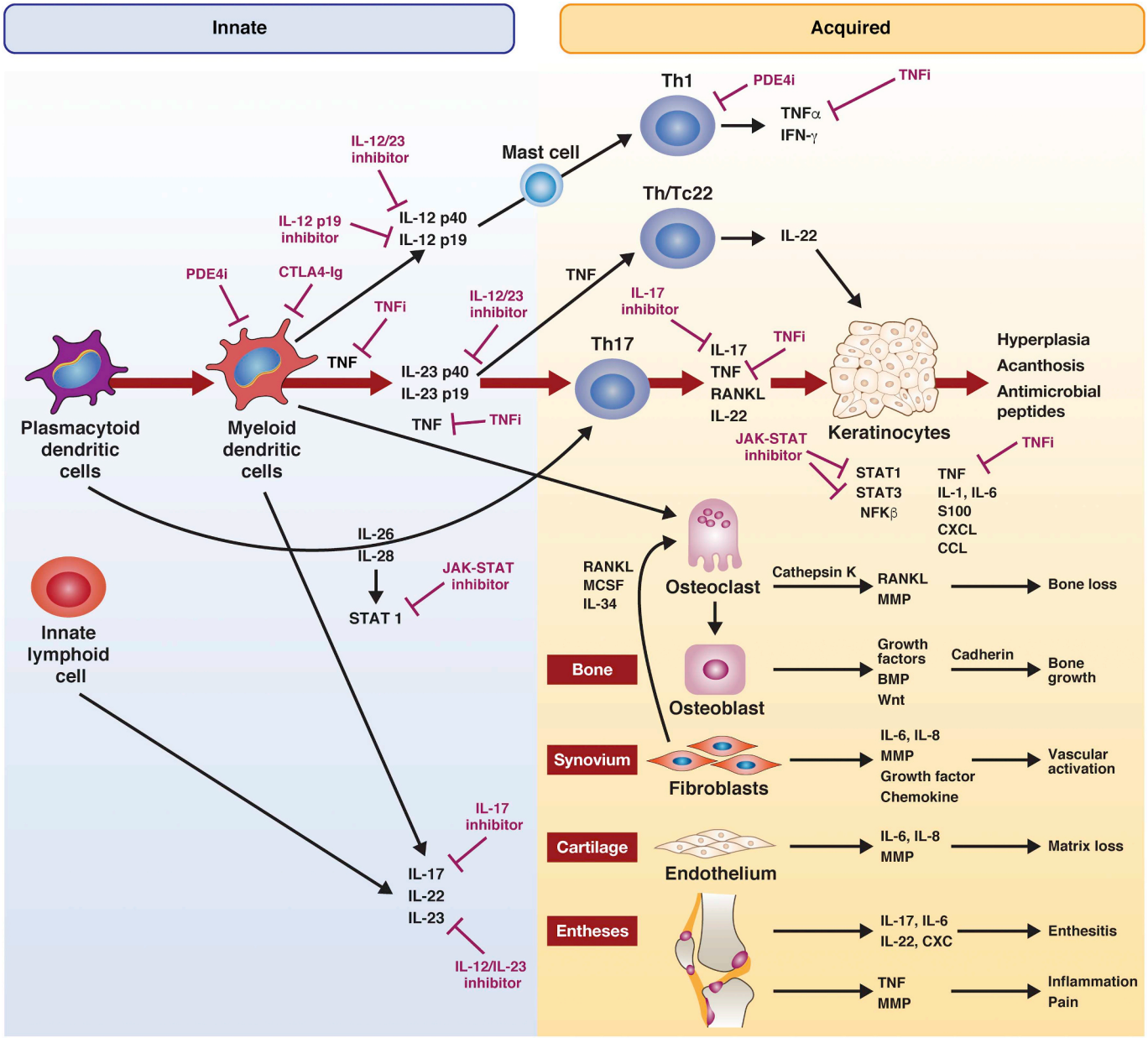

Fig. 1. Pathogenetic construct showing key genetic factors and inflammatory pathways associated with cutaneous psoriasis and psoriatic arthritis.
CCL, chemokine (C-C motif) ligand; CTLA4, cytotoxic T lymphocyte antigen-4; CXC, chemokine (C-X-C motif) ligand 2; i, inhibitor; IFN, interferon; IL, interleukin; JAK, Janus kinase; MCSF, macrophage colony-stimulating factor; MMP, matrix metalloproteinase; PDE4, phosphodiesterase 4; RANKL, receptor activator of nuclear factor-κB ligand; STAT, signal transducer and activator of transcription; Th, T helper; TNF, tumor necrosis factor.

Associations between the genes linked to PsA and other arthropathies or common comorbidities indicate that a substantial proportion of these genes are also associated with PsC (Table 1) [19,64,65]. Also, different genetic variants at the same loci of the *IL13* and *IL23R* genes have been identified as possible markers to differentiate risk of PsA from risk of PsC [66]. A recent genotyping study by Bowes and colleagues identified chromosome 5q31 as a locus specifically associated with PsA risk; however, this risk was independent of the *IL13* PsC-associated variant. In the same study, unique SNPs were identified at the *IL23R* locus for PsC (rs9988642) and PsA (rs12044149), indicating that there may be a specific variant associated with PsA [66]. Findings such as these highlight the complexities of using genetic variations to predict risks of PsA and associated comorbidities. Nonetheless, it is important to note that most genes identified in our PsA searches are associated with one or more arthropathies (eg, RA and SpA) or comorbidities commonly associated with PsA (eg, cardiovascular disease, IBD, and other autoimmune disorders) (Table 1) [65].

