Bull Yamaguchi Med Sch 43(3-4) : 1996

HLA-A*0207, *Streptococcus Pyogenes* and Psoriatic Arthritis: Immunogenetic Studies

Masahiko Muto

Department of Dermatology, Yamaguchi University School of Medicine, Ube Yamaguchi 755, Japan
(Received October 9, 1996)

Key words: HLA-A*0207, *Streptococcus Pyogenes*, Psoriatic Arthritis

Introduction

We previously reported a strong association between HLA-A2 and psoriatic arthritis (PA) (1). HLA-A2 is insufficient to cause the disease, although this allele represents an important clue to genetic predisposition. A role of Group A streptococci in the development of PA has been suggested by the exacerbation of disease following streptococcal infection (2).

In this short article, we present clear evidence for HLA-A*0207-linked genetic control to *Streptococcus pyogenes* infection and its crucial role in the pathogenesis of PA.

I. The expression of epitopes cross-reactive with *Stretococcus pyogenes* on the human tissues, detected by mouse monoclonal antibodies directed against type 12 Group A streptococcal cell wall antigens

Two monoclonal antibodies (mAb), 7.30 and 18.20, against the streptococcal cell wall antigen reacted with both epidermis and dermis of normal and psoriatic skin. Inflammatory cells in psoriatic lesional skin were labelled in the upper dermis. Uninvolved skin from psoriatic patients exhibited a fluorescence pattern indistinguishable from normal controls. Furthermore, both mAb reacted with synovial membrane obtained from one patient with PA. These results suggest that psoriatic patients do not have a unique antigenic site responsible for their individual reactivity (3).

II. Determination of HLA-A2 subtypes by HLA-DNA typing with PCR sequence-specific oligonucleotide probes

HLA-A*0207 was present in 57.9% of the 19 patients with PA, compared with 7.2% of the normal control (relative risk = 17.6; corrected $p < 0.01$). Because most of the HLA-A*0207-positive patients were heterozygotes, it is likely that HLA-A*0207-linked dominant gene might be involved in the development of PA.

III. Immune response *in vivo* to recombinant M12 protein in PA

To examine whether the infection of *Streptococcus pyogenes* was involved in the pathogenesis of PA, we investigated the *in vivo* humoral responses of the patients' sera to recombinant M12 protein (AB region; subtype specific N-terminal half, C region; conserved C-terminal half). The data showed that the patients with PA had a significantly higher responsiveness to the C region, but not the AB region, than normal controls (20, 193±3,285

U/ml vs 3,417±395 U/ml in controls; $p<0.001$). This finding suggests that the high immune response to the M protein, regardless of M types, is strongly associated with PA (4).

Ⅳ. Correlation between HLA-A*0207 and antibody levels to the C region of recombinant M12 protein in PA

The mean antibody level to the recombinant M12 (C region) in the HLA-A *0207-positive PA patient group (n=10; 27,700± 2,035 U/ml) was significantly higher than that in the HLA-A*0207-positive normal controls (n=9; 3,825±687 U/ml) ($p<0.01$).

Conclusion

The immunogenetic studies reported in this paper indicate that streptococcal infection may be involved in the pathogenesis of the HLA-A2-associated PA. Second, the susceptibility to PA involves one variant of at least 15 HLA-A2 alleles, HLA-A*0207. The excess of HLA-A*0207 heterozygotes supports a dominant model for the susceptibility to PA. From the observation that HLA-A*0207-positive PA patients showed elevated IgG responses to the M protein, it is possible that HLA-A*0207 plays a role in the initial response to the streptococcal infection in the respiratory tract or urethra. According to the analysis of peptide motifs among HLA-A2 subtypes (A*0201, A*0204, A*0206, and A*0207), HLA-A*0207 can bind peptides with leucine at position 2, aspartic acid at position 3, and leucine at C-terminus site (5). Based on the amino acid sequences of recombinant M12 used in this study, 9 mers showing the peptide motif, which may bind the groove of the HLA-A*0207, were not found. Therefore, concerning the mechanisms of the elevated IgG responses to the C region of recombinant M12 protein among the HLA-A*0207-positive PA patients, it is possible that HLA-A*0207 may poorly present the streptococcal M antigens to cytotoxic T cells, by which HLA class I molecules are recognized. This might explain the altered immune clearance of *Streptococcus pyogenes* in PA.

A close structural similarity has been reported between the 50 kDa type I keratin (K14) and M6 protein, and between human synovium and cartilage and M5 protein (6, 7). These findings support the hypothesis that molecular mimicry may be involved in the pathogenesis of PA. Since HLA-A2 shares short sequences of amino acids with *Streptococcus pyogenes* M proteins, it remains the possibility of molecular mimicry between the M protein and HLA-A2 molecule. Because we have not determined immunodominant epitopes in M12 protein (C region), it remains to be resolved whether the strong IgG response against the C region in PA patient group may also involve cross-reactivity with other tissue antigens, in addition to elevated induction of the immune response by repeated streptococcal infections.

In 1980s, the existence of HLA-linked immune response genes and immune suppression genes to certain specific antigens were reported by many investigators including us (8). Recent advances in genetic engineering may contribute to our further understanding of the molecular basis of HLA-associated recognition structures.

References

1) Muto, M., Nagai, K., Mogami, S., Nakano, J., Sasazuki, T., Asagami, C. : HLA antigens in Japanese patients with psoriatic arthritis. *Tissue Antigens* **45** : 362-364, 1995.

2) Bertrams, J., Lattke, C.L., Kuwert, E. : Correlation of antistreptolysin-O titer to HL-A13 in psoriasis. *N. Engl. J. Med.,* **291** : 631, 1974.

3) Muto, M., Fujikura, Y., Hamamoto, Y., Ichimiya, M., Ohmura, A., Sasazuki, T., Fukumoto, T., Asagami, C. : Immune response to *Streptococcus pyogenes* and the susceptibility to psoriasis. *Australasian J. Dermatol.,* **37** : s54-55, 1996.

4) Muto, M., Date, Y., Ichimiya, M., Moriwaki, Y., Mori, K., Kamikawaji, N., Kimura, A., Sasazuki, T., Asagami, C. : Significance of antibodies to streptococcal M protein in psoriatic arthritis and their association with HLA-A*0207. *Tissue Antigens,* **48** : 645-650, 1996.

5) Sudo, T., Kamikawaji, N., Kimura, A., Date, Y., Savoie C. J., Nakashima, H., Furuichi, E., Kuhara, S., Sasazuki, T. :

Differences in MHC class I self peptide repertoires among HLA-A2 subtypes. *J. Immunol.*, **155** : 4749-4756, 1995.

6) McFadden, J., Gill, G.S., Powles, A.V., Baker, B.S., Valdimasson, H., Fry, L. : Components of streptococcal M surface antigen and human keratin are homologous. *J. Invest. Dermatol.*, **93** : 303, 1989.

7) Baird, R.W., Bronze, M.S., Kraus, W., Hill, H.R., Veasey, L.G., Dale, J.B. : Epitopes of group A streptococcal M protein shared with antigens of articular cartilage and synovium. *J. Immunol.*, **146** : 3132-3137, 1991.

8) Sasazuki, T., Nishimura, Y., Muto, M., Ohta, N. : HLA-linked genes controlling immune response and disease susceptibility. *Immunological Rev.*, **70** : 51-75, 1983.