
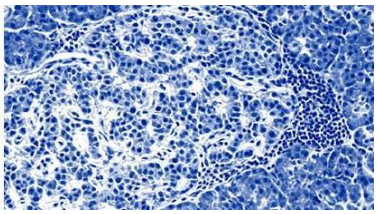

The CD8+ T-cell response against Coxsackievirus is focused on few selected epitopes: implications for vaccination trials

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PURPOSE

Despite increasing evidence for an association between Coxsackievirus B (CVB) infection and type 1 diabetes (T1D), the identity of the viral peptides naturally presented by infected beta cells and the nature of the anti-CVB cytotoxic CD8+ T-cell response are unknown. These questions are relevant in light of upcoming T1D prevention trials exploring the effect of vaccination against CVB. We therefore aimed at identifying the HLA Class I (HLA-I) viral peptidome of CVB-infected beta cells and at characterizing the CD8+ T-cell response against these peptides.

METHODS

Human beta-cell lines were infected with either CVB1 or CVB3. The HLA-I-bound peptides were identified by mass spectrometry and those restricted for HLA-A2 or –A3 were retained. This list was complemented by a parallel *in silico* search. After confirming the *in vitro* binding of these peptides to HLA-A2/A3, we tested their recognition by circulating CD8+ T cells from CVB seropositive donors by combinatorial HLA-I multimer assays, and CD8+ T-cell clones were generated. The peptides recognized were further studied in nPOD splenocytes.

SUMMARY OF RESULTS

The repertoire of HLA-I-bound viral peptides displayed by infected beta cells was limited to few selected sequences, largely overlapping between CVB1 and CVB3 serotypes. Only a fraction of these peptides was recognized by circulating CD8+ T cells from seropositive donors. Moreover, few of these epitopes were associated with cognate CD8+ T cells displaying an effector/memory phenotype, indicating that the anti-CVB immune memory is restricted to even fewer epitopes. Overall, CD8+ T-cell responses were dominated by only 2 peptides in most individuals, both in the blood and in the spleen. CD8+ T-cell clones raised

against one of these peptides were cytotoxic against target cells pulsed with their cognate peptide.

CONCLUSIONS

Surprisingly, CVB infection seems to induce a limited CD8+ T-cell memory response in terms of antigen coverage. This feature could favor repeated or chronic infections, thus lending rationale to CVB vaccination trials. The next questions are whether this poor memory response is found preferentially in T1D-prone patients, and whether the peptides identified can be used to evaluate the efficacy of CVB vaccines at boosting responses against dominant and subdominant epitopes.