The role of Rab37 in exocytosis and the tumor microenvironment

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Main Text

Accumulating evidence indicates the implication of Rab small GTPase-mediated exocytosis in shaping the tumor microenvironment. We investigate the role of Rab37 in modulating tumor microenvironmental cells including macrophages and T cells, and develop neutralizing antibodies targeting the protumor secretory factors mediated by Rab37. We identify previously uncharacterized mechanisms by which Rab37 mediates exocytosis of interleukin 6 (IL-6) and chitinase 3-like-1 (CHI3L1) to promote STAT3 signaling and PD-1 expression in $CD8^+$ T cells, while Rab37 regulates ST2L (also known as IL-1 receptor like 1), the natural receptor of IL-33 to activate recruitment of tumor-associated macrophages. Importantly, Rab37 mediates intracellular trafficking and membrane presentation of PD-1 to sustain T cell exhaustion. However, glycosylation mutant PD-1 delays cargo recruitment to the Rab37 vesicles, thus stalling membrane presentation. Moreover, our newly developed CHI3L1 neutralizing antibody and ST2L/IL-33 blocking antibodies inhibited tumor growth and metastases *in vivo*. Lung cancer patients with high CHI3L1 plasma concentration correlated with poor survival. These studies advance our understanding of Rab37-mediated exocytosis and potential immunotherapies targeting the protumor secretory pathways for cancer treatment. Our recent findings on Rab37-mediated autophagy secretion will also be discussed.

Model