# Spliced HLA bound peptides; a Black-Swan event in Immunology

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January 4, 2021

## Abstract

Peptides that bind to and are presented on the cell surface by Human Leukocyte Antigens (HLA) molecules play a critical role in adaptive immunity. For a long time, it was believed all of the HLA bound peptides were generated through simple proteolysis of linear sequences of cellular proteins, and therefore, are templated in the genome and proteome. However, evidence for untemplated peptide ligands of HLA molecules has accumulated over the last two decades, with a recent global analysis of HLA-bound peptides suggesting that a considerable proportion of HLA bound peptides are potentially generated through splicing/fusion of discontinuous peptide segments from one or two distinct proteins. In this review, we will review recent discoveries and debates on the contribution of spliced peptides to the HLA class I immunopeptidome, consider biochemical rules for splicing, and the potential role of these spliced peptides in immune recognition.

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