THE AETIOPATHOGENESIS OF PSORIASIS IN 2014: AN UPDATE

***Paola Di Meglio,[1] Rose K. Mak[2]**

1. MRC National Institute for Medical Research, London, UK
2. St. Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK
**Correspondence to pdimegl@nimr.mrc.ac.uk*

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ABSTRACT

Psoriasis is a common inflammatory skin disease and its immuno-aetiopathogenesis has been extensively studied, using both human clinical samples and animal models of disease in the last four decades. This large effort has resulted in the identification of a number of psoriasis-susceptibility genes, T cells as critical effector cells in disease pathogenesis, and in a number of pro-inflammatory cytokines underlying the disease. More importantly, these findings have been translated into novel targeted therapies already in the clinic or in the advanced stage of clinical trials. Here, we review the more recent genetic and immunological findings and identify research gaps and future directions to take to further improve our understanding of one of the most common skin diseases.

Keywords: Genetics, skin, immune system, targeted therapies.

INTRODUCTION

Psoriasis is one of the most common skin inflammatory conditions, and thus, it has received a great deal of attention from clinicians and basic scientists alike in the past four decades, becoming a model to study chronic skin inflammation. The complexity of its aetiopathogenesis, resulting from the interaction of genetic, environmental, and immunological factors,[1,2] has been greatly unravelled thanks to a number of landmark studies which have investigated genetic susceptibility, as well as cellular and molecular mechanisms of disease, using both human clinical samples and animal models of disease. The critical pathogenic role of effector T cells, as well as key pro-inflammatory cytokines, such as tumour necrosis factor (TNF), interleukin-23 (IL-23), and IL-17, have been firmly established. Here, we review the more recent psoriasis literature, highlighting how this large and integrative research approach has resulted in the elucidation of many underlying pathogenic mechanisms, and it has been translated in a second wave of biologic drugs targeting the IL-23/IL-17 axis. Moreover, we describe future directions being explored and identify research gaps which need to be filled in order to further enhance our understanding of the disease and ultimately provide better patient care.

RECENT INSIGHTS FROM GENETIC STUDIES IN PSORIASIS

The existence of a genetic predisposition to psoriasis has long been known as population, family, and twins studies show higher incidences of psoriasis in relatives, as well as higher concordance rates in monozygotic twins.[3] However, the actual identification of psoriasis susceptibility genes has taken place in the last 7 years, with the only exception being *HLA-C*, in the psoriasis susceptibility 1 (PSORS1) locus, whose association to psoriasis had already been shown by means of linkage, sequence, and haplotype analysis.[4-8] Advances in high-throughput genotyping technologies and the completion of the genome-wide database of common genetic sequence variation (HapMap project), have paved the way to the identification of 36 independent psoriasis-

associated regions within individuals of European ancestry, plus 5 more uniquely associated in the Chinese population by means of genome-wide association studies (GWAS)[9-17] and subsequent meta-analysis (Table 1).[18,19]

Although some of these regions span more than one gene, GWAS have clearly identified a number of more than plausible psoriasis-susceptibility genes, encompassing both skin-related genes (such as the *LCE* gene[12,18]) and immune-related genes, with the latter belonging to either the innate or the adaptive immunity, as well bridging the two arms of the immune system. Among immune genes, the over-representation of four fundamental immunological processes and pathways strongly points towards their critical contribution to disease susceptibility: antigen presentation (*HLA-C* and *ERAP-1*), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κb) signalling (e.g. *TNFAIP3*, *TNIP1*, *TRAF3IP2*, *CARD14*), IL-23/IL-17 pathway (e.g. *IL-23*, *IL12B*, and *IL23R*), and Type 1 interferon pathway (e.g. *IL28RA* and *RNF114*).[3] The *HLA-C* association has not only the greatest statistical significance observed in GWAS studies[18] but also accounts for about 6% of the total genetic variance,[20] which is at least 10-fold more than that explained by any other known psoriasis susceptibility locus.[18] Nevertheless, despite the strong genetic evidence and the obvious immunological function of *HLA-C*,[21] functional studies addressing the precise mechanism by which the HLA-Cw*0602 susceptibility allele predisposes to psoriasis are still needed, especially those aimed at identifying HLA-Cw*0602 specific antigen or interacting proteins. Of interest is also *CARD14*, located in PSORS2.[18,22,23] *CARD14* is an activator of NF-κB, primarily expressed in skin epidermis, thus suggesting that intrinsic defects in keratinocytes (KC) can promote psoriasis in some instances.

