Review

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Posted Date: 21 July 2023

doi: 10.20944/preprints202307.1499.v1

Keywords: psoriasis; genetics; epigenomics

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Genetic and Epigenetic Mechanisms of Psoriasis

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Abstract: Psoriasis is considered an immune-mediated disease involving the innate and adaptative immune system triggered by environmental risk factors in genetically susceptible individuals. However, its physiopathology is not fully understood yet. Recent technological advances, specially genome and epigenome-wide studies, have allowed a more sensitive study of the genetic and epigenetic mechanisms, allowing an enhanced understanding of its physiopathology and facilitating the development of new drugs. In this review, we aim to summarize the current evidence on genetic and epigenetic mechanisms of psoriasis.

Keywords: psoriasis; genetics; epigenomics

Introduction

Psoriasis is a chronic inflammatory skin disease affecting about 2% of individuals in Europe and North America [1]. Although multiple types of psoriasis have been reported, including plaque psoriasis (psoriasis vulgaris), guttate, inverse, pustular and erythrodermic psoriasis [1], most scientific research refers to the psoriasis vulgaris variant, which affects approximately 85 to 90% of all patients with the disease [2]. It is usually manifested as raised, well-demarcated, erythematous oval plaques with adherent silvery scalesresulting from abnormal epidermal hyperproliferation and differentiation, together with increased infiltration and activation of immune cells [3].

Psoriasis is associated with a significative psychological burden. In fact, health-related quality of life is impaired more in psoriasis than in other chronic diseases such as cancer, myocardial infarction, and congestive heart failure [1]. Furthermore, psoriasis has been related to several comorbidities such as psoriatic arthritis, hypertension, diabetes mellitus or cardiovascular diseases, among others [4]. Thus, the disease carries a major burden on health care systems and on society in general [2].

The etiopathogenesis of psoriasis is complex and not completely understood. Psoriasis is nowadays considered an immune-mediated disease where a complex interaction between the innate and adaptive immune system is caused by the interplay of individual genetic susceptibility and environmental risk factors [4,5].

Substantial advances have been made in elucidating the molecular mechanisms of psoriasis in recent years. Genome-wide studies have brought to light new genes associated with psoriasis and have shown the implications of multiple genes in the pathogenesis of the disease, with therapeutic implications [6]. At the same time, recent technological advances have allowed a more comprehensive and sensitive study of the epigenetic mechanisms that regulate psoriasis gene expression at both transcriptional and post-transcriptional levels [7]. This greater genetic and epigenetic understanding holds great promise for the identification of novel drug targets for the treatment of psoriasis.

The aim of this review is to summarize the current evidence on the genetic and epigenetic mechanisms of psoriasis.

Material and Methods

An electronic literature search was conducted on the Medline/PubMed database until June 2023 using Medical Subject Headings terms and relevant medical terminology. The search criteria

 doi:10.20944/preprints202307.1499.v1

included the terms 'psoriasis', 'genetic testing', 'genomics', 'genetics', 'epigenomics', 'epigenetics'. We considered original genome studies, reviews, systematic reviews and meta-analyses, specifically related to the genetic or epigenetic study of psoriasis. English language manuscripts were included. On the other hand, letters to the editor, editorials, experts' opinions, congress proceedings, studies including patients with psoriatic arthritis alone, those related to specific psoriasis treatments or focused on transcriptomics or proteomics analysis were excluded. The selection of publications was performed by two independent researchers (LM, LP) and discrepancies were resolved by consensus.

A total of 321 articles were initially identified, from which 18 were duplicates / redundant and therefore excluded. Studies that did not offer pertinent information according to the research objectives (163) were excluded, as were 34 studies focused on psoriatic arthritis. After a comprehensive review of the full-text articles, 84 studies were finally eligible for inclusion in the review.

