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Review

Genetic and epigenetic basis of psoriasis pathogenesis

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ABSTRACT

Psoriasis is a chronic inflammatory skin disease whose prevalence varies among different populations worldwide. It is a complex multi-factorial disease and the exact etiology is largely unknown. Family based studies have indicated a genetic predisposition; however they cannot fully explain the disease pathogenesis. In addition to genetic susceptibility, environmental as well as gender and age related factors were also been found to be associated. Recently, imbalances in epigenetic networks are indicated to be causative elements in psoriasis. The present knowledge of epigenetic involvement, mainly the DNA methylation, chromatin modifications and miRNA deregulation is surveyed here. An integrated approach considering genetic and epigenetic anomalies in the light of immunological network may explore the pathogenesis of psoriasis.

1. Introduction

Psoriasis is a chronic and recurrent inflammatory skin disease with variable morphology, distribution, severity and course. Prevalence of psoriasis varies from 1 to 12% among different populations worldwide (Chandran and Raychaudhuri, 2010; Gervin et al., 2012). It was initially considered to be a disease that involved intense proliferation and abnormal differentiation of keratinocytes. However, current understanding suggests that psoriasis is a skin-specific T-cell mediated autoimmune disease involving hyperkeratosis and parakeratosis (Lowes et al., 2013; Mak et al., 2009). A plausible mechanistic hypothesis about the pathogenesis of psoriasis suggests abnormal activation and migration of T-cells into the skin and eventual aggregation of inflammatory cells, followed by psoriatic-plaque development, mediated by $CD4^+$ and $CD8^+$ T-cells (Gervin et al., 2012; Lowes et al., 2013; Nickoloff and Nestle, 2004).

Different clinical features including the shape, redness and localization of plaques help in discerning the different forms of psoriasis. The most common form, the generalized plaque type, is characterized by sharply circumscribed, round or oval nummular plaques that appear as dry, red and raised lesions covered by silvery white scales. A second type of psoriasis, namely pustular psoriasis is typically characterized by blisters surrounded by red skin. Guttate psoriasis, the most common type occurring in children and people below the age of 30, comprise of plaques relatively smaller in size, less scaly than the plaque type psoriasis. One of the major triggers of guttate psoriasis is a streptococcal throat infection and often develops suddenly after an influenza attack. A fourth type of clinical manifestation, known as inverse psoriasis is found in skin folds such as the groin and armpits and is worsened by friction and sweating. The fifth type and the least found psoriasis is the erythrodermic type which is manifested by inflammation, itching and painful red rashes, at times covering the entire body of the patient. Psoriasis may be symptomatic to some patients with intense pruritus or burning.

2. Genetic basis of psoriasis

Psoriasis is a multi-factorial genetic disorder where the manifestation and severity of the disease is probably dependent on the patient's genetic background and environmental factors (Abele et al., 1963; Aschner et al., 1957; Bowcock, 2005; Feng et al., 2009; Liu et al., 2008; Lu, 2013; Zhang et al., 2013). Significantly higher incidence of the disease among relatives of patients and higher concordance rate among monozygotic twins (65–72%) over dizygotic twins (15–30%) suggest the involvement of genetic factors (Duffy et al., 1993; Gervin et al., 2012; Lonnberg et al., 2013; Pedersen et al., 2008; Wuepper et al., 1990). However, the inheritance pattern could be explained only in few cases. (Hebert et al., 2012;

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Henseler and Christophers, 1985; Villanova et al., 2013). The search for genes responsible for familial psoriasis through genome-wide linkage scans identified several putative susceptible loci. The Major Histocompatibility Complex (MHC) class I is identified as a chief susceptibility factor for psoriasis (Nair et al., 2000). The gene locus at 6p21 primarily associated with psoriasis development has been documented as the psoriasis susceptibility region 1 (PSORS1) (Fan et al., 2008; Nair et al., 2006; Sagoo et al., 2004; Trembath et al., 1997). The *HLA-Cw6* gene has been found to be the strongest susceptibility allele of the PSORS1 locus to early-onset chronic plaque type and guttate psoriasis (Henseler and Christophers, 1985). At PSORS1, the coiled coil α-helical rod protein 1 (*CCHCR1*) and corneodesmosin (*CDSN*) has been found to possess a regulatory role toward keratinocyte proliferation (Capon et al., 2004b).

2.1. Genome-wide association studies

PSORS1 accounts for 35–50% of the psoriasis heritability. Other associated genetic loci have also been identified(Gandhi et al., 2011; Lesueur et al., 2007) through several gene specific as well as genome-wide association studies (GWAS) performed among different populations (Table 1) (Ammar et al., 2013; Ellinghaus et al., 2012; Jordan et al., 2012a; Liu et al., 2008; Nair et al., 2009; Shaiq et al., 2013; Strange et al., 2010; Tsoi et al., 2012; Zhang et al., 2009b). A GWAS in European population identified seven susceptible loci involved in IL23, NFκB and Th2 mediated immune response mechanisms(Nair et al., 2009). Other recent studies demonstrated the role of IL23/Th17 axis in the pathogenesis of psoriasis(Lowes et al., 2013). IL17 and other gene products of Th17 cells interact with keratinocytes to bring about the disease pathogenesis. Inhibiting IL-23 subunits or IL-17 have shown different degrees of therapeutic success(Lowes et al., 2013). However, the therapeutic strategies developed to block these known pathways mainly target the maintenance phase of the disease, the actual stimuli which triggers the initiation of the disease is still largely unknown and demands further studies.

