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ERAAP modulation
A possible novel strategy for cancer immunotherapy?

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Recent findings demonstrate that loss of ERAAP, an endoplasmic reticulum aminopeptidase involved in antigen processing, plays a key role in stimulating anti-tumor innate and adaptive immune responses. We show that MHC class I molecules produced in the absence of ERAAP retain their capability of presenting antigens to CD8+ T cells, but not of inhibiting NK cells.

The major histocompatibility complex class I (MHC I) antigen-processing pathway produces peptides from intracellular proteins and present them at the cell surface for recognition by Natural Killer (NK) cells and CD8+ T cells.[1] Precursor peptides are generated in the cytoplasm and translocated to the endoplasmic reticulum (ER) where they are further processed by ER aminopeptidases, i.e., ERAAP in mice[2] and ERAP1 and ERAP2 in humans,[3-5] before being assembled with MHC I molecules.

MHC I molecules 'preferentially' bind peptides of 8–10 amino acids. The length restriction is imposed by a conserved network of hydrogen bonds on MHC I residues. Thus, binding of longer peptides compromises the stability of peptide-MHC I (pMHC I) complexes.

ERAAP is critical in presentation of antigen to CD8+ T cells, since many peptides delivered by the transporter associated with antigen processing (TAP) exceed the optimal length for binding to MHC I molecules. Immunization of ERAAP-deficient mice with cells from wild-type mice, or vice versa, resulted in potent CD8+ T-cell responses,[6,7] suggesting that loss of ERAAP alters the composition of pMHC I repertoire. Consistent with these findings, mass spectrometry analysis revealed a marked increase in the length of endogenous peptides presented by MHC I molecules in mice lacking ERAAP.[8] However, whether ERAAP-dependent pMHC I alterations affect host immune responses against tumors is still unknown.

To address this question, we stably suppressed ERAAP expression in the murine T-cell lymphoma RMA by siRNA and evaluated the relevance of the loss of ER peptide trimming on tumorigenicity. We demonstrated that ERAAP silencing results in tumor rejection in syngeneic mice by triggering NK cell, and subsequently T cell (CD4+ and CD8+) anti-tumor responses.[9] This rejection was mainly due to an immediate NK cell response and depends on the MHC I peptide presented by ERAAP-silenced RMA cells, because replacement of the endogenous peptides with a high-affinity peptide with optimal length was sufficient to restore an NK-protective effect of MHC I through the NK inhibitory receptor Ly49C/I.[9]

NK cells were clearly the major players in the control of tumor growth, not only because in vivo depletion of host NK cells restored the growth of ERAAP-silenced RMA cells, but also because the immediate burst of NK-mediated apoptotic death leading to tumor clearance in vivo began just 4 hours following tumor inoculation, a delay that is not consistent with any adaptive host response. On the other hand, in vivo depletion of host CD4+ or CD8+ T cells results in delayed tumor growth and death of 40–20% of mice, respectively.[9] These results fit well with the hypothesis that CD4+ and CD8+ effectors are involved in the control of tumor cells that have escaped NK cells surveillance.

In summary, we provided the first demonstration that the experimental modulation of ERAAP interferes with tumor immunogenicity, in spite of the relatively modest impact on overall MHC I expression. This increased immunogenicity is largely due to the enhanced susceptibility of ERAAP-interfered cells to NK cell-mediated lysis as a consequence of impaired interaction between Ly49C/I and MHC I molecules. Thus, ERAAP inhibition, like MHC I downregulation, is able to shift the balance of activating and inhibitory signals towards NK cell activation resulting in target cell killing (**Fig. 1**).

It will be of interest to determine whether in humans, as shown in mice, manipulation of ER aminopeptidases could induce immune-mediated control of cancer. Notably, the possibility of targeting ER aminopeptidases might provide innovative immunotherapies in human cancer.