Results

Genetics

Psoriasis is significantly more likely to occur in first- and second-degree relatives of patients with psoriasis than in the general population [5,8], and concordance is greater in monozygotic than in dizygotic twins [5,9], pointing to a strong genetic influence on the disease. In fact, heritability of psoriasis has been estimated to be higher than 60% [5,9], even though psoriasis is not a monogenic disease, but a complex and multifactorial disease involving multiple susceptibility genetic loci. Early analyses on this topic were carried out by family-based linkage disequilibrium studies [10], since genetic variants or loci which are in close proximity on the same chromosome are less likely to be separated by recombination during meiosis, thus tending to be inherited together and being correlated in the population [5]. Areas thought to harbor psoriasis genes related with psoriasis susceptibility were initially named PSORS (psoriasis-susceptibility) loci [11]. There are at least 12 different PSORS loci that were mainly identified through linkage analysis of multiply affected psoriasis families [11]. Loci in the major histocompatibility complex (MHC) I, on the short arm of chromosome 6, were among the first and most repetitive genetic susceptibility regions found in psoriasis [6]. In fact, the first gene variant discovered to be associated with psoriasis susceptibility, PSORS 1, was the human leukocyte antigen (HLA)-Cw6, which is located at chromosomal position 6p21.3 [11,12].

Since the Human Genome Project was completed in 2001, technological developments allowed for the affordable study of whole genome instead of individual variants or single genes [13]. Genome-wide association studies (GWAS) analyzed several million genetic markers or single nucleotide polymorphisms (SNP) across the genome in large populations, allowing the detection of small differences in allele frequencies between disease cases and unaffected controls [5]. GWAS allowed confirmation of loci previously identified by linkage analysis and identified new loci related to psoriasis susceptibility, beyond the MHC [14,15]. These findings have greatly advanced the understanding of disease mechanisms and associated pathways. Specifically, apart from the MHC system, the genes found to be related with psoriasis belong to the functional pathways of skin barrier, innate immune system –with especial relevance of nuclear factor-kappa B (NF-kB) and interferon (IFN) signaling–, and adaptative immune system, with involvement of CD8+ and CD4+ T lymphocytes, especially Th17 [6]. Table 1 summarizes main genes associated to psoriasis.

Table 1. Genes associated to psoriasis.

Pathway	Gene	Function
Antigen presentation	HLA-C*0602	Antigen presentation
	ERAP1	Modification of MHC-I-binding peptides
Th1 Signaling Pathway	IL12B	p40 subunit of IL12
	TYK2	Downstream molecule of IL12 receptor
	ZC3H12C	Macrophage activation

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	STAT5A/B	Signaling pathway of IL2 familiy cytokines
	ILF3	IL2 expression in T-cells
Th17 Signaling Pathway	TYK2	Downstream molecule of IL23 receptor
	JAK2	Downstream molecule of IL23 receptor
	STAT3	Downstream molecule of IL23 receptor
	SOCS1	Th17 differentiation
	ETS1	Th17 differentiation
	IL17RD	IL17 receptor
	IL22	Differentiation and proliferation of keratinocytes
	TRAF3IP2	Signaling pathway of IL17A/F
	KLF4	Regulation of IL17A production
Innate immunity	C-REL	NF-kB pathway activation
	TRAF3IP2	NF-kB pathway activation
	CARD14	NF-kB pathway activation
	MICA	NK, NKT and T-cells activation
	TNFAIP3	NF-kB pathway downregulation
	TNIP1	NF-kB pathway downregulation
	NFKBIA	NF-kB pathway downregulation
	DDX58	INF pathway and antiviral response
	IFIHI	INF pathway and antiviral response
Skin barrier function	DEFB4	Secretion of β-defensins
	LCE3B/C	Epidermis differentiation and hyperproliferation
	GJB2	Connexin 26, epidermal gap junction

Antigen Presentation

The first significant genetic association of psoriasis was found in the MHC I region [6]. MHC I molecules are found on almost all nucleated cells and its function is to present intracellular self or non-self peptides to the immune system [11,16]. This process enables MHC-I to present thousands of peptides, collectively referred to as the 'immunopeptidome'. CD8+T cells read out the immunopeptidome by binding to the peptide-MHC-I complexes with their T cell receptors (TCR) [16].

The MHC region is responsible for one-third of the overall genetic contribution of psoriasis [6], highlighting the role of the antigen presentation pathway in the pathogenesis of psoriasis. Within the MHC, the allele HLA-C*0602 shows the strongest association with psoriasis [17] and is considered the PSORS1 risk variant [6]. The HLA- C*0602 allele is found in 20-50% of patients with psoriasis, depending on the population studied, and in only up to 16% of controls [11]. This allele has also been related to guttate psoriasis, Koebner phenomenon, psoriasis improvement during pregnancy, psoriasis nail disease and poor response to treatment [6]. In fact, the strong genetic association of psoriasis with MHC-I alleles provides de basis for considering this disease among the MHC-I-opathies, a group of conditions characterized by disease-associated MHC-I alleles that present specific self-immunogenic peptides that trigger autoimmune reactions [16]. Indeed, CD8+ T cells that react against melanocyte-derived antigens have been identified in psoriasis associated with HLA-C*0602 [16,18,19]. Other pathogenic theories suggest that MHC-I molecules could misfold and accumulate in the endoplasmic reticulum or that the predisposing MHC-I proteins could be recognized by killer-cell immunoglobulin-like receptors (KIRs) or leucocyte immunoglobulin-like receptors (LILRs) on the cell surface of natural killer (NK) cells [16].

