



**Karolinska
Institutet**

Institutionen för medicin, Huddinge

MHC-CLASS I RESTRICTED PEPTIDE- BASED IMMUNOMODULATION OF CD8⁺ T AND NK CELLS

AKADEMISK AVHANDLING

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av

Adil Doganay Duru

Huvudhandledare:

Docent Adnane Achour
Karolinska Institutet
Institutionen för medicin, Huddinge

Bihandledare:

Professor Klas Kärre
Karolinska Institutet
Institutionen för mikrobiologi, tumör- och
cellbiologi

Docent Michael Uhlin
Karolinska Institutet
Institutionen för laboratoriemedicin

Docent Jacob Odeberg
Karolinska Institutet
Institutionen för medicin, Solna

Fakultetsopponent:

Docent Sebastian Springer
Jacobs University Bremen, Germany
School of Engineering & Science

Betygsnämnd:

Docent Vivianne Malmström
Karolinska Institutet
Institutionen för medicin, Solna

Docent Doreen Dobritzsch
Karolinska Institutet
Institutionen för medicinsk biokemi och
biofysik

Docent Amelie Eriksson Kalström
Kungliga Tekniska Högskolan
Skolan för bioteknologi

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ABSTRACT

The main aims of the immune system are to protect the host from potential threats by distinguishing self from non-self and altered-self. T cells and NK cells play a key role in the identification and elimination of threats by scanning a repertoire of peptide epitopes presented by major histocompatibility complex (MHC) molecules. Thus, MHC molecules play a pivotal role in the initiation and/or modulation of both T and NK cell effector functions, acting as 'windows' of the cells presenting their inner condition. This thesis focuses on the molecular interactions between T cell receptors (TCRs), NK cell receptors (NKR) and MHC class I molecules (MHC-I). The presented results demonstrate that it is possible to efficiently manipulate T and NK cell responses through MHC-restricted epitopes and altered peptide ligands (APL).

Primarily, our investigations of the potential impact of post-translationally modified (PTM) peptides on immunosurveillance revealed the first structural and biochemical evidence for how nitrotyrosinated neoantigens may enable viral escape from immune recognition, as well as break immune tolerance by either impairing MHC/peptide complex (pMHC) stability and/or altering interactions with the TCR surface.

Moreover, structural alterations can change the biochemistry of TCR-pMHC interactions, which may affect the immunogenicity of altered peptide ligands (APLs). We demonstrated that a TCR specific for an immunodominant epitope makes use of a different thermodynamic strategy to cross-react with a weak agonist APL in order to adapt to structural modifications in the pMHC. Thus, understanding the molecular constraints of TCR interactions with MHC-restricted epitopes and APLs is essential to develop novel approaches to modulate T cell responses and to achieve "T cell cross-reactivity", which is the main objective of designing APLs targeting viral and tumor-associated antigens.

Additionally, we have demonstrated that it is possible to modulate T cell responses through the use of an unconventional peptide modification strategy that systematically targets evolutionarily conserved residues of the MHC in order to improve pMHC stability and thus immunogenicity. Importantly, introduced modifications efficiently improved the immunogenicity of a viral escape epitope and immunization with the modified epitope generated distinct and focused cross-reactive T cell populations against the original peptide. Thus, targeting evolutionarily conserved residues of MHC provides a novel approach to optimize MHC-I restricted epitopes for future anti-viral or -tumor vaccines.

Finally, our findings suggest that, in interactions between NK cells and normal cells, MHC-I is in most cases expressed in excess ensuring self-tolerance and preventing autoimmunity. More interestingly, we demonstrated that NK cell activation can be modulated through the use of MHC-I restricted peptides. This may have future implications in attempts to sensitize the immune system against previously inert targets, which stands out as an important outcome in the frame of this thesis.