The Characterization of Pathogenic and Non-pathogenic HLA-B27 Protein

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Ankylosing spondylitis (AS) is characterized by chronic inflammation of the axial and peripheral joints and ligamentous attachments. The major histocompatibility complex (MHC) haplotype HLA-B27 has the strongest genetic association with the disease. Among these subtypes of HLA-B27, B*2702, B*2703, B*2704, B*2705 and B*2710 are reported to significantly increase risk, whereas B*2706 and B*2709 are not associated with disease. To date, three major hypothesis have been raised. The first one is that the arthritogenic peptide presented by HLA-B27 activates CD8⁺ T cells to cause inflammatory arthritis. The second theory is that misfolding of HLA-B27 in the endoplasmic reticulum leads to endoplasmic reticulum stress resulting in the activation of unfolded protein responses (UPRs) and the upregulation of IL-23 in dendritic cells. The third theory is that the HLA-B27 has an ability to aberrantly fold to form homodimers and this homodimer can be recognized by killer-immunoglobulin-like receptors. Despite these theories have been studied, the pathogenic role of HLA-B27 still remains unclear.

In the present study, in order to clarify the function of HLA-B27 at the cellular level, we established human-derived B cell line C1R stably expressing pathogenic HLA-B27 subtypes (B*2704 or B*2705) or non-pathogenic subtype (B*2706). We examined the localization of HLA-B27 using confocal microscopy. We also investigated their associated molecules using Liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Confocal microscopic analysis demonstrated that either B*2704 or B*2705 form smaller uneven multiple clusters on the cell surface compared to that of B*2706 which form a single large dense cluster on the cell surface. LC-MS/MS analysis showed that the molecules which bind to both B*2704 and B*2705 but not B*2706 were Target of Myb protein 1 (Tom1) and MHC class I molecules. Tom1 is an adaptor protein required for the maturation of autophagosomes and their fusion with lysosomes. Tom1 also participates in immune receptor recycling and Toll-like receptor signaling. Therefore, pathogenic HLA-B27 might have some effect on immune receptor or Toll-like receptor-mediated signals by the alteration of intracellular vesicle trafficking. The other associated molecule was MHC class I molecules heterodimer with other MHC class I molecules in addition to HLA-B27 or β 2-microglobulin. Although the direct evidence of their association should be demonstrated in the future studies, a new type of heterodimer may have some effect on immune responses.

To summarize these results, the AS-sensitive subtype and insensitive subtypes of HLA-B27 differed in quantitative, qualitative, and diversity. It was also speculated that they might lead to the pathogenesis of AS.

Key words: ankylosing spondylitis (AS), HLA-B27, target of Myb protein 1 (Tom1)

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