In summary, these extensive studies have identified genes that are prognostic factors for PsA development (eg, *HLA-B* genes and chromosome 5q31) and genetic markers that are associated with specific disease phenotypes (eg, *HLA-B*08* and *HLA-B*27*).

4. Inflammatory biomarkers of PsA identified as therapeutic targets

Although genetics may underlie the susceptibility of PsA, it is their downstream effects, mediated by epigenetics of the immune system and

Table 2
Summary of approved biologic agents indicated for the treatment of psoriatic arthritis.

Drug	Mechanism of action	Indication	Administration	Pivotal studies
TNF inhibitors				
TNF-α is produced by innate lymphoid cells, which mediate enthesitis, and lymphocyte-synoviocyte interactions, which mediate synovial inflammation [189,190]. TNF-α activates osteoclasts, which mediate bone resorption [190].				
Adalimumab [191]	Human monoclonal antibody that binds specifically to TNF-α and blocks its interaction with the p55 and p75 cell-surface TNF receptors; also lyses surface TNF-expressing cells in vitro in the presence of complement	Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA	Subcutaneous administration of 40 mg every other week	ADEPT [89]
Etanercept [192]	Dimeric soluble form of the p75 TNF-α receptor that can bind TNF-α molecules	Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with PsA	Subcutaneous administration of 50 mg weekly	Mease et al. [88]
Certolizumab pegol [193]	PEGylated humanized antigen-binding fragment that can bind TNF-α molecules	Treatment of adult patients with active PsA	Subcutaneous administration of 400 mg initially and at week 2 and 4, followed by 200 mg every other week	RAPID-PsA [194]
Golimumab [195]	Human monoclonal antibody that binds to the soluble and transmembrane bioactive forms of human TNF-α, preventing the binding of TNF-α to its receptors and inhibiting its biological activity	Treatment of adult patients with active PsA	Subcutaneous administration of 50 mg monthly	GO-REVEAL [196]
Infliximab [197]	Chimeric antibody that neutralizes the biological activity of TNF-α by binding with high affinity to the soluble and transmembrane forms of TNF-α, and inhibiting binding of TNF-α to its receptors	In patients with PsA, reduces signs and symptoms of active arthritis, inhibits the progression of structural damage, and improves physical function	Intravenous administration of 5 mg/kg at 0, 2, 6 weeks and maintenance regimen every 8 weeks thereafter	IMPACT [198] IMPACT-2 [199]
IL-12/23 inhibitor				
IL-12 and IL-23 are produced by dendritic cells, which mediate T cell activation [200]. Il-12 and IL-23 activate CD4+ and CD8+ cells, which mediate enthesitis, skin inflammation, and synovitis [200,201].				
Ustekinumab [202]	Human IgG1κ monoclonal antibody that binds to the p40 protein subunit used by both the IL-12 and IL-23 cytokines	Treatment of adult patients with active PsA	Subcutaneous administration of 45 mg once a month for 2 doses and then every 12 weeks	PSUMMIT 1 [203] PSUMMIT 2 [204]
IL-17A inhibitor				
IL-17 is produced by innate lymphoid cells, which mediate enthesitis, and by CD4+ and CD8+ cells, which mediate enthesitis, skin inflammation, and synovitis [189,205]. IL-17 activates lymphocyte-synoviocyte interactions, which mediate synovial inflammation, and keratinocytes, which mediate hyperkeratosis and systemic inflammation [205,206].				
Secukinumab [207]	Human IgG1 monoclonal antibody that selectively binds IL-17A and inhibits its interaction with the IL-17 receptor	Treatment of adult patients with active PsA	Subcutaneous administration of 150 mg at 0, 1, 2, 3, and 4 weeks and every 4 weeks thereafter. If a patient continues to have active PsA, consider a dosage of 300 mg	FUTURE 1 [98] FUTURE 2 [99]
Ixekizumab [208]	Humanized IgG4 monoclonal antibody that selectively binds IL-17A and inhibits its interaction with the IL-17 receptor	Treatment of adult patients with active PsA	Subcutaneous administration of 160 mg initially followed by 80 mg every 4 weeks	SPIRIT-P1 [104,105]
PDE4 inhibitor				
Apremilast [123]	Oral small-molecule inhibitor of PDE4 specific for cAMP, with PDE4 inhibition resulting in increased intracellular cAMP levels	Treatment of adult patients with active PsA	Oral administration twice daily of 30 mg	PALACE 1 [121]
JAK inhibitor				
Tofacitinib [209]	Oral small-molecule inhibitor of JAK1, JAK2, and JAK3	Treatment of adult patients with active PsA who have had an inadequate response or intolerance to methotrexate or other DMARDs	Oral administration twice daily of 5 mg	OPAL Broaden [125] OPAL Beyond [126]

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Table 2 (*continued*)

Drug	Mechanism of action	Indication	Administration	Pivotal studies
T-cell signaling inhibitor				
Abatacept [210]	Fusion protein of the extracellular domain of human CTLA-4 linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human IgG1. Selective costimulation modulator, which inhibits T cell activation by binding to CD80 and CD86, thereby blocking interaction with CD28	Treatment of adult patients with active PsA	Subcutaneous administration of 125 mg once weekly	ASTRAEA [117]

cAMP, cyclic adenosine monophosphate; CD, cluster of differentiation; CTLA-4, human cytotoxic T-lymphocyte associated antigen 4; DMARD, disease-modifying antirheumatic drug; Ig, immunoglobulin; IL, interleukin; JAK, Janus kinase; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; TNF, tumor necrosis factor.

