hRAB37 mediates exocytosis of thrombospondin 1 to suppress angiogenesis.

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Introduction: Our lab previously identified a novel Rab small GTPase protein, hRAB37, which plays critical roles in regulating exocytosis of secreted glycoproteins, thrombospondin 1 (TSP1) to suppress cancer metastasis. TSP1 is known to inhibit angiogenesis. However, the role of hRAB37 in regulating angiogenesis remains unclear. Purpose: Therefore, we aimed to investigate the interplay between the hRAB37 and tumor microenvironment focusing on endothelial cells motility and angiogenesis. Methods: We performed co-culture system by growing the human umbilical vein endothelial cells (HUVECs) with hRAB37-high expressing or hRAB37-low expressing cancer cells. Results and Discussion: The results showed that the HUVECs motility and tube formation ability were inhibited by co-culturing with hRAB37-high expressing cancer cells. Furthermore, the HUVECs motility recovered when co-cultured with hRAB37-high expressing cells knocking down of TSP1. Notably, the tube formation ability of HUVECs increased when cultured with the conditioned medium taken from TSP1 knockdown cells or from hRAB37-high expressing cells adding the TSP1 neutralized antibody. The in vivo xenograft data showed less infiltrated endothelial cells in tumor xenograft derived from hRAB37-high expressing xenograft compared with hRAB37-low expressing xenograft by immunohistochemistry analysis. These results suggested that the HUVECs motility and tube formation ability are inhibited by hRAB37, in part by exocytosis of TSP1, a known anti-angiogenesis factor. Clinically, the correlation between high hRAB37 protein expression, high TSP1 secretion, and low angiogenesis marker expression can be observed in clinical samples from esophageal cancer patients. Conclusion: Our results provide evidence of interplay between hRAB37, TSP1 and endothelial cells in regulation of angiogenesis.