Other loci related to antigen presentation have been associated with psoriasis susceptibility. GWAS have revealed that there are non-additive gene to gene interactions between the HLA-class I

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risk alleles and certain variants of the endoplasmic reticulum aminopeptidase 1 (ERAP1) that can be associated with psoriasis susceptibility [18]. ERAP1 encodes an aminopeptidase involved in N-terminal trimming of MHC-I-binding peptides in the endoplasmic reticulum to make them adequate for antigen presentation [17,18].

These associations suggest that psoriasis is, at least in some cases, caused by a T-cell mediated reaction to an autoantigen that is preferentially presented on HLA-C*0602 and processed by transcripts of particular ERAP1 alleles [11]. However, there is not a unique confirmed "auto-antigen" [11]. On the other hand, the T-cell infiltrate in psoriasis plaques is highly polyclonal and not dominated by a heavy clonal expansion of any distinct T-cell responding to a specific epitope [11].

Other loci found in the proximity of the MHC region are associated with an increased risk of psoriasis [20]. The MHC class I polypeptide-related sequence A (MICA) is found in the proximity of the HLA-B locus in the MHC region. Its expression is thought to be stress-induced and it is a ligand for NKG2D, an activating receptor found on natural killer cells, NKT-cells, and T-cells [11].

Th1 Signaling Pathway

Psoriasis has traditionally been considered a Th1 mediated disease [6], since interferon (IFN)-γ producing T-cells are increased in psoriatic lesions[21]. Myeloid dendritic cells, stimulated by factors such as tumor necrosis factor (TNF)-α, IFN-α, IFN-λ, interleukin (IL)-6, and IL-1β, instruct T-cells to differentiate to Th1 cells and secrete IL-12 [6].

Several genetic psoriasis susceptibility loci involved in various aspects of the Th1 signaling pathway have been identified, including IL12B [22] and TYK2 [23](coding for the p40 subunit of IL-12 and tyrosine kinase 2, involved in signal transduction following activation of the IL-12 and other receptors), ZC3H12C [24](transcript involved in macrophage activation), STAT5A and STAT5B (coding for the corresponding signal transducer and activator of transcription molecules involved in signaling of IL-2 family cytokines such as IL-2, IL-7, IL-15, and IL-21) and ILF3 (coding for a nuclear transcription factor determining IL-2 expression in T cells) (Table 1) [6].

Th17 Signaling Pathway

The discovery of Th17 and the Th17 polarizing cytokine IL-23 brought to light the crucial role of the IL-23/IL-17 pathway in psoriasis [21, 25]. Transforming growth factor (TGF)-β, IL-6, IL-1β, and IL-23 promote Th17 cell differentiation and production of IL-17, which has pro-inflammatory effects mediated by activation of dendritic cells, macrophages, endothelial cells, chondrocytes, fibroblasts, and osteoblasts [6]. Both IL-17 and IL-23 interact with the innate immune system by activating nuclear factor kappa B (NF-κB) transcription factor [26].

The IL-23 cytokine is composed of subunits p19 and p40, whereas the IL-23 receptor is a heterodimer composed of IL-12RB1 (shared with the IL-12) and IL-23R [11]. Several SNPs associated with psoriasis risk have been identified in genomic regions corresponding to both subunits of IL-23 (p19 and p40) and to IL23R [22,27]. It is worth mentioning that IL-12 is composed by two subunits, p35 and p40, the later shared with IL-23 and encoded by the IL12B gene; early studies of IL-12 function, which used either anti–IL-12p40 antibodies or IL-12p40– deficient mice, attributed functions to IL-12 that are now being correctly ascribed to IL-23 [27].