inflammatory processes, that result in the symptoms of clinical disease. Many of the innate and adaptive immune inflammatory processes and mediators that drive PsA and PsC pathogenesis are similar, and models describing the pathogenesis of PsA have been adapted from studies in PsC [18]. In both cutaneous disease and PsA, an environmental trigger may initiate an innate immune response in genetically susceptible individuals [18]. In PsA, this response is followed by inflammatory infiltration of monocytes, dendritic cells, other antigen presenting cells, neutrophils, and T cells into the entheses and synovium. Activated T cells then interact with antigen-presenting dendritic cells, and tissue inflammation develops in the entheses, synovium, tenosynovium, joint capsules, and skin [67,68]. This inflammation is characterized, in part, by overexpression of several different proinflammatory cytokines [18,22]. The main proinflammatory cytokine mediators are TNF-α, IFNs, and interleukins that are released by innate, adaptive, and resident immune cells, including keratinocytes, NK T cells, plasmacytoid dendritic cells, and macrophages in skin and synovial tissue [68]. Plasmacytoid dendritic cells activate inflammatory myeloid dendritic cells to release IL-12 and IL-23, which activate T helper cells that produce IL-17, TNF-α, and IL-22 that drive the process of disease manifestation in PsA [69,70]. Activated dendritic cells also affect other cell types, including keratinocytes, leukocytes, neutrophils, endothelial cells, and vascular smooth muscle cells, further modulating chemotaxis, proliferation, and production of additional inflammatory mediators [71,72]. Furthermore, innate immune cells are being recognized as an increasingly important source of IL-17 [73]. In addition to their roles in inflammation, these cytokines are involved in activation of the nuclear factor-kappa B (NF-kB) pathway in fibroblasts and synovial cells, which induces expression of cytokines that promote osteoclastogenesis and bone absorption, leading to destructive arthritis [22].

Key inflammatory markers of PsA that have been identified as therapeutic targets and evaluated in clinical studies in patients with PsA include TNF-α, IL-12/23, IL-17A, IL-6, cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), phosphodiesterase 4 (PDE4), and JAKs. In PsA, IL-17 gene signatures are more upregulated in skin compared to synovium, whereas TNF-α gene signatures may be equally upregulated in both skin and synovium, though different immune molecules affect these expressions [60]. Additionally, in response to IL-23, an IL-17 gene signature is observed in entheseal tissue from a mouse model of arthritis [74]. In the same animal model, IL-23, independently of IL-17, induces synovitis and bone loss [75].

The availability of different biologic agents has increased the number of therapeutic alternatives available for the management of PsA. Through increased understanding of the pathogenesis of PsA, attempts to construct therapies to inhibit disease progression and improve quality of life have become goals of individualized therapy. Table 2 provides a summary of the characteristics of currently licensed biologic therapies for the treatment of PsA, and Table 3 summarizes the efficacy of approved and investigational biologic agents in PsA, as well as pertinent safety considerations for each agent. Genetic associations between comorbidities or disease associations and PsA are described in Table 4. Fig. 1 illustrates the placements of therapies within the pathomechanistic pathways identified in PsA.

4.1. Tumor necrosis factor-α

TNF-α has various functions associated with the immunopathogenesis of PsA and is produced by multiple cell types (Fig. 1). A link has been observed between production of TNF-α and obesity, a known risk factor for PsA that is characterized by a proinflammatory state and increased levels of adipose tissue that produces adipokines [76]. Adipocytes produce TNF-α and leptin [76]. In turn, leptin increases production of TNF-α and other cytokines from macrophages [76]. Furthermore, activated dendritic cells induce

Table 3
Summary of efficacy results and safety considerations for approved and investigational biologic therapies in PsA.

