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Proteogenomics and immunopeptidomics for the development of personalized cancer immunotherapy

The remarkable clinical efficacy of the immune checkpoint blockade therapies has motivated researchers to discover immunogenic epitopes and exploit them for personalized vaccines and T cell based therapies. We and others have shown that the direct identification of tissue-derived immunogenic mutated neoantigens by mass spectrometry (MS) is feasible. In contrast to the private mutated neoantigens, tumor-specific antigens that are shared across patients may be more attractive for immunotherapy.

We have developed a novel analytical pipeline that can precisely characterize the non-canonical HLA binding peptide repertoire. The workflow incorporates whole exome sequencing, both bulk and single cell transcriptomics, ribosome profiling, and a combination of two MS/MS search tools with group-specific false discovery rate calculations for accurate HLAp identification. We identified more than 400 non-canonical HLAp derived from the expressed lncRNAs, transposable elements and alternative open reading frames. Several non-canonical HLAIp were experimentally confirmed to be shared across tumors through targeted MS, by which synthetic heavy isotope-labelled peptides were spiked into the peptidomic sample. Furthermore, we confirmed the immunogenicity of non-canonical peptide derived from an open reading frame downstream of the melanoma stem cell marker gene ABCB5. This analytical platform holds great promise for the discovery of novel cancer antigens for cancer immunotherapy.