TARGETING ENDOPLASMIC RETICULUM STRESS-RESPONSIVE PERK IN MELANOMA ELICITS PARAPOTOSIS-MEDIATED IMMUNOGENIC CELL DEATH AND INDUCTION OF TYPE I INTERFERON-DEPENDENT ADAPTIVE ANTITUMOR IMMUNITY

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Background In order to survive the hostile tumor microenvironment, cancer cells activate endoplasmic reticulum (ER) stress-associated response proteins, including the protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK). Although intrinsic adaptation to chronic ER stress via PERK has been reported to limit the antitumor potential of immune cells, whether PERK activation in melanoma cancer cells contributes to immune evasion remains poorly understood and therapeutically untargeted.

Methods To establish the mechanistic role and therapeutic potential of targeting PERK in melanoma, we utilized both genetic and pharmacological approaches in both syngeneic transplantable and autochthonous inducible melanoma murine models. To substantiate these findings in a clinical context, we also leveraged bioinformatic interrogation of multiple independent human cohorts and tissue microarray analysis of human melanoma samples.

Results After the elimination or inhibition of PERK, melanoma cells undergoing ER stress activated a process characterized by the accumulation of misfolded proteins, ER enlargement, massive cytoplasmic vacuolation, and elevation of reactive oxygen species, which culminated in paraptosis and release of immunogenic cell death (ICD) mediators. Induction of paraptosis in PERK-ablated melanoma cells was dependent on factor SEC61b. Injection of PERK-null melanoma cells into mice or treatment of melanoma-bearing mice with PERK inhibitors resulted in the accumulation of ICD mediators, dramatic anti-tumor responses, robust protective T cell immunity, and activation of abscopal responses. Notably, we detected the expansion of monocyte-derived dendritic cells (MoDC) in PERK-null tumor beds, which produced Type I IFNs in response to the accumulated ICD mediators. Subsequently, MoDC-derived IFNB1 directed CCR2 driven recruitment of splenic common monocyte progenitors (cMoPs) which further developed into MoDCs and perpetuated the development of anti-tumor immunity. Blockade of Type I IFN receptor, elimination of IFNb, or deletion of STAT1, prevented the differentiation of cMoPs into MoDC. Additional studies in human settings substantiated the clinical impact of the activation of PERK signaling in melanoma. Higher expression of active PERK in cancer cells from human melanoma tumors correlated with limited intra-tumoral T cell frequency. In addition, elevated expression of a PERK-activation signature in different human melanoma cohorts corresponded to lower overall survival and impaired response to immunotherapy. Consistently, inhibition or ablation of PERK in murine melanoma tumors augmented response to checkpoint immunotherapy.

Conclusions Collectively, our findings underline the immunotherapeutic potential of targeting PERK in melanoma, support further development of ER-targeted treatment approaches in cancer and reinforce the benefit of combining ER-stress targeted therapies with checkpoint immunotherapy in cancer.