Drug	N	Time at primary endpoint	PsC		PsA		Special considerations from prescribing information
			PASI75	PASI90	ACR20	ACR70	
Approved therapies							
Adalimumab [89] ADEPT	315	12 weeks	49% (PBO 4%)	30% (PBO 0)	58% (PBO 14%)	20% (PBO 1%)	• Serious infections • Invasive fungal infections • Malignancies • Anaphylaxis or other serious allergic reactions • Hepatitis B virus reactivation • Demyelinating disease • Cytopenias, pancytopenia • Heart failure • Lupus-like syndrome
Etanercept [84] Mease et al.	205	12 weeks	23%[a] (PBO 3%)	NR	59% (PBO 15%)	~13% (PBO 0)	• Serious infections • Invasive fungal infections • Malignancies • Anaphylaxis or other serious allergic reactions • Hepatitis B virus reactivation • Demyelinating disease • Cytopenias, pancytopenia • Heart failure • Lupus-like syndrome
Certolizumab pegol [194] RAPID-PsA (200 mg, 77% TNF-naïve)	409	12 weeks	47% (PBO 14%)	22% (PBO 5%)	58% (PBO 24%)	25% (PBO 3%)	• Serious infections • Invasive fungal infections • Malignancies • Anaphylaxis or other serious allergic reactions • Hepatitis B virus reactivation • Demyelinating disease • Cytopenias, pancytopenia • Heart failure • Lupus-like syndrome
Golimumab [196] GO-REVEAL (50 mg, 100% TNF-naive)	405	14 weeks	40% (PBO 2.5%)	21% (PBO 0)	51% (PBO 9%)	~10% (PBO 0)	• Serious infections • Invasive fungal infections • Malignancies • Anaphylaxis or other serious allergic reactions • Hepatitis B virus reactivation • Demyelinating disease • Cytopenias, pancytopenia • Heart failure • Lupus-like syndrome
Infliximab [198,199] IMPACT	104	16 weeks	68% (PBO 0)	36% (PBO 0)	65% (PBO 10%)	29% (PBO 0)	• Serious infections • Invasive fungal infections • Malignancies • Anaphylaxis or other serious allergic reactions • Hepatitis B virus reactivation • Demyelinating disease • Cytopenias, pancytopenia • Heart failure • Lupus-like syndrome • Hepatotoxicity • Cardiovascular and cerebrovascular reactions
IMPACT-2 (100% TNF-naïve)	200	14 weeks	64% (PBO 2%)	41% (PBO 0)	58% (PBO 11%)	15% (PBO 1%)	
Ustekinumab [203,204] PSUMMIT-1 (45 mg, 100% TNF-naïve)	615	24 weeks	57% (PBO 11%)	43% (PBO 3%)	42% (PBO 23%)	12% (PBO 2%)	• Serious infections • Malignancies • Anaphylaxis or other serious allergic reactions • Reversible posterior leukoencephalopathy syndrome
PSUMMIT-2 (45 mg, 43% TNF-naive)	312	24 weeks	51% (PBO 5%)	30% (PBO 4%)	44% (PBO 20%)	7% (PBO 3%)	
Secukinumab [98,99] FUTURE-1 (150 mg, 71% TNF-naïve)	606	24 weeks	61% (PBO 8%)	45% (PBO 4%)	50% (PBO 17%)	19% (PBO 2%)	• Serious infections • Inflammatory bowel disease • Anaphylaxis or other serious allergic reactions
FUTURE-2 (300 mg, 67% TNF-naive)	397	24 weeks	63% (PBO 16%)	49% (PBO 9%)	54% (PBO 15%)	20% (PBO 1%)	
Ixekizumab [104,105] SPIRIT-P1 (80 mg Q4W, 100% biologic-naive)	417	24 weeks	71% (PBO 10%)	56% (PBO 6%)	58% (PBO 30%)	23% (PBO 6%)	• Serious infections • Inflammatory bowel disease • Anaphylaxis or other serious allergic reactions
SPIRIT-P2 (80 mg Q4W, 0% TNF-naïve)	363	24 weeks	56% (PBO 15%)	44% (PBO 12%)	53% (PBO 19%)	22% (PBO 0%)	
Apremilast [120,121] PALACE-1 (30 mg bid, 76% biologic-naive)	504	16 weeks	21% (PBO 5%)	NR	40% (PBO 19%)	NR	• Diarrhea, nausea, and vomiting • Depression • Weight decrease • Drug interactions (use with strong cytochrome P450 enzyme inducers is not recommended) • Serious infections

(*continued on next page*)

Table 3 (*continued*)

Drug	N	Time at primary endpoint	PsC		PsA		Special considerations from prescribing information
			PASI75	PASI90	ACR20	ACR70	
Tofacitinib [125,126]							• Malignancies
OPAL Broaden (5 mg bid, 100% TNF-naive)	422	12 weeks	43% (PBO 15%)	NR	50% (PBO 33%)	17% (PBO 5%)	• Gastrointestinal perforations • Changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids
OPAL Beyond (5 mg bid, 0% TNF-naive)	395	12 weeks	21% (PBO 14%)	NR	50% (PBO 24%)	17% (PBO 10%)	
Abatacept [117] (125 mg, 40% TNF-naïve)	424	24 weeks	16% (PBO 10%)	NR	39% (PBO 22%)	10% (PBO 7%)	• Serious infections (with concomitant use of a TNF antagonist) • Anaphylaxis or other serious allergic reactions • More frequent respiratory adverse events in patients with chronic obstructive pulmonary disease
Experimental Therapies in PsA							
Brodalumab [211]							• Suicidal ideation and behavior
Mease et al. (140 mg, 47% biologic-naive) Phase 2	168	12 weeks	NR	NR	37% (PBO 18%)	5% (PBO 0)	• Serious infections • Crohn's disease

The proportion of TNF/biologic-naïve patients receiving active drug is provided if this information was reported in the study citation.
ACR, American College of Rheumatology; NR, not reported; PASI, Psoriasis Area and Severity Index; PBO, placebo; PsA, psoriatic arthritis; PsC, cutaneous psoriasis; TNF, tumor necrosis factor.
[a] At week 24.

Table 4
Genetic associations between PsA and comorbidities or disease associations.

Safety consideration	Genetic link
Inflammatory bowel disease [172,212,213]	*SLC22A5* *IL23R* *NOD1/CARD4*
Cardiovascular disease [214,215]	*HLA-B*13:01* (more severe atherosclerosis)
More severe atherosclerosis	*HLA-C*06:02* (more severe atherosclerosis)
Cardiac syndrome	*HLA-B*27* (cardiac syndrome)
Malignancy [215]	*HLA-B*27* (leukemia)
Leukemia	

differentiation of Th1 cells, which produce IFN-γ and TNF-α, and Th17 cells, which produce IL-17, IL-22, TNF-α, and IL-1 [76]. A primary function of TNF-α is activation of the NF-κB pathway, a classical proinflammatory pathway [77]. TNF-α is also involved in the production of MMPs from macrophages, which subsequently contribute to cartilage degradation [78]. In addition, TNF-α is associated with the expression of vascular endothelial growth factor and other markers of angiogenesis, which are postulated to increase vascularity in the synovium [79]. TNF-α also promotes OCP differentiation and migration in response to synovial and subchondral bone inflammation, causing progressive bone damage [22].

