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Immunogenetic Approach to Psoriasis

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Abstract Human leukocyte antigen system A (HLA) genes, especially HLA-C*06:02, have been proposed as major candidate genes for psoriasis, which is a T-cell driven immune disease that shows altered keratinocyte differentiation.

Herein I would like to summarize an immunogenetic approach to psoriasis, which is a description of research that was mainly carried out by my colleagues during my service as Professor and Chairman (1997-2016) at the Department of Dermatology, Yamaguchi University Graduate School of Medicine.

Key words: psoriasis, disease susceptibility, HLA, genetic polymorphisms

Introduction

Psoriasis is a chronic cutaneous inflammatory disease that is characterized by altered keratinocyte differentiation and variable clinical manifestations; thus it is occasionally associated with joint, cardiovascular, and hematological involvements as well as with skin lesions.[1] The genetic basis underlying disease susceptibility to psoriasis is not completely understood, although the major psoriasis susceptibility locus 1 (*PSORS1*) is speculated to be the major disease susceptibility locus for psoriasis.[2] *PSORS1* involves HLA-C alleles, especially HLA-C*06:02.

Regarding the association of cytokines and psoriasis, tumor necrosis factor (TNF)-α is a potent inflammatory cytokine that is highly expressed in psoriatic skin. TNF-α is now known to have a crucial role in psoriasis pathogenesis, as demonstrated by the efficacy of TNF-α targeted therapeutics. Additionally, the Th17/IL-23 pathway is highly increased in psoriatic skin lesions[3] and is central to psoriasis pathogenesis, as genetic susceptibility to psoriasis was linked to IL-12B and IL-23 receptor genes.[4] A Th17 T-cell subset with the ability to produce IL-17 and IL-22 is known to differentiate from naïve CD4+T cells after IL-6 and TGF-β stimulation, and IL-23 is a major survival factor for this cell subset.[5] Furthermore the CD8+T cells seen in affected psoriatic skin lesions can produce IL-17. Recently 160 genes including IL-8 and IL-1β were found to be synergistically upregulated by TNF-α and IL-17.[6] Based on these combined data, it can be said that psoriasis is a complex inflammatory skin disease.

I feel honored and humbled that the organizers entrusted me with the writing of this review article. I would like to describe the relationship between HLA and disease susceptibility to psoriasis, using a population-based case-control study and a family study that were mainly done during my service as Professor and Chairman (1997-2016) at the Department of Dermatology, Yamaguchi University Graduate School of Medicine.

Genetic Control of Disease Susceptibility to Psoriasis

Since the initial reports by Russell, T. et al.[7] and Whites, S. et al.,[8] there has been much evidence showing that several genes within the HLA region located on human chromosome 6p21 are associated with susceptibility to psoriasis. However, most of the above studies were performed as population-based

case-control studies. Psoriasis is composed of psoriasis vulgaris (PV), which is the most common type; psoriatic arthritis (PA), which is usually accompanied by seronegative arthropathy; generalized pustular psoriasis (GPP), which is associated with high fever and aseptic multiple pustules known as Kogoj's spongiform microabscess; and psoriatic erythroderma. In Japan, palmoplantar pustulosis with sterile pustules is considered as a separate and clinical entity that is different from psoriasis, except for the presence of an IL-36RN mutation.[9] Patients with psoriasis often experience increased co-morbidities affecting cardiovascular organs.[10] The risk seems to be greatest in younger psoriatics with more extensive lesions. In a Japanese population-based study, the prevalence of psoriasis in the population was approximately 0.03%,[11] whereas the prevalence of psoriasis in Caucasians is 1-3%.

HLA-C*06:02 has been considered to be the major causative gene within the *PSORS1*. Other HLA-C alleles that are associated with psoriasis susceptibility are HLA-C*07, HLA-C*04, and HLA-C*12, although their association with psoriasis is not as strong compared with that of HLA-C*06:02, which is the top risk HLA-C allele.

