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Review article

The immunogenetics of Psoriasis: A comprehensive review

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ABSTRACT

Psoriasis vulgaris is a common, chronic inflammatory skin disease with a complex etiology involving genetic risk factors and environmental triggers. Here we describe the many known genetic predispositions of psoriasis with respect to immune genes and their encoded pathways in psoriasis susceptibility. These genes span an array of functions that involve antigen presentation (*HLA-Cw6*, *ERAP1*, *ERAP2*, *MICA*), the IL-23 axis (*IL12Bp40*, *IL23Ap19*, *IL23R*, *JAK2*, *TYK2*), T-cell development and T-cells polarization (*RUNX1*, *RUNX3*, *STAT3*, *TAGAP*, *IL4*, *IL13*), innate immunity (*CARD14*, *c-REL*, *TRAF3IP2*, *DDX58*, *IFIH1*), and negative regulators of immune responses (*TNIP1*, *TNFAIP3*, *NFKBIA*, *ZC3H12C*, *IL36RN*, *SOCS1*). The contribution of some of these gene products to psoriatic disease has also been revealed in recent years through targeting of key immune components, such as the Th17/IL-23 axis which has been highly successful in disease treatment. However, many of the genetic findings involve immune genes with less clear roles in psoriasis pathogenesis. This is particularly the case for those genes involved in innate immunity and negative regulation of immune specific pathways. It is possible that risk alleles of these genes decrease the threshold for the initial activation of the innate immune response. This could then lead to the onslaught of the pathogenic adaptive immune response known to be active in psoriatic skin. However, precisely how these various genes affect immunobiology need to be determined and some are speculated upon in this review. These novel genetic findings also open opportunities to explore novel therapeutic targets and potentially the development of personalized medicine, as well as discover new biology of human skin disease.

1. Introduction

Psoriasis is a chronic, inflammatory skin disease, characterized by raised, red scaly plaques [1]. This disease affect affects about 2–3% of the world-wide population, although it is more prevalent in American, Canadian, and European populations [2]. Psoriasis is also associated with several co-morbidities, suggesting that the underlying pathogenesis of the disease is more than “skin deep” [3].

Psoriasis arises through chronic interactions between hyper-proliferative keratinocytes and infiltrating, activated immune cells. Initially, psoriasis was considered solely to be due to dysfunction of limiting keratinocyte proliferation [4]. Infiltration of immune cells was noticed, but not considered to be key in pathogenesis, and rather just a consequence of the hyper-proliferating keratinocytes. However, the critical role of the immune system in psoriasis pathogenesis was discovered when administration of immune suppressive agents, such as cyclosporine, denileukin diftitox, and alefacept, proved successful in ameliorating disease [5–8]. Over the next several years, the cellular and molecular contributions to the overactive immune response were further elucidated. It was found that T-cells, particularly those with Th1 and Th17 polarization, are heavily present in psoriatic lesions [1,9]. Additionally, TNFα and iNOS producing inflammatory DCs (TIP-DCs), massively infiltrate psoriatic skin, and these TIP-DCs have the ability to polarize T-cells to Th1 and Th17 fates [4,10,11]. Lastly, psoriatic skin is infiltrated by a myriad of other immune cells including macrophages and innate immune cells, as well as an increased amount of endothelial cells (angiogenesis); these other cell types may certainly also play a role in psoriasis pathogenesis [1].

Similar to other autoimmune diseases, the genetics of psoriasis is complex and multifactorial. There is clear evidence of an important genetic component to psoriasis. This is supported by

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both twin and family studies [12]. The concordance rate of monozygotic twins is approximately 70% and for dizygotic twins is about 20% [13].

Areas of chromosomes which were thought to harbor psoriasis genes were initially entitled *PSORS* (**psor**iasis-**s**usceptibility) loci. There are at least 12 different *PSORS* loci that were mainly identified through linkage analysis of multiply affected psoriasis families [1]. However, the gene or gene(s) for most *PSORS* loci that are responsible for susceptibility is not known. In recent years, our understanding of psoriasis pathogenesis has been enriched by genome-wide association studies (GWAS) where large cohorts of psoriasis cases and matched controls have been typed for single nucleotide polymorphisms (SNPs) and tested for a statistically significant excess of one SNP allele in cases versus controls. These studies have revealed over 50 regions associated with psoriasis risk and within some of these regions there is more than one independent susceptibility factor. In all of these studies, a dominant function of a significant percentage of these genes is related to the immune system. Here we summarize what is currently known about the immunogenetics of psoriasis pathogenesis.

2. Antigen presentation

The first gene that was discovered to be significantly associated with psoriasis susceptibility was HLA-Cw6, which is located at *PSORS1* at chromosomal position 6p21.3 [13,14]. HLA-Cw6 is found in about 4–16% of healthy controls [15] and in about 20%-to over 50% of psoriasis cases, depending on the population being studied. HLA-Cw6 encodes a major histocompatibility complex I (MHCI) allele. MHCI molecules are present on almost all nucleated cells and are key molecules for immune surveillance since they present intracellular peptides (both self and non-self peptides) to the immune system. MHCI is also critical for CD8+ T-cells priming and subsequent cytolytic targeting of cells. This finding supported the important role of T-cells in the pathogenesis of psoriasis.

