UPR activation in cancer cells promotes anti-cancer immune response through DPM1-dependent control of PD-L1 glycosylation.

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The tumor microenvironment (TME) is characterized by hostile conditions such as nutrient deprivation, hypoxia or acidosis. Exposure of immune and cancer cells to these conditions can compromise the endoplasmic reticulum (ER) protein homeostasis, leading to a cellular state called "**ER stress".** To restore the ER proteostasis, the sensing and response to ER stress is coordinated by the unfolded protein response (UPR), a signaling pathway governed by 3 ER stress sensors, among which IRE1-α is the most conserved. These UPR-mediated adaptations play a pro- or anti-tumorigenic role, underlying the lack of comprehensive understanding of how UPR may affect cancer development and anti-tumor immunity.

Recently, we established that moderate but chronic IRE1a activation resulted in reduced tumor expansion by inducing an anticancer immune response. To better uncover how IRE1-α mediates this effect, we characterized IRE1-α interactome using a proximity-dependent biotin identification system (BioID). Among the different partners identified, we selected DPM1, a key player in protein N- and O-glycosylation. For a rapid characterization of the functional efficiency of glycosylation in our cells, we used a newly modified version of the Halo Tag technology (a tool mainly used for protein labeling), in which a sequon of N-glycosylation was introduced to prevent its interaction with its ligand. When cells are incubated with an HaloTag **Oregon Green Ligand (G2801),** the appearance of Halo signals is a reliable marker of abnormal N-glycosylation. Our Results showed that DPM1 controlled the immunogenicity of tumoral cells. Indeed, we demonstrated in hot and cold tumor models that DPM1 KO prevented tumor growth only in the presence of a functional adaptive immune system (CD8+ T cells dependent). Mechanistically, DPM1 KO modulates the production of key cytokines and cell surface expression of PD-L1 (a major player in the control of adaptive immune response) through DPM1-dependent control of PD-L1 glycosylation by increasing its degradation through the ER Associated Degradation pathway. Therefore, DPM1 KO in cancer cells promotes M1 macrophages polarization overcoming immunosuppression and enhances cytotoxic T cell activity.

Thus, our work reveals how tumoral UPR can limit tumor growth and suggests that DPM1 inhibition is a promising strategy for improving cancer immunotherapy.