The IL-23 receptor lacks intrinsic signaling activity and requires interactions with downstream molecules (Tyk2 for IL-12RB1 and Jak2 for IL-23R). Signaling results in phosphorylation, activation and nuclear translocation of STAT3 [11]. Mutations in genes coding for Tyk2, Jak2 and STAT3 have been found to be associated with psoriasis [28,29]. Other genetic variants associated with psoriasis and related to IL-23 correspond to SOCS1 (coding for a suppressor of cytokine signal involved in Th17 differentiation) and ETS1 (coding ETS protooncogene 1 protein, involved in negative regulation of Th17 differentiation) [6].

To date, an association of the IL17A gene with psoriasis has not yet been established. However, a SNP in the IL17R is associated with disease susceptibility [30]. IL-22 is a Th17 cytokine that leads to differentiation and proliferation of keratinocytes and has been found to be upregulated in psoriatic skin [31,32]. IL22 has been associated with psoriasis by GWAS, with a quantitative effect: the greater

 doi:10.20944/preprints202307.1499.v1

the copy number of the IL-22 gene, the greater the risk of nail disease [28]. Other loci related to the IL-17/IL-23 axis and involved in psoriasis susceptibility correspond to genes coding for IL-6, with a protective effect, TRAF3 interacting protein 2 (TRAF3IP2) or KLF4 genes [6].

In psoriasis patients there is an altered balance of regulatory T cells (Tregs) and Th17 cells [33–36]. Tregs are lymphocytes that regulate the immune system and suppress the immune response [33], thus preventing development of autoimmune disease. Tregs inhibit the activity of CD4+ and CD8+ T cells leading to decreased production of pro-inflammatory cytokines [28]. Some polymorphisms identified in genes such as TNF, IL12RB2, and IL12B, could be also involved in the production, differentiation, or activity of Tregs, pointing to a genetic background of Treg dysfunction in psoriasis.

Innate Immunity

Initial activation of the innate immune system is required for subsequent activation of the adaptive response [11]. Many SNPs have identified gene candidates in psoriasis corresponding to innate immunity pathways. Transcription of these innate immune genes in psoriatic patients may decrease the threshold needed to initiate the pathogenic adaptive immune response [11].

NF-kB mediates the transcription of numerous genes involved in intracellular signaling and is one of the most important factors related to the innate response. The NF-kB pathway is activated in psoriatic lesions and many genes encoding components of the NF-kB pathway are associated with psoriasis [37,38]. Among genes associated with the activation of the NF-kB pathway stand out C-REL, also related with keratinocyte growth [39], TRAF3IP2 [40], highlighting the interactions between innate and adaptative immune system, or genes encoding CARD proteins [41].

Some genes associated with psoriasis susceptibility are related not with activation of the NF-kB pathway but with its downregulation; mutations in negative regulators resulting in reduced ability to control inflammation may be as important as mutations resulting in overactive immune responses [11]. The former genes include those coding for TNF-α-inducible protein 3 (TNFAIP3) and TNFAIP3 interacting protein 1 (TNIP1), which prevent the degradation of the NF-kB inhibitor [42], the NF-kB inhibitor alpha (NFKBIA) which encodes the inhibitor of NF-kB signaling [43], and the zinc finger DHHC-type containing 23 (ZC3H12C), coding a protein that inhibits vascular inflammation [24].

Innate immune gene associations with psoriasis have also been found in the interferon pathway and antiviral response genes, including IFIHI and DDX58. They encode innate pattern-recognition receptors, RIG-I and MDA5, which recognize viral RNA with subsequent activation of an anti-viral response, ending up in induction of type-I interferons and other innate inflammatory molecules [44]. These mutations might lead to a decreased threshold for triggering either self- or non-self stimuli and be a key initiating step in lesion development [11].

Skin Barrier Function

The role of the immune system is crucial in the pathogenesis of psoriasis, but there is a component of epithelial disorder, since epidermal keratinocytes are strongly involved in the initiation of psoriasis [6,17]. Polymorphisms in skin barrier regulatory genes such as defensins, late cornified envelope (LCE) genes and connexin have been identified. The DEFB4 gene is overexpressed in the psoriatic skin leading to an increase in secretion of β-defensins in response to Th1 or Th17-related mediators, and variations in DEFB4 gene copy numbers are associated with psoriasis risk [45]. LCE genes, specifically LCE3B and LCE3C, located in the PSORS4 locus, have been shown to be related with psoriasis risk by both copy number variation studies and GWAS [17,46]. Finally, a variant in the GJB2 gene, encoding a connexin, was identified as a psoriasis risk locus by GWAS [42].