Table 1: Psoriasis susceptibility genes identified by genome-wide association studies (GWAS).

Chr	Gene(s)	Protein Function	Pathway	Reference
1	*LCE3B/3C/3D*	Keratinocyte structural protein	Skin barrier formation	10, 12, 14
1	*IL28RA*	IL-29 receptor subunit	IFN signalling	15
1	*IL23R*	Unique subunit of IL-23 receptor complex	IL-23/IL-17 axis	9, 11, 14, 15, 18
1	*RUNX3*	Transcription factor	T-bet pathway	18
1	*TNFRSF9**	Adaptor molecules involved in T cell biology	T cell differentiation	18, 19
2	*REL*	NF-κB subunit	NF-κB signalling	15
2	*IFIH1*	Innate antiviral receptor	IFN signalling	15
2	*B3GNT2*	Enzyme	Carbohydrate metabolism	18
5	*TNIP1*	Inhibitor of TNF-induced NF-κB activation	NF-κB signalling	11, 15, 17
5	*IL12B*	Shared subunit of IL-12/IL-23	IL-23/IL-17 axis	9, 11, 12, 14, 18
5	*ERAP1*	Enzyme processing MHC class I ligands	Antigen presentation	15, 16
5	*IL4/IL13*	IL-4 and IL-13 cytokines	IL-4/IL-13 signalling	11
6	*TNFAIP3*	Inhibitor of TNF-induced NF-κB activation	NF-κB signalling	11, 15
6	*TRAF3IP3*	Adaptor molecule mediating IL-17-induced NF-κB activation	IL-23/IL-17 axis, NF-κB signalling	14, 15
6	*IRF4**	Transcription factor	IL-17 signalling	18
6	*HLA-C*	MHC Class 1 antigen	Antigen presentation	9, 11, 12, 14, 15, 18
6	*TAGAP*	Rho GTPase-activating protein	T cell activation	18

Table 1 continued.

Chr	Gene(s)	Protein Function	Pathway	Reference
7	*ELMO1*	Involved in TLR-mediated IFN-α signalling	IFN signalling	18
9	*KLF4*	Transcription factor	Skin barrier formation, IL-17 signalling	18
9	*DDX58*	Innate antiviral receptor	IFN signalling	18
10	*ZMIZ1*	Protein inhibitor of activated STAT(PIAS) family of proteins	TGF-β signalling	18, 19
11	*PRDX5*	Antioxidant enzyme	Intracellular redox signalling	18, 19
11	*ETS1*	Transcription factor	Unknown	18
11	*ZC3H12C*	Zinc finger protein with putative RNase function	Unknown	18
12	*IL23A*	Unique subunit of IL-23	IL-23/IL-17 axis	11, 15
14	*NFKBIA*	Inhibitor of NF-κB activation	NF-κB signalling	15, 16
16	*FBXL19*	Putative inhibitor of NF-κB activation	NF-κB signalling	16
16	*SOCS1*	Suppressor of cytokine signalling	Type 2 IFN signalling	18
17	*CARD14*	Activator of NF-κB pathway	NF-κB signalling	18, 22, 23
17	*NOS2*	Induced nitric oxide synthase	Inflammation	16
17	*STAT3**	Transcription factor	IL-23/IL-17 axis	18
18	*MBD2**	Transcriptional repressor	Unknown	18
19	*CARM1**	Transcriptional co-activator of NF-κB	NF-κB signalling	18
19	*TYK2*	Tyrosine kinase associated with cytokine receptors	IL-23/IL-17 axis, IFN signalling	15
20	*RNF114*	E3 ubiquitin ligase	IFN signalling	9, 11, 15, 16
22	*UBE2L3**	Ubiquitin conjugating enzyme	NF-κB signalling	18, 19

* Indicates more than one gene present in the associated locus; the one listed is the more plausible/interesting from a biological point of view.