For patients with PsA, TNF-α inhibitors improve the signs and symptoms of joint and peripheral tissue inflammation, and improve functional status, quality of life, and skin and nail manifestations (Fig. 1) [80]. TNF-α inhibitors indicated for the treatment of PsA include etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol (Table 2). Studies have shown that these TNF-α inhibitors may reduce T-cell infiltration in the skin, and T-cell and macrophage infiltration in the synovium [81,82]. Anti-TNF-α therapy also reduces the levels of circulating OCPs in patients with PsA [83]. In clinical trials, TNF-α inhibitors are associated with slowing or preventing radiographic disease progression in PsA [84,85]. Clinical improvements with TNF-α inhibitor therapy can be sustained to 5 years, and in real-world data, drug survival is high after 4 years of treatment [86,87]. TNF-α inhibitors are believed to reduce bone erosion; however, the effect of TNF-α inhibition on bony-spur formation remains to be elucidated [18]. While TNF-α inhibitors are effective treatments for many patients with PsA, an estimated 30% to 40% of patients fail to respond [88,89]. This indicates that although TNF-α is an important driver of disease activity, it may not be the critical molecule in all patients with PsA.

4.2. Interleukin-12 and interleukin-23

IL-12 is produced by Th1 cells, monocytes, and macrophages, and modulates inflammation, Th1 cell differentiation, and NK cell activation in PsC and PsA. IL-23 is a member of the IL-12 family of cytokines and is predominantly produced by myeloid dendritic cells. IL-23 is an upstream cytokine involved in the development and maintenance of a pathogenic Th17 cell phenotype from naïve CD4+ T cells. IL-23 is also involved in osteoclastogenesis and bone erosion [22].

Currently, ustekinumab, an IgG1κ monoclonal antibody that targets the p40 subunit of both IL-12 and IL-23, is approved for use in PsA (Table 2). Inhibition of the p40 subunit results in inhibition of both Th1 and Th17 differentiation and downstream effects on inflammation and bone destruction (Fig. 1). In large-scale clinical studies, subcutaneously administered ustekinumab significantly inhibited radiographic progression of joint damage compared with placebo in patients with active PsA, and this improvement was maintained through 2 years [90,91]. A phase 3 trial of guselkumab, a monoclonal antibody directed against the p19 subunit of IL-23 in PsA, is ongoing (NCT03162796).

4.3. Interleukin-17

IL-17A is a product of Th17 cells, mast cells, macrophages,

neutrophils, NK cells, and CD8 T cells [22,92]. IL-17A levels are increased in the circulation of individuals with PsA, playing a role in pathogenic processes associated with angiogenesis, fibrogenesis, and osteoclastogenesis in PsA [18,93]. IL-17A acts on multiple cell types (eg, cutaneous keratinocytes and synovial-like joint fibroblasts) to increase the production of mediators of the chronic inflammatory state. In addition, IL-17A acts on osteoblasts and OCPs to promote bone resorption, which may contribute to joint damage [18]. Furthermore, levels of IL-17–producing CD8 T cells are significantly increased in the synovial fluid of patients with PsA, and the level of increase is significantly correlated with disease activity, erosion status, and synovitis [94]. IL-17 also plays a key role in enthesitis. In an enthesitis mouse model, neutralization of IL-17 resulted in decreased inflammation and paw swelling [74]. The source of IL-17 was shown to be T-cells (γδ T-cells) in this report, and group 3 innate lymphoid cells (ILC3) are another potential source of IL-17 [74,95]. IL-23–activated myeloid cells also produce IL-17 and IL-23 overexpression has been observed to drive the development of enthesitis [74,96]. Other animal models have shown a key role for IL-17 in bone formation, bone loss, and epidermal hyperplasia [58,97].

The IL-17A inhibitor, secukinumab, is approved for the treatment of active PsA. In the phase 3 FUTURE 1 and FUTURE 2 studies, treatment with secukinumab was associated with early and significant improvements in joint and skin signs and symptoms of PsA, physical functioning, and quality of life compared with placebo [98,99]. In FUTURE 5, significant improvements were observed in reducing structural damage progression after 24 weeks [100]. Secukinumab was efficacious in both patients naïve and those previously exposed to TNF-α inhibitors [101]. In biologic-naïve patients at 24 weeks, secukinumab 150 mg provided American College of Rheumatology (ACR) 20 response rates of 64% and ACR 50 responses rates of 44% [101]. After 3 years of treatment with secukinumab 150 mg in a mixed population of patients naïve and previously exposed to TNF-α inhibitors, ACR 20 response rates were achieved by 77% of patients and ACR50 response rates were achieved by 55% of patients [102]. Furthermore, progression of structural damage was inhibited in more than 80% of patients receiving secukinumab for 2 years in FUTURE 1 [103].

Ixekizumab, another IL-17A inhibitor, is also approved for the treatment of PsA. Findings from the SPIRIT-P1 and SPIRIT-P2 phase 3 trials demonstrated that treatment with ixekizumab was efficacious in both biologic-naïve patients and individuals previously treated with TNF-α inhibitors [104,105]. In biologic-naïve patients, ixekizumab Q4W provided ACR20 response rates of 58% and ACR50 response rates of 40% after 24 weeks [104]. Additionally, ixekizumab inhibited structural damage progression after 24 weeks of treatment [104].

Brodalumab is a subcutaneously administered human monoclonal antibody against IL-17R [22]. Although phase 3 clinical trials of brodalumab in PsA were terminated due to concerns of suicidal ideation, it is approved for the treatment of moderate-to-severe PsC with a Risk Evaluation and Mitigation Strategy. While the emerging IL-17 antagonists are proving to be effective treatments for both the skin and joint symptoms of PsA, they are showing marked improvements in other manifestations of disease such as enthesitis, dactylitis, and radiographic progression [98–100,104–108]. An investigational dual variable domain immunoglobulin that inhibits both IL-17A and TNF-α, ABT-122 had similar but not additional efficacy compared with adalimumab and further development in PsA is not being pursued [109].

