ERAP1 as a regulator of the immunopeptidome, proteome and cellular homeostasis of cancer cells

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Endoplasmic reticulum aminopeptidase 1 (ERAP1) metabolizes peptides inside the ER and shapes the peptide repertoire available for binding to Major Histocompatibility Complex Class I molecules (MHC-I), also known as the immunopeptidome. Moreover, it may have additional effects on cellular homeostasis, which have not been thoroughly explored. To address these questions, we utilized genetic silencing of ERAP1 expression as well as a selective allosteric ERAP1 inhibitor to probe changes in the immunopeptidome and proteome of the A375 melanoma cancer cell line. We observed significant immunopeptidome shifts for both methods of ERAP1 functional disruption, which were distinct for each method. Both methods of inhibition led to mild enhancement of cancer cell killing by stimulated human PBMCs from a healthy donor. ERAP1 functional disruption also resulted in significant proteomic alterations in pathways related to metabolism and cellular stress. Similar proteomic changes were also observed in the leukemia cell line THP-1. Biochemical analyses suggested that ERAP1 inhibition affected endoplasmic reticulum stress, reactive oxygen species production and mitochondrial metabolism. Although the proteomics shifts were significant, their potential in shaping immunopeptidome shifts was limited since only 15.8% of differentially presented peptides belonged to proteins with altered expression and 5.0% of proteins with altered expression were represented in the immunopeptidome shifts. Taken together, our findings suggest that modulation of ERAP1 activity can generate unique immunopeptidomes, primarily due to altered peptide processing in the ER, but also induce changes in the cellular proteome and metabolic state which may have additional effects on cancer cells.

References:

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