Genetics of Generalized Pustular Psoriasis

In contrast to psoriasis vulgaris, the pathogenesis of pustular psoriasis seems to be closely related to an autoinflammatory disorder with special contribution of neutrophils and participation of IL-36 cytokines, which in turn explain differences in their clinical presentation [47]. Mutations underlying the presentation of generalized pustular psoriasis as monogenic autoinflammatory

 doi:10.20944/preprints202307.1499.v1

disorder are also specific. Genetic variants related to generalized pustular psoriasis susceptibility include IL36RN, resulting in DITRA (Deficiency of The Interleukin-36-Receptor Antagonist) a monogenic autoinflammatory disorder [47], linked with a more severe disease phenotype and earlier age of onset [17] and CARD 14 (caspase recruitment domain family member 14), which is primarily expressed in keratinocytes and activates NF-kB signaling. Mutations activating CARD 14 have also been found in plaque psoriasis, psoriatic arthritis, and localized pustular psoriasis, besides generalized pustular psoriasis [47]. Mutations in the adaptor-related protein complex 1 subunit sigma 3 (AP1S3) have also been found in generalized pustular psoriasis. Keratinocytes lacking AP1S3 can show a dysregulated autophagy leading to marked upregulation of the IL-1 signaling pathway and IL-36 cytokines [48]. Myeloperoxidase (MPO) is a lysosomal hemoprotein found in neutrophilic granules and it is involved in antimicrobial activity [47]. Mutations in MPO genes causing MPO deficiency, found in several forms of pustular psoriasis, may lead to increased activity of neutrophilic proteases [49]. Other genes involved in pustular psoriasis are SERPINA1 and SERPINA3 (serine protease inhibitors that inhibit cathepsin G, neutrophil elastase and proteinase 3), TNIP1 and IL1RN [47].

Genetics in Psoriatic Arthritis

Psoriasis and psoriatic arthritis share multiple genetic risk variants related to innate, adaptive immune, and autoinflammatory pathways [50,51]. However, genetic variants specifically related to psoriatic arthritis have been reported, and patterns of cytokine gene expression have been shown to differ between skin and synovial tissue [50]. Whereas the association of HLA-C*06:02 with psoriasis is stronger than with psoriatic arthritis, other HLA variants such as HLA-B*27, HLA-B*39, HLA-B*38, and HLA-B*08 have been related with the risk of psoriatic arthritis [50]. Moreover, the HLA-B*08.01 allele has been associated with asymmetric sacroiliitis, peripheral arthritis, ankylosis and increased join damage, whereas HLA-B*27 is associated with symmetric sacroiliitis, dactylitis, and enthesitis[52]. On the other hand, polymorphisms in IL23R, TNFAIP3, and PTPN22 (tyrosine-protein phosphatase non-receptor type 22), IL12B, RUNX1 (CD8-lymphocyte activation and differentiation), IL13, KIR (killer-cell immunoglobulin-like receptor), and MAGI1 genes have shown association with psoriatic arthritis[6, 50]. Also, variants in the ADAMTS9 gene, involved in the cartilage extracellular matrix, are found to be associated with psoriatic arthritis [50].

Genetics and Psoriasis Treatment

The significant amount of knowledge derived from genetic research has delivered critical insights into the biology of psoriasis, allowing development of increasingly effective therapeutic agents for psoriasis [53]. Genetic polymorphisms responsible of treatment response to the different available psoriasis treatment options have been identified [54–56], including those related to the risk of developing antidrug antibodies [57], and found to correspond in many cases with type I HLA molecules. At the same time, genetic susceptibility to adverse drug reactions has also been described [56,58]. Since a wide range of therapeutic alternatives are available for psoriatic disease, pharmacogenomic tests prior to treatment might facilitate selection of the therapy based on individual probabilities of drug response or adverse events, providing opportunities for personalized medicine.

Epigenetics

Epigenetics is the study of reversible and heritable changes in gene expression not due to DNA sequence alterations [7]. Epigenetic mechanisms induce gene expression changes at a transcriptional o posttranscriptional level through chemical modifications of DNA and histones, which alter chromatin structure and activate transcription factors without affecting the DNA sequence [59]. Epigenetic mechanisms are sensitive to external stimuli and represent the link between genetics and the environment [60]. In fact, in psoriasis, where not only genetics but also environmental factors play etiopathogenetic roles, epigenetics can modulate individual gene expression modifying the

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likelihood of the disease [59]. This is especially important during embryogenesis, when the degree of pluripotency is high, whereas during cell differentiation, the epigenome is stabilized and becomes less responsive to environmental conditions [61]. The role of epigenetics in psoriasis is highlighted by the low concordance (35-72%) between monozygotic twins, who share an identical DNA sequence [62–64]. Epigenetic mechanisms in psoriasis can interfere with gene transcription, including DNA methylation and histone modifications, or translation, through non-coding RNAs that include microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA) [59].