4.4. Interleukin-6

IL-6 is a proinflammatory cytokine produced by macrophages and T cells during acute phase inflammatory responses. IL-6 mediates production of IL-17 and, thus, may play a potentially important role in the development of skin and joint disease. Synovial IL-6 levels are elevated in patients with active PsA [22,110].

Costa and colleagues reported a case of a patient with refractory PsA who responded to tocilizumab, a humanized monoclonal antibody directed against IL-6R [111]. However, no controlled clinical studies of tocilizumab have been conducted or are planned in PsA. In a phase 2b study of patients with PsA, another IL-6 inhibitor, clazakizumab, provided ACR20/50 response rates at week 16 of 39%/17% and Psoriasis Area and Severity Index (PASI) 75 response rates of 5% [112]. In addition, the efficacy of clazakizumab was not dose dependent in patients with PsA. In a phase 2b study of patients with RA, rates of serious adverse events with clazakizumab and methotrexate ranged from 8.3% to 13.6%, compared with 3.3% for methotrexate alone [113]. There are currently no clinical trials registered for clazakizumab in PsA or RA.

4.5. Cytotoxic T lymphocyte antigen-4

Dysregulated T cell activation plays an important role in the pathogenesis of PsC [114], and growing evidence indicates that this dysregulation is also crucial in the development of PsA [115]. An important treatment strategy for PsC and PsA, therefore, is the targeting of T cells or of T cell activation. Abatacept is a fusion protein construct consisting of the extracellular domain of CTLA-4 linked to a modified Fc portion of human IgG1, which inhibits T-cell activation by binding to CD80/CD86 ligands on the surface of antigen-presenting cells [80,116]. This action indirectly reduces production of proinflammatory cytokines and autoantibodies [116]. Abatacept is currently approved for the treatment of RA, juvenile idiopathic arthritis, and PsA. In a phase 3 study of abatacept in PsA, ACR20 response rates were achieved by 39% of patients and PASI50 response rates were achieved by 27% of patients at week 24 [117]. Abatacept has also been observed to decrease expression of CD4 + FOXP3 + regulatory T cells in the synovium of patients with PsA, but clinical efficacy data for PsA were not evaluated in this study [118].

4.6. Phosphodiesterase 4

Phosphodiesterase (PDE) 4 is a member of the major enzyme class that maintains homeostasis by degrading cyclic adenosine monophosphate (cAMP) into adenosine monophosphate and is the dominant form of PDE in immune cells. Apremilast is an orally administered, selective inhibitor of PDE4 [80]. Apremilast treatment is associated with increased levels of intracellular cAMP, which causes downregulation of the inflammatory response by decreasing levels of proinflammatory cytokines such as TNF-α, IL-12, and IL-23, and increasing levels of anti-inflammatory cytokines such as IL-10 [80]. It was recently reported that PDE4B and PDE4D isoform expression is upregulated in the dermal fibroblasts of patients with inflammatory diseases and that PDE4 interacts with the CD271 nerve growth factor receptor in tissue remodeling and wound healing [119].

Apremilast reduces dermal fibroblast migration and differentiation [119]. In the phase 3 PALACE 1 study, treatment with apremilast was associated with improvements in measures of PsA disease activity, physical function, associated PsC symptoms, health-related quality of life, and fatigue [120,121]. Based on key results from the PALACE clinical development program (PALACE 1–4), apremilast was recently approved for the treatment of active PsA [80]. In some patients, dose-limiting gastrointestinal adverse events prevent them from taking a maximally effective dose [122]. Depression and weight loss have also been reported with apremilast [123].

4.7. Janus kinase/signal transducers and activators of transcription

Janus kinases, including JAK1, JAK2, JAK3, and tyrosine protein kinase 2, are intracellular tyrosine kinases that regulate cytokine signaling by associating with specific cytokine receptors and facilitating activators of STAT proteins. In patients with PsA, activation of JAK1 and the downstream STAT3 and STAT1 are increased in the synovial fluid of affected joints [80].

Tofacitinib is an oral inhibitor of JAK3, JAK1, and JAK2 that is approved for RA and PsA. By inhibiting JAK3, expressed by lymphocytes, tofacitinib inhibits IL-2, IL-4, IL-15, and IL-21 and by blocking JAK1 and JAK2, tofacitinib inhibits IFN-γ, IL-6, IL-12, and IL-23 signaling [80]. These cytokines mediate pathological features of PsA such as enthesitis, synovial inflammation, and bone resorption [96,124]. In a phase 3 trial of patients with PsA who had an inadequate response to conventional disease-modifying antirheumatic drugs, treatment with tofacitinib produced ACR20/50 response rates of 50%/28% and PASI75 response rates of 43% after 3 months [125]. In addition, in a phase 3 trial of patients with PsA who had an inadequate response to TNF-α inhibitors, treatment with tofacitinib produced ACR20/50 response rates of 50%/30% and PASI75 response rates of 21% after 3 months [126].

Baricitinib, a selective JAK1/2 inhibitor, recently showed promising clinical activity in a phase 2b trial of patients with moderate-to-severe PsC [127]; however, no studies in PsA have been reported.

5. Biomarkers and next-generation clinical tools

The available biologic agents that inhibit TNF-α can be highly effective and well tolerated in many patients with PsA, slowing disease progression and improving quality of life [80]. Recent approvals of ustekinumab, secukinumab, ixekizumab, apremilast, and tofacitinib have expanded the therapeutic armamentarium for patients with PsA, providing treatments with different mechanisms of action than TNF-α inhibition. However, there is a proportion of patients with PsA who are not responsive to currently available therapies, highlighting the unmet clinical need for novel therapeutic targets and effective treatments for PsA [19].