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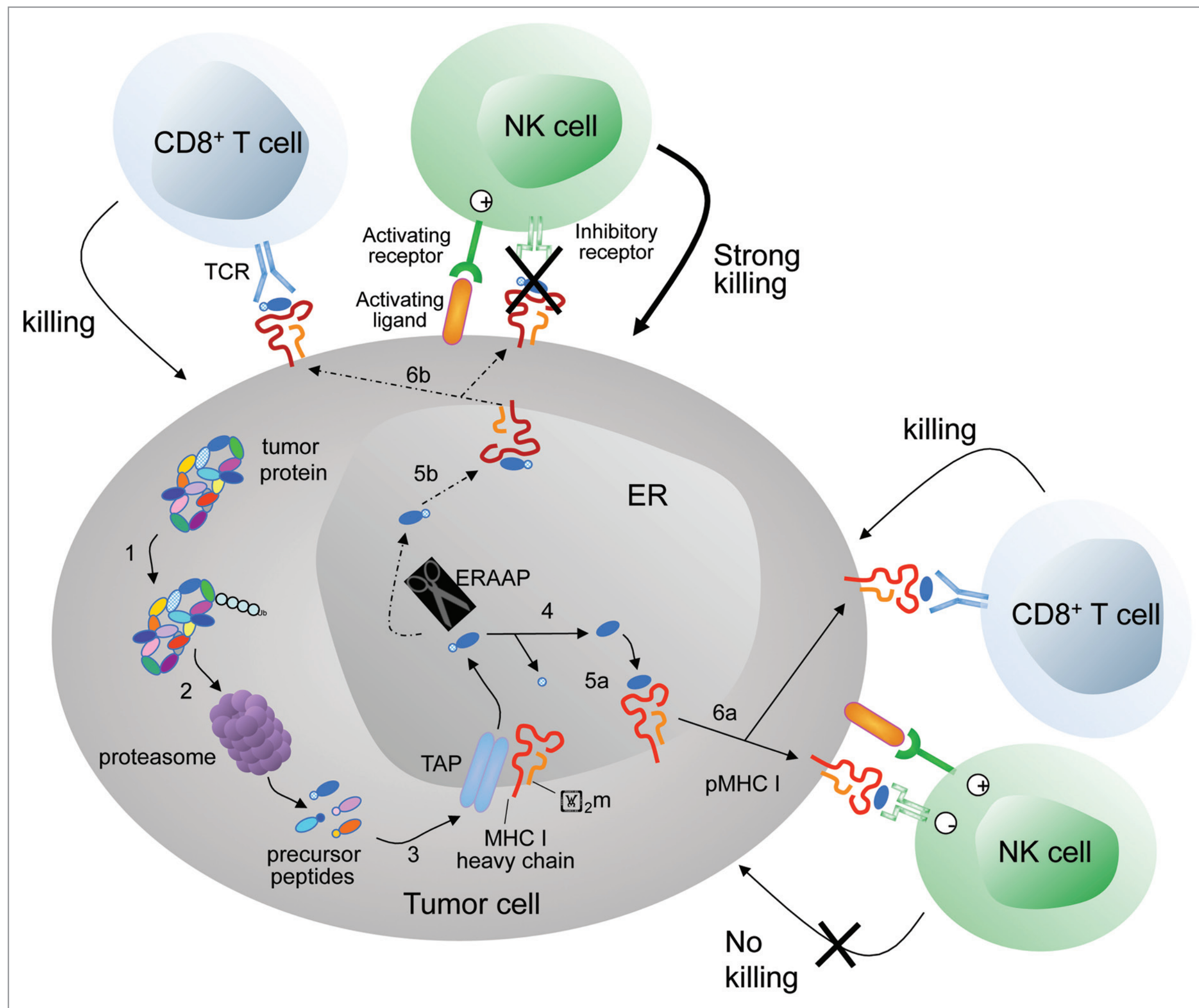

Figure 1. Activation of NK cells by ERAAP-silenced cells. Proteins that are synthesized in the cell are polyubiquitinated in the cytoplasm (1) and degraded by the proteasomes together with additional cytosolic proteases (2). The peptides that are produced are either of the ideal length for binding to MHC class I (MHC I) molecules or are amino-terminally extended precursors. TAP transports peptides into the endoplasmic reticulum (ER) (3) where they are further trimmed at the N-terminus by ER aminopeptidases (4), i.e., ERAAP in mice and ERAP1 and ERAP2 in human. Peptides with the appropriate length and MHC I binding motif are loaded onto MHC I molecules (5a). The binding of peptides with high affinity to the MHC I heavy chain-$\beta_2$microglubulin (β_2m) complex induces a final folding and allows the peptide-MHC I complexes (pMHC I) to exit from the ER to the plasma membrane (6a) where they are recognized by T cells antigen receptors (TCR) on CD8+ T cells and by inhibitory receptors on NK cells. In the absence of ERAAP, a distinct repertoire of pMHC I complexes is produced and exported to the cell membrane (5b and 6b). These unstable complexes are sufficiently conformed to present antigens to CD8+ T cells but not enough to inhibit NK cells. Thus, inhibition of ERAAP shifts the balance of activating and inhibitory signals towards NK cell activation and induction of cytolytic effector functions resulting in target-cell killing.

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