DNA Methylation

DNA methylation consists in the transfer of a methyl group to the cytosine 5′ position of CpG dinucleotides by DNA methyltransferases (DNMTs) [65]. CpG dinucleotide methylation allows binding of methylcytosine-binding proteins (MBPs), which lead to chromatin compaction [65]. Methylation of the promoter or enhancer region of a gene leads to decreased binding of transcription factors that mediate or enhance gene transcriptional activity, and subsequent repression of gene transcription [65]. Conversely, loss of DNA methylation in this region leads to re-activation of gene expression [65].

DNA methylation in psoriasis has been shown to occur in multiple immune active locations besides the skin and has been related to disease activity, physical location of lesions and different tissue types involved [66]. Epigenome-wide methylation studies have discovered differentially methylated genes and pathways in psoriatic lesions compared with healthy controls or psoriatic lesions compared with non lesional skin of psoriatic patients [61,67–69]. However, compared with psoriatic lesions, the methylation pattern of non lesional skin of psoriatic patients was more similar to that of healthy patients [66]. Table 2 summarizes main DNA methylation changes described in psoriasis.

Table 2. Main non-coding RNAs associated to psoriasis.

Epigenetic change		Function
miRNA downregulation	miRNA125b	Keratinocyte proliferation and differentiation
	miR-203	Keratinocyte proliferation
	mir-383	Keratinocyte apoptosis and inflammation
	214-3p	Cell cycle check-points and keratinocyte proliferation
	miR-125a-5p	Keratinocyte proliferation
miRNA upregulation	miR-378a	Psoriatic inflammation
	Mir-31	Keratinocyte proliferation
	mir-210	Inflammation
	miR-200c	Associated with PASI
	miR-155	Psoriatic inflammation
lncRNA upregulation	lncRNA-RP6- 65G23.1	Immune response, keratinocyte proliferation, apoptosis suppression
	MIR31HG	Keratinocyte proliferation
	MSX2P1	Keratinocyte proliferation
	XIST	Keratinocyte proliferation
	FABP5P3	Keratinocyte proliferation and inflammation
	KLDHC7B-DT	Keratinocyte proliferation and inflammation

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	SPRR2C	Keratinocyte proliferation and apoptosis
lncRNA downregulation	MEG3	Keratinocyte proliferation and apoptosis
	GAS5	Related to psoriasis severity
	PRINS	Keratinocyte proliferation and inflammation
	NEAT1	Keratinocyte proliferation
circRNA downregulation	circRAB3B	Keratinocyte proliferation
circRNA upregulation	circOAS3	Keratinocyte proliferation and apoptosis
	circEIF5	Keratinocyte proliferation
	circ_0060531	Keratinocyte proliferation, migration &inflammation
	hsa_circ_0003738	Treg modulation
	hsa_circ_0061012	Keratinocyte proliferation and migration

When comparing psoriasis involved skin to adjacent normal skin of patients with psoriasis, differentially methylated CpGs are found, several of them located at promoters of known PSORS genes, such as S100A9, PTPN22, SELENBP1, CARD14, and KAZN [69]. Characteristically, psoriatic skin with Munro's microabscess, has shown to be enriched with differentially methylated genes involved in neutrophil chemotaxis, suggesting that DNA methylation profile can also be related with psoriasis histopathological features [69]. Other differentially methylated loci in psoriatic lesions compared with normal skin of patients with psoriasis and with normal skin from healthy controls are S100A8 (involved in epidermal differentiation), CYP2S1 (metabolism of retinoic acid) and EIF2C2 (with a role in RNA processing) [68].

Differential methylation pattern can also be found in psoriatic scales, as hypomethylation of CpG sites in psoriatic scales compared with psoriatic skin lesions is observed, which is closely related to disease severity [70]. Such is the case of the MGRN1 gene, coding a protein involved in degradation of misfolded proteins [70].

