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Rigidification of MHC-I/peptide complexes is an essential step for enhanced T cell recognition of cancer-associated neo-epitopes associated with impaired processing

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MHC-I down-regulation represents a significant challenge for T cell-based immunotherapy. T cell epitopes associated with impaired peptide processing (TEIPP) constitute a novel category of immunogenic neo-antigens that are selectively presented on TAP-deficient cells. TEIPP neo-epitopes are CD8 T cell targets, derived from non-mutated self-proteins. We recently evaluated thymus selection and peripheral behavior of TEIPP-specific T cells and demonstrated that TEIPP-specific T cells in TAP-deficient mice are deleted by central tolerance, while the same T cells in WT mice are naive and sustain. Thus the results of this study suggest that TEIPPs have potential to be successful targets for eliminating MHC-low tumors and reduce cancer immune escape. The crystal structure of H-2D^b in complex with the first identified TEIPP antigen Trh4 (MCLRMTAVM) demonstrated that, in contrast to prototypic H-2D^b peptides, Trh4 takes a non-canonical binding pattern with extensive sulfur-π interactions. Importantly, the non-canonical methionine at peptide position 5 acts as a main anchor, altering the conformation of H-2D^b residues and thereby forming a unique MHC/peptide conformer that is essential for recognition by TEIPP-specific T cells. We have previously demonstrated that modification of peptide position 3 to a proline in H-2D^b-binding peptides increases significantly the overall stability of MHC-I/peptide complexes and the immunogenicity of endogenous T cells towards cancer-associated epitopes. The results demonstrate that vaccination with Trh4-p3P induced significant CTL responses towards Trh4$^+$-cancer target cells. Importantly, our results stand in strong contrast to the current dogma that stipulates that higher immunogenicity is directly linked to higher MHC/peptide complex stability. Indeed, although much more immunogenic, the H-2D^b/Trh4-p3P complex is clearly less stable than H-2D^b/Thr4. Instead, rigidification of Trh4 and the α2 helix in H-2D^b is directly responsible for enhanced TCR recognition. Our results reveal the importance of the rigidification of the MHC/peptide complex for enhanced T cell recognition.

Biography

Adnane Achour has experience in both Structural Biology and Immunology. The research group uses X-ray crystallography and small angle X-ray scattering (SAXS) to study receptor-ligand interactions between T or NK cell receptors and Major Histocompatibility Complex (MHC) molecules, as well as bacterial adhesins and virulence-associated molecules. All the studies are complemented by a wide array of immunological assays as well as an extensive amount of biochemical techniques, including surface plasmon resonance and circular dichroism. By understanding the structural details of proteins, we can probe their function and potentially design artificial ligands that could modulate their function and activity.

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