A RAB5/RAB4 recycling circuitry induces a proteolytic invasive program and promotes tumor dissemination

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ABSTRACT
The mechanisms by which tumor cells metastasize and the role of endocytic proteins in this process are not well understood. We report that overexpression of the GTPase RAB5A, a master regulator of endocytosis, is predictive of aggressive behavior and metastatic ability in human breast cancers. RAB5A is necessary and sufficient to promote local invasion and distant dissemination of various mammary and non-mammary tumor cell lines, and this pro-metastatic behavior is associated with increased intratumoral cell motility. Specifically, RAB5 is necessary for the formation of invadosomes, membrane protrusions specialized in extracellular matrix (ECM) degradation. RAB5A promotes RAB4- and RABENOSYN-5-dependent endo/exocytic cycles (EECs) of critical cargos (MT1-MMP and ß3 integrin) required for invadosome formation in response to motogenic stimuli. This trafficking circuitry is necessary for spatially localized HGF/MET signaling that drives invasive, proteolysis-dependent chemotaxis in vitro and for conversion of ductal carcinoma in situ to invasive ductal carcinoma in vivo. Thus, RAB5A/RAB4 EECs promote tumor dissemination by controlling a proteolytic, mesenchymal invasive program.