Role of Rap1 in Angiogenesis and Tumor Invasion

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Abstract:

Rap1a and Rap1b are two closely related members of the Ras family of small GTPases. Despite their high sequence similarity, the two proteins serve non-redundant functions in cells and organs. Rap1a plays critical roles during mouse development, and both Rap1a and Rap1b are required for angiogenesis. In glioblastoma cells, however, Rap1b plays a more unique role in tumor cell invasion. Loss of rap1a in mice resulted in 40% embryonic lethality, and caused cardiac defects in mouse embryos and cardiac hypertrophy in adult mice. These phenotypes, distinct from those of the rap1b knockout mice, suggest differential roles of the two GTPases during mouse development. Angiogenesis, the formation of new blood vessels by endothelial cells, is impaired by the loss of rap1. Blood vessel growth into FGF2-containing Matrigel plugs was absent from rap1a-/- mice and aortic rings derived from rap1a-/- mice failed to sprout primitive endothelial tubes in response to FGF2 when embedded in Matrigel. Knocking down of either rap1a or rap1b in human micro-vascular endothelial cells (HMVECs) confirmed that Rap1 plays key roles in endothelial cell function. The knockdown of rap1a or 1b resulted in decreased adhesion to extracellular matrices and impaired cell migration. Rap1 deficient endothelial cells failed to form 3-D tubular structures when plated on Matrigel in vitro. The activation of ERK, p38, and Rac, important signaling molecules in angiogenesis, were all reduced in response to FGF2 when either Rap1 protein was depleted. In U373 human glioblastoma multiforme cells, depletion of rap1b, but not rap1a drastically reduced tumor cell invasion by decreasing the activity of secreted

matrix metalloproteinase 2 (MMP2). The adhesion of cells to the extracellular matrices collagen or fibronectin, but not to vitronectin, was decreased upon rap1b depletion. However, a mild increase in proliferation associated with elevation in ERK1/2, p38, Akt and ribosomal S6 protein activation was observed in cells depleted of either rap1a or rap1b. When an MEK1/2 inhibitor U0126 was used, the phosphorylation of p38, Akt and S6 were decreased, however, to various levels, suggesting complex regulatory pathways mediate Rap1 action in glioblastoma cells.

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