Another GWAS in Chinese Han population grouped the affected individuals into two groups, viz. type I psoriasis (age of onset < 40 years) and type II psoriasis (>40 years) (Zhang et al., 2009b). A strong association with the *HLA-Cw6* allele was observed in type I, however not in type II (Zhang et al., 2009b). This study supported the evidence of PSORS1 association. The strongest association was observed within rs10484554 and rs130065. However, *CDSN*, previously reported to be within the PSORS1 locus(Capon et al., 2004b), was found to be about 30 kb away from the region of strongest association. This study revealed a new association within the late cornified envelop (*LCE*) gene cluster located in chromosome 1q21. LCE proteins play a role in epidermal terminal differentiation(Backendorf and Hohl, 1992; Engelkamp et al., 1993; Mischke et al., 1996). Several other studies supported the involvement of *LCE* gene cluster in psoriasis pathogenesis(Li et al., 2011; Xu et al., 2011a). Analyses of 64 previously reported SNPs in two groups of Chinese Han and Chinese Uygur population detected 4 SNPs from *LCE* gene cluster and 2 in *IL12B* with high significance. Remaining 58 SNPs were below the suggested significance level ($P \sim 10^{-5}$) (Zhang et al., 2009b). Recently, exome sequencing in psoriasis patients identified two independent non-synonymous single-nucleotide variants (SNVs) within genes *IL23R* and *GJB2*; while common SNVs within *LCE3D*, *ERAP1*, *CARD14* and *ZNF816A* were also found to be associated with the disease(Tang et al., 2014).

A meta-analysis of GWAS from Michigan, Toronto, Germany and Newfoundland reported 3 new susceptibility loci associated with cutaneous psoriasis and psoriatic arthritis (Stuart et al., 2010). Another GWAS in European population identified association of eight additional loci, out of which seven loci comprised genes having roles in the immune system (*IL28RA*, *IFIH1*, *REL*, *ERAP1*, *TRAF3IP2*, *NFKBIA* and *TYK2*). This study also suggested an interaction between *HLA-C* and *ERAP1* (ER aminopeptidase 1) loci. (Strange et al., 2010). 113 psoriasis-associated markers were identified in a study that included ~25k putative functional SNPs across the genome. They also reported protective effect of missense SNPs in interferon induced with helicase C domain 1 gene (*IFIH1*) (Li et al., 2010). A GWAS on Chinese population showed association of six susceptibility loci containing candidate genes *ERAP1*, *PTTG1*, *CSMD1*, *GJB2*, *SERPINB8* and *ZNF816A*, out of which *ERAP1* and *ZNF816A* were preferentially found to be associated with Type I psoriasis (Sun et al., 2010). A recent study performed on European population identified 15 new susceptibility loci, which included candidate genes responsible for regulation of T-cell function, such as *RUNX3*, *TAGAP* and *STAT3* (Tsoi et al., 2012). Interestingly, these genes were found to be involved in innate host defense mechanisms, including macrophage activation (*ZC3H12C*), NF-κB signaling (*CARD14* and *CARM1*) and interferon-mediated antiviral response (*DDX58*). Mostly, genes involved in immunologic response pathways are seen to be enriched in these GWASs. Since these newly discovered associations were common in case of other autoimmune diseases, these findings signify a better understanding of shared genetic determinants between immune-mediated inflammatory disorders, highlighting the role of skin in innate and acquired immune responses (Tsoi et al., 2012).

2.2. Family based association studies

In order to investigate the inheritance pattern of psoriasis, family based studies were performed through segregation analysis which suggested multifactorial inheritance of psoriasis vulgaris (Pietrzyk et al., 1982b). However, other family studies suggested the involvement of double-recessive genes and dominant factors with limited penetrance (Abele et al., 1963; Aschner et al., 1957; Grayson and Shair, 1959; Kimberling and Dobson, 1973; Ward and Stephens, 1961). This indicated the possibility of two distinct genetic subpopulations of psoriasis, one with multifactorial inheritance and one with multigenic determination (Pietrzyk et al., 1982a,b). In 1994, a family based study identified the psoriasis susceptibility loci (PSORS2), located in the distal end of the human chromosome 17q (Speckman et al., 2003; Tomfohrde et al., 1994). Interestingly, the families positive for the association of this locus showed absence of linkage to *HLA-Cw6* allele, whereas unlinked families showed *HLA* association (Tomfohrde et al., 1994). Subsequent studies of familial psoriasis reported association of a RUNX1 binding site variant between *SLC9A3R1* and *NAT9* in the PSORS2 locus (Helms et al., 2003). Mutation in the *ZNF750* at the PSORS2 locus is reported in seborrhoea-like dermatitis with psoriasiform elements (Birnbaum et al., 2006). A subsequent study comprising a five-generation Chinese family with autosomal-dominant psoriasis indicated the involvement of a promoter sequence variant of *ZNF750* in psoriasis pathogenesis (Yang et al., 2008). Another SNP based study, however, excluded the association of PSORS2 loci with psoriatic arthritis in Italian population (Giardina et al., 2006). Investigation of familial mutations in psoriasis showed a *CARD14* mutation in PSORS2 locus in a family of northern European ancestry and a Taiwanese family, inherited across generations following Mendelian pattern (Jordan et al., 2012b). The north European family showed disruptive splicing of the *CARD14* gene which resulted in inclusion of 22 amino acids. Another case control study by the same group identified fifteen additional rare missense variants in *CARD14* and showed their effects on *NF-κB* activation and the transcriptome of keratinocytes (Jordan et al., 2012a). Besides, several tentative psoriasis linkage sites were found on chromosomal regions 4q34 (PSORS3) (Liu et al., 2008; Matthews et al., 1996; Nair et al., 1997), 1q21 (PSORS4) (Bhalerao and Bowcock, 1998; Capon et al., 1999a,b, 2001; Chen et al., 2009; de Cid et al., 2009; Zhang et al., 2009b), 3q21 (PSORS5)