Abacavir Impairs an HLA-B*57:01-restricted CD8+ T Cell Response to an Immunodominant Epstein-Barr Virus Epitope


1. Department of Infectious Diseases, Murdoch University, Perth, Western Australia, Australia
2. Institute for Immunology & Infectious Diseases, Murdoch University, Royal Perth Hospital, Sir Charles Gairdner Hospital, 3University of Western Australia, 4PathWest, Perth, Western Australia, Australia

Background: Structural and functional studies show that abacavir (ABC) binds non-covalently to HLA-B*57:01 and alters the repertoire of peptide recognition.

Abacavir (ABC) at a range of concentrations previously shown not to affect VSFEIFVGW

We aimed to determine whether the binding of ABC to HLA-B*57:01 has the potential to impact on a specific HLA-B*57:01 restricted CD8+ T-cell response.

More recently the crystal structure of ABC-peptide-HLA-B*57:01 has been resolved and ABC has been shown to rapidly and non-covalently bind to ABC causes a drug hypersensitivity syndrome which is known to be CD8+T cell dependent and specifically restricted through the class I allele HLA-

The presence of abacavir alters the binding specificity of HLA-B*57:01.

To identify prospective HLA B*57:01 epitopes from EBV (strain B95-8), we utilised the NetMHC 3.2 Server (NetMHC-3.0: accurate web server for peptide binding predictions) to identify potential new epitopes. Since our previous studies showed that ABC reacts with HLA B*57:01, we initially focused on HLA-B*57:01 restricted epitopes with a W to V substitution at the C-terminal position in the presence of

In keeping with the altered peptide repertoire model, ABC incubation of 30 minutes or less decreased T-cell reactivity to the VSFIEFVGW peptide, whereas ABC incubation of 60 minutes did not.

Screening for HLA-B*57:01 restricted CD8+ T-cell responses was performed by ELISPOT assay.

RESULTS

CONCLUSIONS

Four HLA-B*57:01 restricted EBV epitopes were characterized using a combination of binding and functional approaches with two of the epitopes confirmed by overlapping peptide screening approach.

This ABC-induced down-modulation occurred in a dose dependent manner, suggesting that drugs that bind non-covalently to HLA molecules may modulate immune responses.

•These findings suggest that small molecules such as ABC may non-covalently bind to HLA molecules and result in up or down modulation of functional HLA-B*57:01 restricted epitopes with a W to V substitution at the C-terminal position in the presence of ABC.

Correspondence: e.phillips@uwa.edu.au

Figure 1. Identification of abacavir binding to HLA-B*57:01

Figure 2. Effects of abacavir treatment on peptide specific ELISPOT responses

Figure 3. Titration of abacavir on VSFIEFVGW specific T-cell responses

Table 1. Abacavir sensitivity of HLA-B*57:01 restricted epitopes

Figure 4. Abacavir inhibits stimulated cytokine production of peptide specific T-cells

Table 2. C-terminal residue ABC treated and untreated cells. Two tailed Fisher’s exact test. All T-cell relevant controls for which two or more peptides were identified are listed.