A role of Agrin in maintaining the stability of vascular endothelial growth factor receptor-2 during tumor angiogenesis

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Abstract

Endothelial cell (EC) recruitment is central to the vascularization of tumors. Though several proteoglycans have been implicated in cancer and angiogenesis, their roles in EC recruitment and vascularization during tumorigenesis remain poorly understood. Here we reveal that Agrin which is secreted in liver cancer promotes angiogenesis by recruiting ECs within tumors and metastatic lesions and facilitates adhesion of cancer cells to ECs. In ECs, Agrin-induced angiogenesis and adherence to cancer cells are mediated by Integrin-β1, Lrp4-MuSK pathways involving focal adhesion kinase. Mechanistically, we uncover that Agrin regulates VEGFR2 levels that sustain the angiogenic property of ECs and adherence to cancer cells. Agrin attributes an ECM stiffness-based stabilization of VEGFR2 by enhancing interactions with Integrin-β1-Lrp4 and additionally stimulates endothelial Nitric-oxide synthase (e-NOS) signaling. Therefore, we propose that cross-talk between Agrin expressing cancer and endothelial cells favor angiogenesis via sustaining the VEGFR2 pathway.

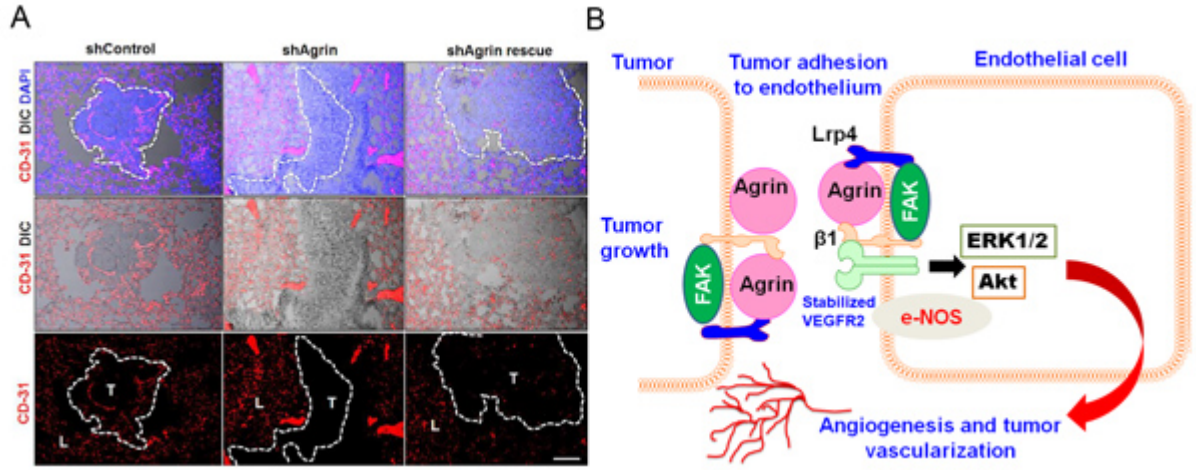

Figure Legend: Agrin signaling network in tumor angiogenesis.
(A) Agrin recruits blood vessels (red) within metastatic tumors (T) (dashed lines) colonizing mice lungs (L)
(B) Schematic showing Agrin crosstalk between HCC and endothelial cells regulating angiogenesis