HLA-Cw6 is not the only antigen presentation associated molecule associated with psoriasis. A recent GWAS also revealed a role of the ERAP1 loci in and this was enriched in individuals carrying the HLA-Cw6 mutation [16,17]. ERAP1 (endoplasmic reticulum aminopeptidase 1) plays a role in processing of peptides for loading onto MHC class I. Due to these associations, it could be postulated that psoriasis is caused by a T-cell mediated reaction to an auto-antigen, one that is most easily presented on HLA-Cw6 and via processing by particular mutations in ERAP1. Additionally, ERAP2 is also a likely candidate gene of a PSORS locus at chromosomal position 5q15 [18]. However, despite these associations of psoriasis with the MHCI allele HLA-Cw6 and MHCI processing enzymes, we still do not have a confirmed “auto-antigen”. Additionally, it has been determined through deep sequencing of the T-cell repertoire that the T-cell infiltrate is highly polyclonal, and is not dominated by a heavy clonal expansion of a particular T-cell responding to a specific epitope (JLH and JGK, unpublished results).

Although more related to the innate immune response, MICA (MHC class I polypeptide-related sequence A) is also associated with psoriasis [19]. Expression of MICA is thought to mainly be stress-induced and is a ligand for NKG2D, an activating receptor found on natural killer (NK) cells, NKT-cells, and T-cells [20]. Although the exact role of NK and NKTs cells in psoriasis have not been thoroughly explored, these innate immune cells can make several inflammatory cytokines that are known to be increased in psoriasis lesions, such as TNFα, IFNγ, and IL-22.

3. The IL12/23 axis

As a specific auto-antigen in psoriasis proved troubling to identify, attention turned to elucidation of exactly how the immune system was responding in psoriatic lesions. It was first revealed that IFNγ producing T-cells are massively increased in psoriatic lesions [21]. Dendritic cells can instruct T-cells during priming to adopt a Th1 fate through secretion of the cytokine IL-12. IL-12 is composed of two subunits, p35 and p40. It was found that p40 expression is increased in psoriasis. Therefore targeting of the IL-12/IFNγ/Th1 axis was the next logical step in disease treatment. However, treatment with anti-IFNγ proved disappointing in preliminary clinical trials [22], resulting in the need for a deeper look into psoriasis pathogenesis. It was not until several years later, with the discovery of the Th17 subset and the key Th17 polarizing cytokine IL-23, that a role for the Th17 axis in psoriasis became apparent [23,24]. IL-23 and IL-12 share the common p40 subunit; however IL-23 is produced by the combination of p40 with the p19 subunit [25] (Fig. 1). Although expression of p35 is not increased in psoriasis, expression of both p40 and p19 are drastically increased in psoriasis lesions, and subsequently there is increased expression of biologically active IL-23 in psoriatic lesional skin.

The immunogenetic association of IL-23 with psoriasis has proven quite strong. There have been several SNPs identified in genomic regions harboring genes for both subunits of the IL-23 cytokine: *IL12Bp40* and *IL23Ap19* [26] and coding SNPs in the IL-23 receptor (*IL23R*) that are associated with psoriasis [26–28]. The most consistently associated SNP within *IL23R* encodes a R381Q amino acid substitution, where the rarer Q allele results in decreased IL-23 signaling and is therefore protective against several autoimmune diseases, including psoriasis [29].

The IL-23 receptor is a heterodimeric receptor, composed of IL-12RB1 and IL-23R. These receptor components lack intrinsic signaling activity, and signal through the interactions with downstream molecules. IL-12B1 requires Tyk2 for signaling, whereas IL-23R requires Jak2 [30,31]. GWAS studies of psoriasis have found associations with *TYK2* [16], as well as an association of *JAK2* with both psoriasis and Crohn's disease [32]. Additionally, GWAS studies have found psoriasis associations with mutations in *STAT3* (signal transducer and activator of transcription 3), a key molecule for downstream signaling through several cytokines, one of which is IL-23 [33].

The importance of IL-23 in psoriasis pathogenesis has been further confirmed by the recent major success of targeting this cytokine in treatment of psoriasis [34–36]. Monoclonal antibody treatment targeting both the common p40 subunit and the IL-23 specific p19 subunit have demonstrated outstanding clinical efficacy. In conjunction with the heavy genetic link to the IL-23 cytokine components and the IL-23 receptor, the transcripts of all three of these products are also significantly increased in psoriatic lesional skin [1]. Thus, the genetics, the transcriptomics, and the clinical success of blocking this cytokine all point towards a key role of IL-23 in psoriasis pathogenesis. In turn, IL-23 regulates activation and expansion of Th17 T-cells that are defined by production of IL-17A and IL-17F, and as discussed below in Section 4, the pathogenic activity of IL-17 in psoriasis vulgaris is now well defined.

4. T-cell polarization

As mentioned in Section 1, the critical role of T-cells in psoriasis was initially discovered by observing the improvement in disease when general T-cell suppressive agents were utilized. T-cells can be subdivided into two classes: CD8+ cytotoxic T-cells and CD4+ helper T-cells, both which are found to be increased in psoriatic lesional skin. Regarding CD4+ T-helper cells, this cell type can be polarized to different fates depending on the needs of the immune response. Initially, CD4+ T-helper cell fates were considered to be one of two-options: Th1 or Th2. Th1 T-cells produce IFNγ and are

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