Psoriasis

Subjects: Dermatology

Contributor: Geneviève Rioux , Zainab Ridha , Mélissa Simard , Florence Turgeon , Sylvain L. Guérin , Roxane Pouliot

Psoriasis is a common immune-mediated inflammatory skin disease characterized by well-demarcated scaly raised plaques.

Psoriasis keratinocytes transcriptome

1. Introduction

The disease has a different prevalence, depending on ethnicity and geographical distribution. Plaque, erythrodermic, pustular, inverse and guttate psoriasis are the diverse subtypes of psoriasis, according to the onset of the disease. Plaque psoriasis, also known as psoriasis vulgaris, is the most common clinical subtype, affecting about 90% of patients[1][2]. The lesions are well-defined papulosquamous scales characterized by the focal formation of erythematous, raised plaques that constantly shed scales derived from excessive growth of skin epithelial cells[3]. The growth and dilation of superficial blood vessels, which causes redness, and the hyperplasia of the epidermis explain the clinical features of this chronic disease. The most affected body parts include elbows, knees, scalp, sacroiliac, lower back and nails[4]. In psoriasis vulgaris, the plaques are generally symmetrically distributed, suggesting a connection with the nervous system. The skin lesions develop after the immune system sends incorrect signals, increasing the mitotic rate of keratinocytes, leading to incomplete cornification and to a poorly adherent stratum corneum[5]. Psoriasis impacts general health since it is related to many other comorbidities, such as psoriatic arthritis, inflammatory bowel disease, hypertension, atherogenic dyslipidemia, diabetes, and many others[6]. Affected patients can also suffer from depression and anxiety. Therefore, psychological consequences have to be considered[7]. This skin disease has been recognized as a T lymphocyte mediated autoimmune skin condition. It is caused by various cutaneous cellular changes, including epidermal keratinocyte hyperplasia, T lymphocyte infiltration, vascular hyperplasia, presence of neutrophils, and other forms of leucocytes in infected skin[3]. The exact etiology is not yet fully understood[8].

2. The Genetic Basis of Psoriasis

2.1. Genetic Factors

The worldwide prevalence of psoriasis is about 2%. More than 125 million individuals are affected, with an estimated heritability between 66% and 90%[9][10][11]. Epidemiological studies involving cohorts of 95 or more subjects have found a higher concordance rate among monozygotic twins compared to dizygotic twins (35–72%

vs. 15–23%, respectively)[12][13][14]. Moreover, a significantly higher incidence of the disease is observed among patients' relatives[15]. The assessment of the sera of 346 subjects from a kindred of 815 Caucasian Americans spanning six generations has highlighted the implication of genetic factors[16]. Although psoriasis can affect people of all ages, there is a bimodal age of onset: early-onset occurs before 40 years old and represents 75% of the cases, while the late-onset occurs at a mean age of 56–60 years[17][18]. The role of molecular genetics in psoriasis has been proven to be involved in the disease's pathology in previous years. Large-scale studies involving more than 2600 and 5000 psoriatic individuals have identified multiple loci associated with psoriasis in the human genome[19][20]. The principal locus that has been demonstrated to be connected to the disease is PSORS1, encoding the gene variant *HLA-Cw6*, which is carried by up to 85% of patients with early-onset psoriasis in comparison with 15% in late-onset psoriasis[17]. More recently, further studies consisting of over 15,000 psoriatic cases carried out by Tsoi and his colleagues have led to the identification of additional loci associated with psoriasis, raising the number of documented psoriasis susceptibility loci to 41 in Caucasians and 49 worldwide[21][22].

2.2. Differences between Men and Women

The prevalence of psoriasis is considered to be balanced between men and women[23]. Only a few studies in the literature explored the differences in genetic risks between the two sexes. However, some have pointed out sex-related differences in the severity of psoriasis and divergent genetic factors. In a study involving 369 patients with familial psoriasis, Gudjonsson et al. stated that *HLA-Cw6*-positive female patients may have an earlier onset of psoriasis than *HLA-Cw6*-positive males[24]. Research by Quiero et al. on psoriasis arthritis (PsA) showed variations in gender distribution of certain genetic markers from the major histocompatibility complex (MHC) region when patients were separated by age at the beginning of the disorder[25]. Moreover, Huffmeier et al. found a significantly higher concentration of the *PTPN22**620W allele carriers in males than in females in a study of 375 patients with PsA[26]. Furthermore, the higher proportion of men with access to systemic treatment compared to women has raised questions about the severity of psoriasis between both genders. Studies have confirmed that psoriasis affects men more severely than women by highlighting a superior median of the psoriasis area severity index (PASI) score in men than in women[27][28][29]. A study investigating 461 psoriatic patients revealed a strong association between the score value rs1062470AA genotype (*PSORS1C1*/*CDSN*) and the PASI score in males only, increasing their risk of disease severity and pointing out that it might be gender-dependent[28]. Males with AA genotype had a significantly higher PASI score in comparison to others. This was not observed in female patients. Interestingly, independently of rs1062470 genotype, males had considerably higher PASI scores than females except for the earliest onset of the disease, suggesting that psoriasis is more severe in men than in women[29][30]. Another association of rs887466 (*PSORS1C3*) with psoriasis risk in men and women was noted by Wiśniewski and his colleagues[28]. The protective effect of the A allele and AA genotype was only visible for men. However, it remains unclear why this effect is only observed in male patients. Other studies, each involving around 50 male patients with psoriasis, have linked serum testosterone levels to psoriasis, suggesting the involvement of sex hormones in the pathology[31][32]. Finally, in a study of 121 male patients with psoriasis, Allam et al. also reported that the severity of psoriasis is inversely correlated with serum testosterone levels in men[33].

