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The PVRL4 encoded gene Nectin-4 promotes breast cancer induced angiogenesis via. endothelial integrin-β4

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Cancer stem cells secrete diffusible factors into the microenvironment that bind to specific endothelial cell receptors and initiate an angiogenesis cascade. Tumor-induced angiogenesis is an important parameter of tumorigenesis and is critical for tumor growth and metastasis. A PVRL-4 encoded gene, Nectin-4, has potential roles in cancer cell growth and aggressiveness and it is only expressed in cancer cells. There is evidence that Nectin-4 plays a role in tumorigenesis, but the function of Nectin-4 in tumor angiogenesis has lacked thorough evidence of mechanism. Using highly metastatic breast cancer cells and Human Umbilical Vein Endothelial Cells (HUVECs), we have developed an excellent angiogenesis model and systematically studied the contribution of Nectin-4 to angiogenesis. We also provide in-depth *in ovo, in vivo* and *in vivo* evidence that Nectin-4 causes angiogenesis and propose that Nectin-4 is an angiogenesis biomarker in breast cancer. Following hypoxia, the expression of ADAM-17 in Metastatic Breast Cancer Stem Cells (mBCSCs) causes the shedding of the ecto-domain of Nectin-4 into the microenvironment, which physically interacts with integrin-β4 specifically on endothelial cells. This interaction promotes angiogenesis via. the Src, PI3K, AKT, iNOS pathway and not by Phospho-Erk or NF-κβ pathways. *In vitro, in ovo* and *in vivo* induction and abrogation of an angiogenesis cascade in the presence and absence of the Nectin-4 ecto-domain, respectively, confirms its role in angiogenesis. Thus, disrupting the interaction between Nectin-4 ecto-domain and integrin-β4 may provide a means of targeting mBCSC-induced angiogenesis.

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