IL: interleukin; IFN: interferon; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; TNF: tumour necrosis factor; MHC: major histocompatibility complex; TLR: toll-like receptor; STAT: signal transducer and activator of transcription; PIAS: protein inhibitor of activated STAT; TGF-β: transforming growth factor beta.

The signals identified in the European population collectively account for approximately 20% of estimated psoriasis heritability, and the gene variants identified have only modest-effect size (OR between 1.09 and 1.88, with HLA standing out with OR 4.3218), thus, calling for more genetic studies to explain this so called 'missing heritability'.[24] Whether we are dealing with yet unidentified rare variants with large effect, or rather with the co-existence of many common variants of weak effect, is currently under investigation. Interestingly, two recent re-sequencing studies have shown that rare variants at known immune-related loci have a negligible role in psoriasis genetic susceptibility.[25,26] Thus, the estimated missing heritability might lie in those common variants with suggestive associations just below the standard genome-wide significance threshold of $p<5x10^{-8}$, which would possibly require carefully stratified patient cohorts, taking into account disease heterogeneity (e.g. small plaque versus large plaque) to be found convincingly associated. Another possibility is that the actual missing heritability has been overestimated, owing to the existence of gene-gene and gene-environment interactions,[27] which should also be investigated.

Lastly, GWAS have mainly identified susceptibility genes, not causative alleles, and only in very few cases the genetic associations have been followed on by functional studies addressing the biological consequences of carrying the associated risk allele. One study has linked the genetic association between *IL23R* and psoriasis with reduced IL-17 responses in carriers of the protective Arg381Gln *IL23R* allele.[28,29] Although challenging, the functional investigation of GWAS-identified genetic determinants is urgently needed to better exploit them in a clinical setting, e.g. to develop novel targeted therapies or in pharmacogenetic studies, assessing their role as biomarkers with response-to-treatment predictive roles.[30]

RECENT INSIGHTS FROM HUMAN STUDIES

The almost unique accessibility of skin for tissue biopsy and the fact that psoriasis is a common disease have allowed the study of the cellular and molecular determinants of psoriasis in greater detail. Moreover, recently developed technologies have allowed deeper analysis of biological samples available in limited quantity, in a high throughput manner, permitting almost simultaneous genomics, proteomics, and transcriptomics analysis. The psoriasis field has embraced and made use of these novel technologies with enthusiasm and a number of studies have contributed to define and refine the so called 'psoriasis transcriptome', or the list of genes, mainly of epithelial origin, differentially expressed in lesional versus non-lesional skin via array-based analysis[31-33] and RNA-sequencing.[34,35] Moreover, by performing increasingly deeper immunophenotyping of clinical material, the cellular signature of psoriasis blood and skin has been unveiled, identifying critical players.[36-38]

One of the most debated questions in the psoriasis field has historically been whether psoriasis is primarily an epithelial or immune-mediated disease, with researchers torn between the prominent changes in the skin and the increasingly recognised importance of immune-mediated mechanisms, especially highlighted by the success of the first wave of biologic drugs targeting T cells (alefacept, a LFA-3/immunoglobulin [Ig]G1 fusion protein targeting CD2+ T cells and efalizumab, a humanised antibody binding CD11a, withdrawn in 2009) and cytokines (anti-TNF agents: etanercept, a human p75 TNF receptor fusion protein; infliximab, a humanised chimeric anti-TNF monoclonal antibody; and adalimumab, a fully human monoclonal antibody).[39,40] In the last five decades, the pendulum has shifted back and forth from KC to immune cells many times,[41] according to the latest discovery pointing towards one or the other side. Currently, this debate seems to be much more sedated, as the current view of psoriasis pathogenesis implies that a pathogenic cross-talk between epithelial and immune cells sustain the aberrant immune and epidermal response seen in psoriasis.[42,43]