2.3. Genes Related to Immune Response

Psoriasis undoubtedly has an immunological component since therapies targeting T cell activation as well as effector cytokines produced by these cells were shown to be efficient in this disease[34][35]. Genome-wide association studies have also revealed that several genes involved in the pathology were linked to the immune system[19][20]. IL-23 is an upstream regulatory cytokine that promotes the survival and expansion of IL-17-producing T cells. Three genes involved in IL-23 signaling, namely *IL12B* (encoding the p40 subunit common to IL-12 and IL-23), *IL23A* (encoding the p19 subunit of IL-23) and *IL23R* (encoding a subunit of the IL-23 receptor), have a confirmed association with the disease[20]. Moreover, single-nucleotide polymorphisms (SNPs) located in the 3'-untranslated-region as well as ~60kb upstream of the *IL12B* coding region mark risk haplotypes (rs3212227 and rs6887695, respectively), while R381Q amino acid substitution within the *IL23R* gene provides a protective role against psoriasis[36][37]. Furthermore, the role of innate immunity in the pathogenesis of psoriasis has been put forward by Tsoi and his colleagues with the identification of additional psoriasis susceptibility loci[22]. Among the newly identified loci, five are specifically associated with psoriasis and are involved in innate immune responses (*DDX58*, *KLF4*, *ZC3H12C*, *CARD14* and *CARM1*). In addition, three genes that are part of an immunoregulatory network downstream of the IL-17 receptor have been identified as potential psoriasis candidate genes (*TRAF3IP2*, *NFKBIZ* and *TNFAIP3*). Finally, the abundant production of TNFα in psoriatic skin is a key feature of the disease. Studies have revealed an association between psoriasis and polymorphisms in the TNFα promoter region, affecting its production and therefore suggesting a disturbance in the recognition of regulatory DNA target sites by transcription factors important for the expression of that gene. More specifically, the replacement of guanine with adenine in position-238 is linked to a higher production of TNFα, and consequently to a higher risk of psoriasis in the Caucasian population[38][39]. However, as reported by Liu et al., the gene that encodes TNFα lies in the MHC region and has an association with human leukocyte antigen (HLA) class I alleles such as HLA-C. Therefore, these associations could be due to the proximity with HLA-C[40].

3. Implication of Keratinocytes

Over the years, keratinocytes were discovered to be crucial in the initiation, maintenance, and regulation of immune skin reactions. They act as an executor in response to inflammatory mediators, including IL-17 and IL-36, for developing the full-blown psoriatic phenotype. Keratinocytes also produce a variety of cytokines, chemokines and antimicrobial peptides that participate in the amplification of the local inflammatory response and the maintenance of an inflammatory cascade by maintaining epidermal hyperplasia[41][42]. The explanation of psoriasis is constantly fluctuating between keratinocytes and immune cells. Before 1970, keratinocytes were commonly acknowledged as the main actor in the evolution of psoriasis. However, T cells were later discovered to play a role in the pathogenesis. Therefore, it is now believed that the crosstalk between keratinocytes and immune cells, particularly T cells and dendritic cells, plays critical roles in the pathogenesis of psoriasis[43]. Anne Bowcock, a geneticist at Washington University in St. Louis, gave the first indication that keratinocytes play a major role in the development of psoriasis. Indeed, she revealed that two mutations in the gene encoding for the caspase recruitment domain-containing protein 14 (CARD14), are primarily observed in keratinocytes and might induce

psoriasis by triggering expression of NF-κB, an inducible transcription factor that regulates a large array of genes involved in different processes of the immune and inflammatory responses[44][45]. About twenty CARD14 variants were found in patients suffering from psoriasis[46]. Some mutations constitutively activated CARD14 by self-aggregation, resulting in the expression of pro-inflammatory factors and the development of psoriasis[46][47]. Furthermore, a mutation of glutamic acid in position 138 in the coiled-coil domain of CARD14 (Card14DE138) results in a gain-of-function mutation. This mutation leads to hyperactivation of CARD14 and is sufficient to orchestrate the complex processes that drive IL-23/IL-17-mediated psoriasiform skin inflammation in vivo[48]. These results help identify a variety of genes involved in innate immunity, emphasizing the importance of keratinocytes as potential initiators of psoriasis. Moreover, Gilliet and his colleagues established that keratinocytes play a role in the initiation of psoriasis after injury by secreting the antimicrobial peptides LL-37 conjugated with self-DNA to activate toll-like receptor 9 in plasmacytoid dendritic cells[49]. Cutaneous injury activates toll-like receptor 3 in keratinocytes to produce various proinflammatory cytokines, such as TNF- , IL-6, and IL-36.

The production of psoriasis-associated inflammatory cytokines can also be induced by mechanical stretches[50][51]. These studies confirm that cytokines produced by keratinocytes can play a significant role in the development of this condition, and that keratinocytes are important in the initiation of cutaneous inflammation by activating immune cells.

The debate over whether abnormalities in the keratinocytes or of the immune system are responsible for triggering the disease is still emerging, suggesting a dynamic contribution of keratinocytes to the pathogenesis[44][45][52][53].

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