Anti-interferon-γ autoantibody: a new form of adult onset immunodeficiency to mycobacterial infection in Southeast Asia

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Anti-Interferon (IFN) -γ autoantibodies are an emerge etiology to cause the adult-onset immunodeficiency with mycobacterial or other opportunistic infections in patients. IFN-γ has an important role in antimycobacterial immunity and is produced principally by T cells and natural killer cells after stimulation with microbial products and interleukin-12. Genetic defects in IFN-γ-mediated immunity cause Mendelian susceptibility to mycobacterial disease (MSMD) in children and young adults, who contract disseminated mycobacterial infection from weakly virulent mycobacteria, such as bacille Calmette-Guérin (BCG) vaccines and nontuberculous mycobacteria. The striking clinical similarities between such individuals and those with MSMD strongly suggest that autoantibodies against IFN-γ are the cause of mycobacterial infection, rather than a consequence.

Our laboratory had identified a high prevalence of anti-IFN-γ autoantibodies in patients with disseminated mycobacterial infections in Taiwan. We found that this disease is strongly limited to the individuals with HLA-DRB1*15:02/16:02 and –DQB1*05:01/05:02 in South-East Asia, which provides genetic basic to explain the ethic/region restriction of this disease. Moreover, we found that these anti-IFN-γ autoantibodies recognize a major epitope (P121–131) at the C-terminus of IFN-γ. The amino acid sequence of this epitope is 100% homologous to a stretch of amino acids in the Noc2 protein of *Aspergillus terreus*, a fungus present in the environment, and autoantibodies from patients bound Noc2. We also generated an epitope-erased IFN-γ (EE-IFN-γ), in which the major neutralizing epitope region was modified. The binding affinity of anti-IFN-γ autoantibodies for EE-IFN-γ was reduced by about 40% compared with unmodified IFN-γ and activated the IFN-γR downstream signaling pathway ex vivo, in the presence of patients' plasma. In brief, we identified a common, critical B cell epitope that bound to anti-IFN-γ AutoAbs in patients and propose a molecular mimicry model underlying the production of these antibodies.

In conclusion, our effort shows the under-estimated clinical impact of anti-IFN-γ autoantibody disease in Taiwan and our study reveals the molecular mechanism of this particular disease.