KC, equipped with innate immune receptors and actively taking part in inflammatory skin responses by producing cytokines and chemokines, can nowadays be considered as non-haematopoietic immune cells, having gained the status of skin sentinel cells.[44,45] T cells, especially those permanently residing in the skin, known as tissue resident T memory (T_{rm}) cells,[46] have a leading role as chief driver of the effector responses underlying the disease, as emphasised by the efficacy of anti-T cell therapeutic strategies. On the other hand, dendritic cells, of both plasmacytoid and myeloid lineage, fulfil other important tasks, such as production of activating cytokines, e.g IFNα[47] and IL-23,[48,49] as well as antigen presentation, for instance of self RNA/DNA complexed with LL-37 fragments[50,51] and of possibly other antigens of yet unknown origin. Overall, the critical interplay between these three main cell types is primarily driven by the key pro-inflammatory molecules, TNF, IL-23, and IL-17, whose direct therapeutic targeting has proven to be clinically effective, with other mediators, such as IFN-α, IFN-γ, and IL-22 also contributing to the initiation, amplification, and maintenance of the disease (Figure 1).[2]

One the biggest paradigm shifts in psoriasis research has been from T helper (Th)1 to Th17 disease. The initial definition of psoriasis as Th1 and IFN-γ-driven disease, based on a strong Type 2 IFN transcriptomic signature and the high frequency of Th1 in both psoriasis plaques and peripheral blood,[52-54] has been challenged by the discovery of IL-23 and Th17 cells and a wealth of data indicating a key role for the IL-23/IL-17 axis in psoriasis.[55] Increased levels of IL-23p19, IL-12p40,[48] and IL-23R[56,57] are present in psoriatic skin. Th17 cells, abundantly infiltrating psoriatic skin dermis,[37] are increased in the blood of psoriasis patients[36] and, together with IL-17+ CD8 T cells,[58] are an important source of IL-17A, IL-17F, and IL-22. IL-17A/IFN-γ or IL-17/IL-22 double-producing cells have also been described in psoriasis patients.[36,37,59,60] Moreover,

more innate-like cells, such as γδ-T cells[61,62] and innate lymphoid cells (ILC),[38,63,64] have been recently identified as another source of IL-17 and IL-22 in psoriasis patients. In particular, the Vγ9Vδ2 T cell subset is increased in the skin and simultaneously decreased in the peripheral blood of psoriasis patients,[62] while NCR+ group 3 ILC are increased in both blood and non-lesional psoriatic skin, as compared to the tissues of heathy controls.[38,63,64] Interestingly, both these small subsets of skin-infiltrating T cells appear to have clinical relevance as the number of Vγ9Vδ2 T cells in the circulations correlates negatively with disease severity and positively with successful anti-psoriatic therapy,[62] while that of circulatory NCR+ ILC3 decreased upon successful treatment.[38]

Finally, mast cells and neutrophils might represent other innate sources of IL-17,[65] although more definitive evidences are awaited, and also IL-9 producing cells[66] have been identified in lesional skin but more mechanistic studies are needed to understand their contributions to the disease. IL-17 is central in the pathogenic loop linking T cells and KC,[67] as both IL-17A and IL-17F family members activate KC to produce neutrophil and T cell-recruiting chemokines and antimicrobial peptide.[56] Another IL-17 family member, IL-17C, also induces an autocrine pro inflammatory loop in KC,[68,69] while IL-22 mediates most of the epidermal hyperplasia by impairing KC differentiation.[70,71]

The IL-23/IL-17 axis represents one of the rare instances in which observation in clinical samples have rapidly progressed to preclinical studies and resulted in clinical interventions in <10 years from the discovery of IL-23 and Th17 cells.[72]