It has been suggested that resolved psoriasis lesions generate local disease memory, involving development of tissue-resident memory T cells in the skin, and prompting local relapse. Since the DNA methylation pattern does not change completely in lesional skin after treatment, epigenetic changes could contribute to this local memory [71]. In fact, differential methylation patterns have been observed between paired never-lesional skin and resolved lesions of psoriasis patients [72]. Furthermore, methylation differences between never-lesional psoriatic skin and healthy skin from volunteers, involving the Wnt and cadherin pathway genes, have also been identified and suggest that uninvolved skin might represent a pre-psoriatic state with underlying disease susceptibility [73].

Changes in DNA methylation have also been found in peripheral blood mononuclear cells (PBMCs) of psoriasis patients. In fact, the expression of DNMT1 is increased in PBMCs from patients with psoriasis, while the expression of methyl-CpG binding domain protein 2 (MBD2) and methyl-CpG binding protein 2 (MeCP2), important regulators of DNA methylation, is significantly decreased[74]. Furthermore, differential methylation of the promotors of genes involved in cell communication, signal transduction pathways, nucleotide catabolic processes, skin development and cell migration, have also been observed in mesenchymal stem cells of psoriasis patients [75].

DNA methylation can also play a role in the development of psoriatic arthritis: different DNA methylation patterns in CD8+ T cells may allow differentiation of purely cutaneous psoriasis and psoriatic arthritis [76–78]. The published studies are few and the size samples small, so further research on this issue is needed.

Histone Modification

 doi:10.20944/preprints202307.1499.v1

Histones are highly conserved proteins found in eukaryotic cell nuclei that play an important role in gene regulation. Core histones include histones H2A, H2B, H3, and H4; two of each core histones are assembled into an octamer to form the core particle of a nucleosome with 146 base pairs of DNA wrapped around it. H1 histones serve as linkers of DNA on the entry and exit sites of nucleosomes. Post-transcriptional modifications of histones, including methylation, acetylation, phosphorylation, and ubiquitination can change the accessibility of DNA sequences and consequently alter their transcription [69]. Several histone modifications have been described in psoriasis skin with potential pathogenetic implications.

Histone methylation can result in either an active or repressed status of transcriptional activity, depending on the methylation site and number of methyl groups added. Methylation of H3K9 can modify IL23 expression in keratinocytes [79], whereas H3K4 methylation has been identified in PBMCs from psoriasis patients compared to controls [80]. Reduced levels of methylated H3K27, produced by the Jmjd3 demethylase, are associated with Th17 differentiation [81]. Moreover, methylation levels of H3K27 and H3K4 are different between responders and non-responders to biological treatment, suggesting that these changes could influence response to treatment [80].

Histone acetylation results in weaker interactions between histone and DNA, leading to open chromatin and facilitation of active transcription [3]. Decreased global histone H4 acetylation in PBMCs from psoriasis patients compared to normal controls have been found [80]

As compared with healthy skin, lesional psoriasis skin exhibits dysregulated histone acetyltransferases (HATs) and histone deacetylases (HDACs), the enzymes that maintain the overall equilibrium between histone acetylation and deacetylation [69]. In fact, HDAC-1 has been found to be upregulated in psoriatic skin, which could induce over-expression of VEGF, proliferation of endothelial cells and keratinocyte survival [82]. Elevated H3K9 and H3K27 acetylation in the IL17A promoter region in immune cells of psoriatic patients have been observed, leading to Th17 differentiation and psoriasis development [83].

The BET protein family regulates the transcription of a wide spectrum of proinflammatory and immunoregulatory genes by recognizing acetylated histones and recruiting transcription factors, prompting transcription initiation and elongation [84]. Inhibition of BET proteins has been shown to decrease the expression of RORC, IL-17A and IL-22, all of them important pro-inflammatory factors in psoriasis, representing a potential new therapy for psoriasis [85].

Non Coding RNA

Non-coding RNAs (ncRNAs) are RNAs that are not translated into protein and perform their roles interacting with RNA, DNA and proteins, leading to changes of their structure and ultimately alteration of gene expression [3]. Depending on size, ncRNAs can be categorized into short ncRNAs, long ncRNAs (lncRNAs), and intermediate ncRNAs. Table 2 summarizes main ncRNAs found in psoriasis.