As can be seen in Fig. 1, PDE4 inhibition and JAK inhibition are potential targets being actively pursued as future therapeutics. This pathogenetic construct also allows for the consideration of additional pathways and therapies—new submissions for United States Food and Drug Administration approval have included inhibitors of IL-22, chemokine (C-C motif) ligand 20 (CCL20), and enhancers of regulatory T cells. Another possible future target for the treatment of inflammatory disorders may involve IL-26, which stimulates Th17 cell activation [128]. Likewise, the Wnt/β-catenin pathway has been proposed as a therapeutic target to mitigate bony ankyloses in SpA [129]. However, any therapeutic targeting inhibition of bone formation will require careful evaluation of adverse reactions, as preclinical studies have shown worsening outcomes in mice with RA that were treated with antibody-mediated inhibition of sclerostin, a Wnt/β-catenin inhibitor [130].

With advancements in the understanding of contributing factors to PsA pathogenesis, it is possible that genetic, cellular, soluble, synovial, and imaging features could be used as biomarkers to guide diagnosis, assess prognosis, and monitor response to therapy. Specifically, genetic biomarkers in PsA have the potential for use as diagnostic/prognostic markers because they elucidate why some individuals with PsC develop PsA, while others do not. Genetic biomarkers may provide predictive information about response to therapy as early reports will require confirmation in defined clinical subsets [131]. However, it is challenging to evaluate genetic biomarkers in PsA due to the different clinical presentations of the disease. Our literature findings on genes associated with PsA (Table 1) provide an overview of genes that may serve as genetic biomarkers in the future, helping to guide diagnosis and treatment decisions.

In addition, inflammatory biomarkers in the synovial tissue and fluid in patients with PsA are being investigated as markers of response to therapy [131–133]. These markers, such as metalloproteinases or DC-STAMP+ monocytes, could also be used in drug development to identify new therapeutic targets. To better understand the current state of research into novel markers that could be useful beyond the well-established IL, IFN, and TNF markers in various aspects of disease management, we conducted a literature search to identify candidate markers with an association to PsA. Initially, recent review articles were considered to identify commonly cited candidate markers that are not currently used in routine PsA clinical practice. A PubMed search was then conducted to identify references to support the association of these markers in PsA. The results of this search are shown in Table 5.

To date, no biomarker has been validated in PsA, and assessment of biomarkers currently remain outside of routine clinical practice [132]. The findings in Table 5 highlight the breadth of active research in PsA and the complexity and heterogeneity of pathways that contribute to disease pathogenesis. Early studies have shown that some of these biomarkers (eg, C-reactive protein, apolipoprotein C3, cellular adhesion molecules) are predictive of clinical response to biologic therapies [134]. Advancing our understanding will require careful characterization of the clinical presentation, course, and outcomes in PsA, as well as the genotyping and molecular expression of specific cells and tissues. GWAS will assume greater meaning when communities of dedicated clinicians record clinical data and collaborate with skilled molecular investigators. These efforts can then help answer important questions that will impact clinical practice, such as: (1) which patients with PsC will develop only distal interphalangeal joint involvement or severe osteolysis called arthritis mutilans, and (2) whether the gene expression studies of cells from peripheral blood versus cells from synovial and entheseal tissue show meaningful changes following biologic therapies.

In addition, the metabolic energy induced by the microbiome–microorganisms found in the gut and skin of humans–and aberrant interactions between the human genome and microbiota contribute to the development of inflammatory and autoimmune diseases [135–137]. The commensal composition of the gut microbiome may be different in the various auto-inflammatory and autoimmune diseases, and studies of the therapeutic effect of probiotics, prebiotics, and even fecal microbiotic transplantation on patients with these diseases are preliminary [135,136,138].

In the interim, we recommend that all patients with PsC undergo clinical evaluation for musculoskeletal progression, including any of the validated PsA-directed questionnaires and appropriate imaging studies by ultrasound and/or MRI or PET scans to complement the clinical examination. In addition, HLA-B typing by polymerase chain reaction will alert for susceptibility for progression to PsA. Biomarker studies before and after treatment with effective therapies should be our next priority for clinical investigations.

In summary, over the past several years, as our understanding of the pathogenesis of PsA has improved—particularly related to genetic and inflammatory factors—this knowledge and researchers' cooperative efforts should provide the stimulus for targeted development of new biologic therapies for the varied manifestations of PsA with the aims of reducing disease burden and improving quality of life for patients. Indeed, the latest guidelines assembled by ACR and the National Psoriasis Foundation should serve as a current standard, which will change with continuing investigations [139].

Table 5
Results of literature search for novel markers beyond ILs, IFNs, and TNF-α associated with PsA.

