Variation in ERAP influences risk for HLA-B*57:01 Abacavir Hypersensitivity

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Background

- Abacavir hypersensitivity syndrome (ABC-HSS) is characterized by skin rash, fever, malaise, gastrointestinal and respiratory symptoms in patients taking abacavir. ABC-HSS is life-threatening and cause of significant morbidity.
- ABC-HS develops when HLA-B*57:01 binds ABC in the F pocket of the major histocompatibility complex with ABC HSS or tolerance.
- 55% of individuals who carry HLA-B*57:01 will develop ABC-HS and 100% of ABC-HSS cases carry HLA-B*57:01. However, it is not well understood why the remaining 45% of ABC-HS carry by ABC-HS.

Methods

- Endoplastic reticulum aminopeptidases (ERAP1 and ERAP2) are critical for the first processing of MHC-I A14 ligands in the ER, trimming peptides to the ideal length for MHC-I binding.
- ERAP prefers substrates that are 8-16 residues in length with a C-terminal hydrophobic site which allows rapid trimming of N-extended peptides to 8-9 residues via a "molecular ruler" mechanism (Figure 2) (3,4).
- ERAP function determines patterns of immunodominance, epitope processing and T-cell responses during infection.
- ERAP can influence MHC-I class I expression on the cell surface.
- ERAP1 and ERAP2 genes are located on chromosome 5 and genetic variants and haplotypes of ERAP are associated with Ankylosing spondylitis (AS), psoriasis, and Behçet's disease (ERAP1) and birdshot retinopathy (ERAP2). In each of these diseases, disease-associated variants of ERAP have been shown to interact with HLA-B*57:01.

Results

- Significant SNPs were mapped to the functional domains in the solved crystal structure of ERAP1 (PDB 03DFN) using Coo2.
- In a multivariable model with rs27434(GG), the ERAP2 SNP (rs2248374(G)) that tags haplotype B, characterized by a non-functional truncated protein, was decreased in tolerant individuals (p = 0.04).
- None of the SNPs were significantly associated with outcome after accounting for rs27710.

Conclusions

- Representation of SNPs in ERAP1 and ERAP2 in part explain and differentiate HLA-B*57:01+ ABC-HSS from HLA-B*57:01+ ABC tolerance.
- Distinct SNP locations suggest putative functional influences on ERAP activity among co-occurring polymorphisms.
- ERAP activity may influence the repertoire of peptides presented by HLA-B*57:01 or influence efficacy changes in immunodominant epitopes. This provides a potential mechanistic model for the development of ABC-HSS or ABC tolerance in HLA-B*57:01 carriers.