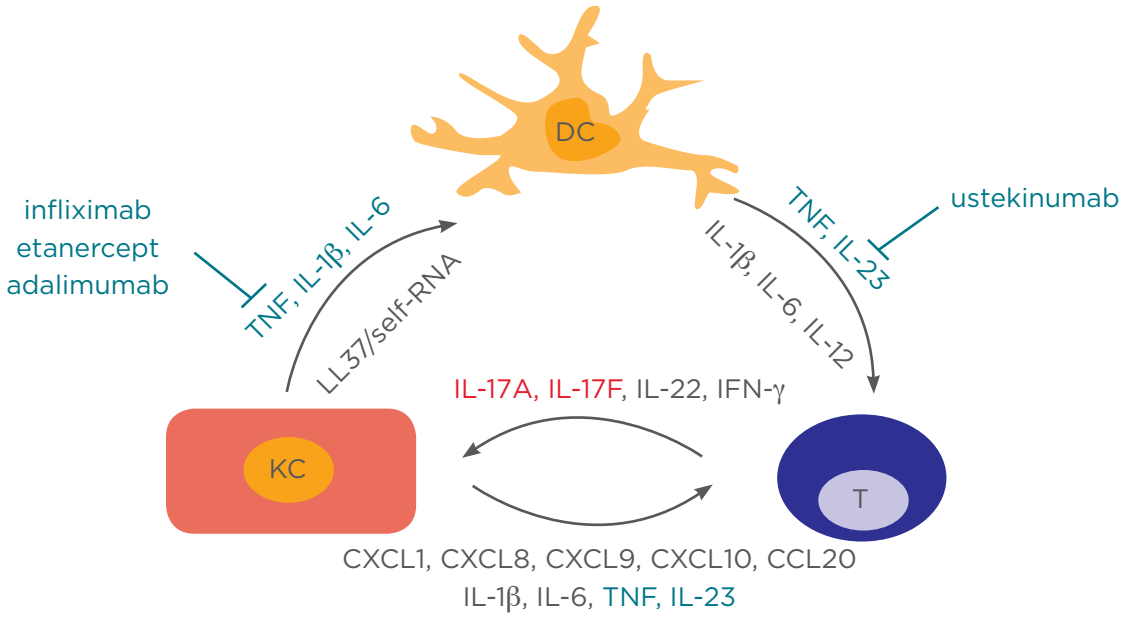

Figure 1: Psoriasis immunopathogenesis.
A pathogenic cross-talk between innate and adaptive immune cells, sustained by pro-inflammatory mediators, underlie the dysregulated immune response observed in psoriasis. The three main cellular players and their products are depicted in this diagram. Keratinocytes (KC) produce key cytokines (tumour necrosis factor [TNF], interleukin [IL]-1β, and IL-6), as well as the antimicrobial peptide LL37 binding self-RNA activating myeloid dendritic cells (DC) in the dermis. Activated DC present not yet identified antigens and secrete mediators such as TNF, IL-23, IL-1β, and IL-6, leading to the differentiation and activation of IL-17-producing T cells (T, here representing both αβ and γδ T cell receptor T cells). T cells, in turn, secrete cytokines (IL-17A, IL-17F, IL-22, interferon [IFN]-γ) that activate the KC aberrant differentiation programme and induce the production of further pro-inflammatory mediators, especially chemokines (C-X-C motif ligand 1 [CXCL1], CXCL8) recruiting neutrophils (not shown) or other immune cells (CXCL9, CXCL10, chemokine C-C motif ligand 20 [CCL20]), as well as other antimicrobial peptides (not shown). Critical pro-inflammatory molecules, effectively targeted by biologic drugs are shown in red. Biologic drugs approved in the treatment of psoriasis and their molecular targets are shown in blue.
Modified from Di Meglio et al.[2]

Ustekinumab, a monoclonal antibody directed against the common IL-12/23p40 subunit, was approved in 2009 and is highly effective in psoriasis;[73] moreover, investigational antibodies targeting IL-23p19, IL-17A, and IL-17R, are showing very high efficacy with good safety profiles in ongoing advanced clinical trials,[74] and will soon offer a further therapeutic choice to treat moderate-to-severe psoriasis.