Another strategy to obtain evidence regarding genetic factors involved in the development of psoriasis is to carry out a family study. Multiplex families with PV were analyzed by the affected sib-pair method. Ten affected siblings were assigned as sharing 2, 1, or 0 HLA haplotypes identical by descent. Out of 10 affected sib-pairs, 1 shared two HLA haplotypes, 8 shared one HLA haplotype, and 1 affected sib-pair was HLA-non-identical; this distortion in the distribution of the shared HLA haplotypes did not reach a statistical significance at the 5 percent level. This lack of significance appears to be due to the small sample size (n = 10).

In addition to psoriasis skin lesions, PA with a seronegative inflammatory arthritis occurs in up to 15% of patients with moderate to severe PV. Considerable impairment of movement is often seen, leading to a decreased quality of life. Our previous HLA association study showed that HLA-A2 and HLA-B27 were serologically associated with peripheral type arthritis and with axial type arthritis including spine, respectively.[12] Most of the HLA-A2 was found to be HLA-A*02:07 but not HLA-A*02:01 (prototype of HLA-A2).[13] Furthermore, HLA-A2 showed a tendency to be in linkage disequilibrium with HLA-B46 or HLA-DR8 (Haplotype frequency of HLA-A2-B46-DR8 = 0.145; $p < 0.05$). The HLA-A2-B46-DR8 haplotype-positive PA patients showed increased serum levels of complement components (C4 and C4a).[14] Increased amounts of serum C4a might be responsible for the development of the exudative lesions in PA. With respect to immune response to pathogens, HLA-A*02:07 was associated with IgG antibody responses against recombinant M protein (C region) derived from *Streptococcus pyogenes*. These findings suggest the possibility that both HLA and HLA-linked complement genes play a genetically determined role in the development of PA. PA is usually accompanied by PV. Therefore, when a patient is initially diagnosed as PV, we should be able to predict the future occurrence of PA, based on the presence of either HLA-A2 (HLA-A*02:07) or HLA-B27.

HLA molecules act not only as a receptor but also as a ligand. Thus, killer cell immunoglobulin-like receptors (KIRs) can interact with HLA expressed on antigen-presenting cells in association with peptide antigens. Various inflammatory cells have been found at the affected skin lesions of psoriasis.[15] Natural killer (NK) cells and NK-T cells bearing natural killer receptors are within this population of cells. These cells express KIRs. Interestingly, NK-T cells with T cell receptors are considered to function as a bridge between innate and adaptive immunity. KIRs are a group of polymorphic receptors that are encoded in a region called the human leukocyte receptor cluster on chromosome 19q13.4. Some activating KIR2DS receptors can bind to the same HLA-C ligands as inhibitory KIR2DL receptors, albeit with a lower affinity. Thus, KIR2DL1 and KIR2DS1 can both recognize HLA-C Asn77Lys80 (HLA-Cw2, -Cw4,-Cw5, -Cw6) on keratinocytes, whereas KIR2DL2 and KIR2DS2 can both bind to HLA-C Ser77Asn80 (HLA-Cw1, -Cw3, -Cw7, -Cw8) on keratinocytes. We previously reported that KIR2DS1 and KIR2DL5 were

significantly increased in PV cases (n = 96), compared with controls (n = 50).[16] Similarly, Martin et al. reported an increase in KIR2DS1 in PA, which is another HLA-Cw6-associated disease.[17] Our work regarding KIRs and disease susceptibility to PV has been cited in the textbook of *Dermatology in General Medicine* edited by Fitzpatrick, T.B., et al. Although the KIR2DS1 molecule appears to be important for the development of psoriasis from the point of view of the association study, we do not know what the biological significance might be of KIRs interacting in an HLA/peptide-dependent manner.

