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ERAP1-ERAP2 dimers trim MHC I-bound precursor peptides: Understanding peptide editing

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Statement of the Problem: The human endoplasmic reticulum amino peptidase 1 (ERAP1) and ERAP2 are critically important in the final processing of MHC class I antigens in the endoplasmic reticulum. To date, the molecular context of peptide trimming by ERAPs and how ERAPs shape antigen repertoires remains open questions.

Methodology: Using a cell-free system composed of ERAP1 and ERAP2 heterodimers (ERAP1/2), MHC class I molecules and N-terminally extended model and natural peptides, we characterized the function of ERAP1/2.

Findings: We provide evidence that ERAP1/2 trims MHC I-bound precursor peptides to the final lengths, albeit more slowly than the corresponding free precursors. We show that trimming of MHC I-bound precursors by ERAP1/2 increases the conformational stability of MHC I/peptide complexes.

Conclusion & Significance: Our study provides new findings on ERAP1/2 as a key antigen processing complex. From our data, we propose a molecular mechanistic model of ERAP1/2 as an editor of class I antigens. Understanding class I antigen processing is significant given the role that class I antigens play in the normal recognition of virally infected and transformed cells by CD8+ T cells.

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Controlling TH17 cells in inflammation and carcinogenesis

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Statement of the Problem: The incidence and prevalence of immune mediated inflammatory diseases (IMIDs) are steadily increasing. Unfortunately, most therapies used against these diseases have as of yet palliative character and mostly do not offer a cure. Thus, life-long treatment using immune-suppressive agents is required in the majority of cases. As a consequence, patients with IMID must live with the side effects of these treatments, such as increased risk of opportunistic infections and of relapsing flares of the disease itself. Furthermore, chronic inflammation, another possible side effect, can promote the development of certain forms of cancer. Therefore, there is major need for new therapies, which can modulate the immune response more specifically.

Theoretical Orientation: TH17 cells and their associated cytokines play an important but ambiguous role in these diseases. On one hand they play a key role in chronic inflammatory diseases and carcinogenesis. On the other hand, however TH17 cells and their cytokine products, such as IL-22, also have beneficial properties such as promotion of wound healing and defence against pathogens. This obviously reveals that it is crucial to find out the molecular and cellular mechanisms which physiologically control TH17 cells in order to not just simply deplete them, but rather reset them to their beneficial state. We have indeed already identified several mechanisms, which explain how TH17 cells and their cytokines can be physiologically controlled (Figure 1). Of note, the intestine plays a key role during this regulation.

Conclusion & Significance: Our data indicated that TH17 cells can be controlled in the intestine. Our aim is to furthermore understand the involved mechanism.

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