RECENT INSIGHTS FROM ANIMAL MODELS OF PSORIASIFORM INFLAMMATION

Different methodological approaches to model psoriasis have been developed: skin xenotransplants, genetic manipulation to overexpress critical genes in the epidermis, and pharmacological treatments. Most probably, the best experimental approach to model psoriasis is using xenotransplants, in which human skin is transplanted onto immuno-compromised murine hosts, with or without concomitant infusion of donor immune cells. These models closely resemble psoriasis, with the notable exception of the systemic disease manifestation (e.g. psoriasis arthritis). However, they are unfortunately both technically and logistically challenging, and their use is severely limited by the scarce availability of human clinical material. Nevertheless, xenotransplant models have been instrumental for the definition of psoriasis as a T cell-dependent disease,[75-77] and have been used in preclinical studies of novel therapeutic compounds.[57,77] In particular, the AGR129 xenotransplantation model, where human non-lesional psoriatic skin is transplanted onto AGR129 mice lacking T/B cells and having severely impaired NK activity, has provided one of the very first evidences of the existence of resident memory T (T_{rm}) cells as fully-fledged psoriatic lesions occur in the absence of T cell recruitment from blood[77] and depend on the ability of locally activated skin T_{rm} cells, present in the initial graft, to migrate into the epidermis.[78]

The extent to which different mouse models can fully recapitulate the development and features of psoriasis is a recurrent discussion point; how faithful can a mouse model of disease be, when not only does psoriasis uniquely occur in humans, but also mouse and human skin have marked structural and cellular differences?[79,80] Both the genetic background and the environmental challenges for mice and humans are quite different, yet still very relevant for disease initiation. In particular, the ontogeny of the inflammatory skin response is unavoidably very different, being provoked by genetic or pharmacological manipulation, with the latter often resulting in short lasting inflammation in the mouse, whereas it is multifactorial and chronic in patients. Thus, it is not surprising that there are discrepancies between the human disease and its experimental models.

Five of the most commonly used mouse models (K5- Tie2, imiquimod, K14-AREG, K5-Stat3C, and K5-TGFbeta1), displaying most of the crucial clinical traits of the disease, have been recently compared at gene expression level to compare their molecular signature to that of psoriasis.[81] Interestingly, the cutaneous gene expression profile of each mouse phenotype exhibited a statistically significant similarity to the expression profile of human psoriasis. However, each model displayed distinctive sets of similarities and differences in comparison to human psoriasis that are worth keeping in mind when choosing which model to use, e.g. using the imiquimod model to study neutrophils.[81]

Nevertheless, lesions from a number of animal models developed over the years have contributed valuable insights to dissect disease pathogenic mechanisms. For instance, mouse models specifically targeting critical transcription factors regulating inflammation, such as signal transducer and activator of transcription 3, NF-κB, and activator protein-1 in KC have lent further support to the importance of the epithelial compartment in disease initiation and highlighted the importance of skin-derived cytokines.[45] More recently, CD8 T cells have been found to play a critical role in initiating skin inflammation and KC proliferation via cytokine production in a transgenic mouse model of psoriasiform inflammation over-expressing RAS in KC.[82] The initial clinical observation of a case of psoriasis exacerbated by topical treatment with imiquimod[83] has been translated into the imiquimod-induced psoriasiform skin inflammation mouse model,[84] which has quickly become one of the most widely used experimental models to study psoriasis, as it is easy, quick, robust, inexpensive, and works on multiple murine strain backgrounds.[85] Imiquimod is a ligand for toll-like receptor (TLR)7 in mice and TLR7/TLR8 in humans, and also interferes with adenosine receptor signalling.[86] In addition, isostearic acid, presented as a vehicle in the commercially available cream containing imiquimod (Aldara™), has been shown to be biologically

