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FOXO1/Sprouty-2 pathway inhibits endothelial cell tumor growth

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Vascular tumors are neoplasms of endothelial cell origin and have a wide spectrum of clinical presentations, ranging from benign infantile hemangiomas in children to low-grade malignant hemangioendotheliomas and highly aggressive angiosarcomas in adults. To date, the molecular basis of vascular tumor pathogenesis is poorly understood and standard therapy for these tumors has limited clinical efficacy. Forkhead box protein O1 (*FOXO1*) is a transcription factor with tumor suppressor function and is dysregulated in human cancer. In this study, we showed that *FOXO1* suppressed vascular tumor growth, and mechanistically, the inhibitory effects of *FOXO1* are mediated by Sprouty2. *FOXO1* expression was reduced in a variety of human vascular tumors examined. Knockdown of *FOXO1* gene expression with short hairpin RNA resulted in increased vascular tumor cell migration and proliferation in vitro and in vivo animal models. Conversely, over-expression of constitutively active *FOXO1* in these cells suppressed cell growth. We observed that *FOXO1* interacted with Sprouty2 promoter in situ in chromatin immunoprecipitation assay and increased Sprouty2 gene expression in tumor cells. Like FOXO1, Sprouty2 expression was reduced in vascular tumors. Over-expression of Sprouty2 decreased tumor cell growth and migration. Conversely, knockdown of Sprouty2 increased tumor growth in vitro and in vivo. Knockdown of Sprouty2 in cells with over-expression of constitutively active *FOXO1* resulted in reduced tumor growth and rescued the *FOXO1* phenotype, indicating that Sprouty2 is an important mediator of the biological effects of FOXO1. Microarray gene expression profiling of human angiosarcoma cells with Sprouty2 knockdown together with network data integration using bioinformatics analysis revealed important Sprouty2-regulated genes that are involved in angiogenesis, apoptosis and growth signal transduction pathways. In summary, these findings demonstrate important growth regulatory role of the FOXO1/Sprouty2 pathway in endothelial cell tumors and highlight the potential roles of novel pathways downstream of Sprouty2 in these lesions.

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