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Broad CD8+ T cell receptor cross-recognition of distinct influenza A strains is facilitated by molecular mimicry in humans

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Newly-emerged and vaccine-mismatched influenza A viruses (IAVs) result in a rapid global spread of the virus due to minimal antibody-mediated immunity. In that case, established CD8+ T-cells can reduce disease severity. However, as mutations occur sporadically within immunogenic IAV-derived T-cell peptides, understanding of T-cell receptor (TCRab) cross-reactivity towards IAV variants is needed for a vaccine design. We investigated TCRab cross-strain recognition across IAV variants within two immunodominant human IAV-specific CD8+ T-cell epitopes, HLA-B*37:01-restricted NP338-346 (B37-NP338) and HLA-A*01:01-restricted NP44-52 (A1-NP44). We found high abundance of cross-reactive TCRab clonotypes recognizing distinct IAV variants. Structures of the wild-type and variant peptides presented revealed preserved conformation of the bound peptides. Structures of a cross-reactive TCR-HLA-B37-NP338 complex suggest that molecular mimicry underpins TCR cross-reactivity towards the mutated variants. Overall, cross-reactive CD8+ T-cell responses, underpinned by molecular mimicry, facilitate recognition of distinct IAV variants, thus CD8+ T-cell targeted vaccines could provide protection across different IAV strains.

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