active and to activate the inflammasome.[87] Studies using the imiquimod-model have, in many cases, confirmed observations made in the clinical samples, highlighting the importance of the IL-23/IL-17/IL-22 pathway,[69,84,88] of the IL-1 family member IL-36,[89] and that of γδ-T cells and ILC as a key source of IL-17 and IL-22 in psoriasiform skin inflammation,[62,88] in keeping with their prominent presence in mouse skin as compared to αβ-T cell during homeostasis. By using the imiquimod model, one of the authors of this review has recently uncovered a protective role in psoriasis for the ligand-activated transcription factor aryl hydrocarbon receptor (AhR),[90] an environmental sensor which responds to a wide range of stimuli (including environmental pollutants and tryptophan metabolites of dietary or light-exposure origin) by inducing detoxifying enzymes. Mice lacking AhR display markedly exacerbated skin inflammation following imiquimod application.[90] In particular, AhR was found to exert its effect in KC as in its absence they become over-reactive to pro-inflammatory stimuli and release a greater amount of cytokines and chemokines, thus instigating an excessive inflammatory reaction. Importantly, the analysis of human psoriasis skin biopsies treated *ex vivo* with AhR ligands confirmed the protective effect of AhR signalling, validating the findings obtained in the mouse model.[90]

FUTURE DIRECTIONS

Despite tremendous advances in our understanding of psoriasis aetiopathogenesis, a number of unresolved questions remain, again requiring a concerted effort between clinicians, geneticists, immunologists, molecular biologists, and bioinformaticians.

First, only the most common form of psoriasis, that is plaque-type, has been thoroughly investigated so far, due to the other forms being relatively infrequent as compared to plaque-type, and their peculiar epidemiological and clinical features (e.g. high prevalence in children and young adults for the guttate form or the extremely severe systemic manifestation for generalised pustular psoriasis [GPP] and erythrodermic psoriasis). Some progress has been recently made with GPP, which has been shown to be inherited as autosomal recessive due to mutations in the *IL36RN* gene encoding the anti-inflammatory IL-36-receptor antagonist, IL-36Ra,[91,92] at least in a number of patients,[93] but more studies are needed to better understand the genetic, cellular, and molecular background, not only of GPP but also of other less common forms of psoriasis. Psoriatic arthritis, a seronegative, chronic inflammatory musculoskeletal disorder that follows psoriasis in up to 30% of psoriasis patients,[94] also requires more studies. Relative to plaque-type psoriasis, geneticists still have the mammoth task of identifying the complete map of psoriasis susceptibility genes and especially, together with immunologists and molecular biologists, the even more challenging task of functionally validating the associations found with the ultimate aim to find causative alleles that can be used for novel drug development, as well as patient stratification for personalised medicine approaches. Moreover, the study of environmental factors leading to disease has to progress from epidemiological analysis to a mechanistic investigation, which also takes into account both genetic and immunological factors.

Finally, as technologies advance, so does the level of resolution of the cellular and molecular analysis of psoriasis specimens. Cell populations recently identified to be differentially present in psoriasis require careful mechanistic investigations to verify whether they can be useful to unlock novel possible therapeutic avenues. On the other hand, the simultaneous analysis of several tissue types from vast cohorts of well-stratified patients is in the pipeline, thanks to a number of large consortiums being currently active, looking for instance at the psoriasis microbiome (MAARS study - Microbes in Allergy and Autoimmunity Related to the Skin)[95] or at identifying biomarkers predicting therapy response (BSTOP study - Biomarkers of Systemic Treatment Outcomes in Psoriasis)[96] and developing an algorithm to guide psoriasis management (PSORT - Psoriasis Stratification to Optimise Relevant Therapy).[97] These efforts will soon generate a conspicuous amount of data which need bioinformaticians with a good understanding of the disease mechanisms to assemble and, at the same time, deconvolute these large datasets in order to mine crucial information that can be used to inform basic and clinical research, and ultimately, clinical practice.

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