Regarding TNF-$\alpha$from the point of view of an immune-modulatory gene linked to the HLA system, we concluded from our work that TNF-αpromoter polymorphisms at nucleotide positions -238, -308, -857, and -863 were not associated with either PA or PV susceptibity.[18] Recently, Murdaca et al. reported that the SNP+489 variant allele A of TNF-α was significantly associated with PA susceptibility.[19]

A very strong association of psoriasis with HLA-C*06:02 has been found among various populations. According to a theory proposed by McMichael, A. and McDevitt, H.,[20] three hypotheses have been put forward to explain the genetic mechanisms of this association. One hypothesis is that HLA-C*06:02 alone is directly involved in psoriasis as a single gene. The second hypothesis is that HLA-C:06:02 itself interacts with at least one other gene on another chromosome. The third hypothesis is that the association observed is due to a gene in linkage disequilibrium with HLA-C*06:02. Currently at least *PSORS2, PSORS3*, and *PSORS4*, as well as the aforementioned *PSORS1*, are known as psoriasis risk regions. These genetic features suggest that many genes (approximately 50 genes) including HLA-C*06:02 might be involved in the development of psoriasis. The combined data suggest that it is reasonable that all three hypotheses can be included in the genetic mechanisms of the association of HLA-C*06:02 with psoriasis.

Breakthrough in GPP Research

GPP is a rare inflammatory skin disease that occurs in association with high fever and the involvement of other organs, and that can be life-threatening. In 2011, Marrakchi, S. et al. reported that GPP patients in nine Tunisian families had either homozygous or compound heterozygous mutations in the interleukin-36 receptor antagonist (IL-36Ra).[21] In Japan, a nationwide collaborative research team, including our group, searched for IL-36RN mutations in two populations of GPP: GPP with preceding PV (n = 20) and GPP without PV (n = 11). The data showed that the majority of GPP alone is caused by a deficiency of IL-36Ra encoded by the most common variants of IL-36RN (c.28C>T (p.Arg10X) and c.115 + 6 T>C (p.Arg10ArgfsX1)), which are present in the homozygous state or as a compound heterozygote.[22] In contrast, GPP with PV was found to have the caspase recruitment domain family, member 14 (CARD14) variant (c.526 G>C(p.Asp176His)), leading to NF-κB activation. This CARD14 mutation that leads to a gain-of-function is not associated with PV or with GPP alone.[23] These observations suggest that the genetic predisposition of GPP with preceding PV differs from that of PV or of GPP without PV. This recent work by our group and Professors Sugiura, K. and Akiyama, M. has been introduced in the newest textbook of *Rook's Textbook of Dermatology*. A recent work by Coto-Segura, P. et al. showed that the common CARD 14 p.Arg820Trp variant might have a significant positive response to anti-TNF therapies.[24]

Quantitative Analysis of Malassezia Flora in Psoriasis

We quantitatively investigated Malassezia species in the scale of PV patients, using a real-time polymerase chain reaction assay. The results indicated that *Malassezia restricta* was the predominant species in the scale.[25] This finding obtained using molecular genetics changed the previously accepted concept that *Malassezia furfur* was the only Malassezia species that causes skin diseases including PV. Furthermore, Malassezia colonization was significantly lower in PV patients with hyperlipidemia (n = 6) than in those with normolipidemia (n = 14). There was no correlation between the Psoriasis Area and Severity Index (PASI) score and the level of Malassezia colonization.[26] Further study in vitro is necessary

to determine whether Malassezia species, especially *Malassezia restricta*, is a true pathogen for the development of psoriasis or not.

Conclusions

Our final goal is to ultimately ascertain the genetic mechanisms of the above described polymorphic phenomena in human immune-mediated diseases and to apply laboratory-obtained data to clinical medicine. From these points of view, understanding of the aforementioned GPP genetics based on molecular study would be very useful in elucidating the role of HLA itself and of HLA-linked genes in the development of psoriasis. Moreover, pathogens such as *Streptococcus pyogenes* and *Malassezia restricta* will be potent tools for examination of mutual immune responses between the affected host and the environment. There is still plenty of work to be done.

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Conflict of Interest

The author declares no conflict of interest.

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