Short ncRNAs include short interfering RNAs (siRNAs), Piwi-interacting RNAs (piRNAs), and microRNAs (miRNAs); the latter are the most relevant regarding psoriasis. Micro RNAs are 17–25 nucleotides long and regulate gene expression, mainly gene silencing, by binding to and eventually leading to degradation of mRNA, modulating methylation of DNA or targeting enzymes necessary for DNA methylation or histone modifications [3,86].

miRNA125b, one of the most downregulated miRNAs in lesional psoriatic skin, has been associated with suppression of keratinocyte proliferation and promotion of keratinocyte differentiation [87,88]. However, many other dysregulated miRNAs, have shown to be involved in psoriasis pathogenesis, modulating the immune response and skin inflammation as well as epithelial differentiation and proliferation [89]. Among them, miR-230 [90], mir-383 [91], Mir-214-3p [92] or miR-125a-5p [93]are downregulated, whereas miR-378a [94], Mir-31 [95], mir-210 [96], miR-200c [97], or miR-155 [98] are upregulated in psoriasis.

Long non-coding RNAs are longer than 200 nucleotides and modulate gene expression through recruitment of transcription factors and chromatin modifying proteins [3] or acting as competitive endogenous RNAs limiting the availability of miRNAs to repress their target genes [86].

 doi:10.20944/preprints202307.1499.v1

Differentially expressed lncRNAs in psoriatic patients are involved in immune related functions and epidermal differentiation [3]. One of the most upregulated lncRNAs in psoriasis is lncRNA-RP6-65G23.1, which promotes keratinocyte proliferation and suppression of apoptosis by altering the expression of Bcl-xl, Bcl2 and the ERK1/2-AKT signaling pathway [99]. Other upregulated lncRNA in psoriasis are MIR31HG [100], MSX2P1 [101], XIST [102], FABP5P3 [103], KLDHC7B-DT [104] or SPRR2C [105], whereas MEG3 [106], GAS5 [107], PRINS [108] or NEAT1 [109] are downregulated in psoriasis.

Circular RNAs (circRNAs) are intermediate single-stranded ncRNAs with the 5′ and 3′ ends covalently joined giving them a continuous circular appearance [86]. They facilitate elimination of miRNAs or RNA-binding proteins, thus modulating gene expression or translation of regulatory proteins [110]. circRNAs can also interact with proteins like RNA polymerase II to drive transcriptional regulation [110]. Dysregulation of circRNAs in psoriasis has been associated with skin inflammation, keratinocyte hyperproliferation, and disease severity [86]. Some circRNAs, such as circRAB3B, which prevents keratinocyte hyper-proliferation through the upregulation of the tumor suppressor gene PTEN, are less abundant in psoriatic skin compared to non-lesional and healthy skin [111]. Conversely, circOAS3 [112], circEIF5 [113], circ_0060531 [114], hsa_circ_0003738 [115], or hsa_circ_0061012 [116] are upregulated in psoriasis.

Conclusions

This narrative review highlights the complexity of the genetics and epigenetics of psoriasis, involving a vast number of genes coding for proteins involved in the activity of the innate and adaptative immune systems along with the skin barrier. The rapid technological development of genetic studies has led to enhanced understanding of the physiopathology of psoriasis and facilitated the development of new drugs. Since genetic variants are associated with disease susceptibility, they could be useful to predict disease risk [117]. Polygenic risk scores consist of weighted sums of the individual risk alleles that might identify those individuals at high risk of psoriasis development or predict its severity, association with psoriatic arthritis or even treatment outcomes. Even though polygenic risk scores have been used in research studies, their clinical utility has yet to be established [117].

Epigenetic alterations also give insight into disease pathology and point towards potential therapeutic approaches. Furthermore, since epigenetic factors play a role in pathogenesis of psoriasis, there is growing interest in development of new drugs targeting epigenetic mechanisms, such as inhibition of DNA methylation [118], histone deacetylation [119] or modification of non-coding RNA [120]. Epigenetic markers could also serve as potential diagnostic or therapeutic response biomarkers. However, the many different cell types that are involved in psoriatic disease increases the complexity of elucidating the role of the epigenome; this review provides only a glimpse and further research is needed in this field.

Author Contributions: All authors have made contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or have drafted the work or substantively revised it; AND have approved the submitted version AND agrees to be personally accountable for the author's own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.

Funding: No funding was obtained.

Conflicts of Interest: L. Mateu-Arrom has no conflicts of interest to declare. L. Puig has perceived consultancy/speaker's honoraria from and/or participated in clinical trials sponsored by Abbvie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Leo-Pharma, Lilly, Novartis, Pfizer, Sandoz, Sanofi, and UCB.

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