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Influenza infection of MHC-I transgenic mice reveals that ERAP is necessary and sufficient for generation of the B27-specific immunodominant epitope

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Background: Although HLA-B27 and ERAP are known to confer susceptibility to spondyloarthritis (SpA), the role of these elements in modulating host response to infection is undefined. Despite co-dominant expression of class I MHC alleles, immune response to viral infections is characterized by immunodominance (ImDc). The exact mechanisms underlying ImDc are not clear. Defining factors contributing to ImDc has proved difficult due to multiple MHC-I allele co-expression in humans and normal mice.

Methods: To overcome this limitation, we generated human MHC-I transgenic (Tg) mice deficient for endogenous mouse MHC-I molecules and expressing only one human MHC-I allele (e.g. HLA-B7, HLA-B27, HLA-A2). To assess whether co-expression of additional MHC-I alleles in the presence or absence of ERAP influences the pattern of anti-flu CTL epitope recognition and ImDc, novel Tg mice in the context of ERAP deficiency were established.

Results: In flu-infected, double Tg A2/B7 or A2/B27 mice, IFN-γ ELISpot assays with the flu epitopes A2/M1.58-66 and B7/NP418-426 or B27/NP383-391 showed specific recognition of both peptides by both alleles respectively. In contrast, flu-infected B7/B27 Tg mice demonstrated a significantly reduced B27-restricted CTL response to NP383 while there was no change in the response of B7-restricted CTL response to NP418. Profiling the T cell response revealed that co-expression of B7 and B27 is associated with i) a partial deletion of Vβ8.1+ B27-restricted /NP383 CD8+ T cells and ii) a failure of Vβ12+ CD8+ T cell expansion following flu infection in B7/B27 Tg mice. Studies in flu infection of ERAP-deficient Tg B27 and Tg B7/B27 mice revealed complete abrogation of the B27-restricted response to NP383-391, indicating the importance of ERAP in generation of this peptide.

Conclusions: The HLA-B27 immundominant response to infection is critically dependent on ERAP. This provides a possible mechanistic basis for the findings in genetic studies of the interdependence of B27 and ERAP in conferring susceptibility to SpA.

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