Marker	Name	Associated pathway or function
Immune/inflammatory factors		
Anti-LL37 antibodies [216]	LL37 is part of the cathelicidin family	Pathogenic autoantibody in PsA
CRP [134,217–221]	C-reactive protein	Acute phase reactant and marker of systemic inflammation
CXC10 [222]	C-X-C motif chemokine 10	Chemoattraction of immune cells
DCs [223,224]	Dendritic cells	Release antimicrobial peptides, chemokines, and cytokines needed for protective immune responses
ENRAGE (S100A12) [134,225]	RAGE-binding protein; binds to receptor for advanced glycation end-products	Calcium-, zinc-, and copper-binding protein involved in regulation of immune and inflammatory responses
E-selectin [226–228]	Endothelial leukocyte adhesion molecule 1	Cell-surface glycoprotein that mediates immuno-adhesion
JAK/STAT [229]	Janus kinase/signal transducer and activator of transcription	JAKs are tyrosine kinases that mediate signaling events in innate and adaptive immunity; when bound to cell-surface receptors, tyrosine residues are phosphorylated, creating docking sites for STATs. STATs mediate cell responses to interleukins and certain growth factors and regulate cell-cycle activities
MCV autoantibodies [230,231]	Mutated citrullinated vimentin autoantibodies	Antibodies targeting citrullinated vimentin, which is a cytoskeletal component of mesenchymal cells; production increases in response to tissue inflammation and apoptosis
MIP-1α and MIP-1β (CCL3 and CCL4) [232]	Macrophage inflammatory protein 1α and 1β (C-C motif chemokines 3 and 4)	Monokines with inflammatory and chemokinetic properties
MPO [134]	Myeloperoxidase	Catalyzes production of hypohalous acids (eg, HClO) in stimulated polymorphonuclear leukocytes to enhance microbicidal activity as part of host defense mechanisms
NF-κB [233]	Nuclear factor kappa B	Rapidly acting primary transcription factor found in all cell types; key regulator of immune responses
NK [234,235]	Natural killer cell	Components of innate immune responses that secrete proinflammatory cytokines; target neoplastic and virus-infected cells as part of host defense
S100A8/A9 [221,225,236,237]	Calprotectin	Proinflammatory leukocyte protein complex secreted by neutrophilic granulocytes and monocytes; calcium-binding protein with antimicrobial activity
TLR-2 [238,239]	Toll-like receptor 2	Involved in innate immune responses; activates inflammatory cells via the NF-κB pathway; its main ligands are peptidoglycan and lipoproteins from gram-positive bacteria
TRAIL [240]	Tumor necrosis factor-related apoptosis-inducing ligand	TNF superfamily ligand that induces apoptosis and is associated with systemic inflammation
TWEAK [241]	Tumor necrosis factor-like weak inducer of apoptosis	Mediates NF-κB activation; promotes angiogenesis and proliferation of endothelial cells; induces proinflammatory cytokines
YKL-40 [242–244]	Also known as chitinase 3-like protein 1 and cartilage glycoprotein-39	Secreted from articular chondrocytes, synovial cells, and macrophages; thought to regulate cell proliferation, angiogenesis, mitogenesis, and remodeling; implicated in Th2 responses and induction of IL-13
Bone loss		
DC-STAMP [62,245]	Dendritic cell-specific transmembrane protein	7-pass transmembrane protein required for fusion of monocytes to form osteoclasts and giant cells
Dkk-1 [246,247]	Dickkopf-1	Inhibitor of Wnt signaling, which inhibits osteoblast differentiation and function and promotes osteoclastogenesis through suppression of osteoprotegerin
M-CSF [246,247]	Macrophage-colony stimulating factor	Promotes macrophage survival and proliferation, and is a regulator of osteoclastogenesis
MMPs (eg, MMP-3 and MMP-9) [221,226–228,248]	Matrix metalloproteinases	Family of proteolytic enzymes that can degrade all components of the extracellular matrix, causing cartilage destruction and joint erosion
RANKL [8,247,249]	Receptor activator of nuclear factor-κB ligand	Mediator of osteoclastogenesis: receptor activator of NF-κB; ligand for osteoprotegerin; key regulator of osteoclast differentiation and activation, and of T-cell–dependent immune responses
Bone formation		
OPG [249]	Osteoprotegerin	Mediator of bone remodeling that acts as a decoy receptor preventing RANKL binding to RANK and inhibiting osteoclastogenesis
VEGF [232,250,251]	Vascular endothelial growth factor	Angiogenic growth factor that mediates vascular remorphology and pathologic formation of new bone in PsA
Cartilage formation/composition		
COMP [248]	Cartilage oligomeric matrix protein	Interacts with collagens and fibronectin to modulate the structural integrity of cartilage; mediates chondrocyte interactions with cartilage extracellular matrix; blocks caspase-3 and induces IAPs to suppress apoptosis
CPII [246,252]	Type II collagen carboxypropeptide	Byproduct of cartilage turnover that is released during procollagen 2 synthesis
Lipid transport		
Apolipoprotein C 3 [134]	—	Component of plasma VLDLs and HDLs; regulates triglyceride homeostasis and hepatic lipoprotein assembly and secretion
Cell-cell adhesion		
CAMs [226,253]	Cellular adhesion molecules	Ligands for leukocyte adhesion proteins; important for cell recognition and leukocyte-endothelial cell adhesion; may regulate immune and inflammatory responses

(*continued on next page*)

Table 5 (*continued*)

Marker	Name	Associated pathway or function
Embryo development		
CEA [134]	Carcinoembryonic antigen	Protein normally found in developing embryos; marker of cancer in adults
Cellular proliferation		
EGF [232]	Epidermal growth factor	Stimulates growth of epidermal and endothelial tissues

IAP, inhibitor of apoptosis; IFN, interferon; IL, interleukin; PsA, psoriatic arthritis; TNF, tumor necrosis factor.

Conflicts of interest

DF reports receiving grant/research support from Amgen, BMS, Novartis, NIH, Pfizer, and Roche/Genentech; serves as a consultant for AbbVie, Amgen, BMS, Cytori, Novartis, Pfizer, Roche/Genentech, and UCB; and serves on the Speaker's Bureau (CME ONLY) for BMS and Actelion.

JB declares no competing interests.

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Author contributions

DEF conceived of the concept for this review, and participated in its design and coordination, drafted and reviewed the content of the manuscript. JB conceived of the concept for this review, and participated in its design and coordination, drafted and reviewed the content of the manuscript. JSL conceived of the concept for this review, and participated in its design and coordination, drafted and reviewed the content of the manuscript. All authors read and approved the final manuscript.

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