Serine-glycine metabolism drives VEGFR2 modulated tumorigenesis

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Vascular endothelial growth factor receptor 2 (VEGFR2) is a classical receptor tyrosine kinase (RTK) expressed in several tumors where it regulates proliferation, migration and metabolism. Despite VEGFR2 representing an attractive therapeutic target, the clinical application of tyrosine kinase inhibitors has shown limited responses and rapid development of resistance. Recently, our laboratory demonstrated that inactive VEGFR2 leads to tumor growth and rewires metabolism. To elucidate this behavior, we expressed inactive VEGFR2R1032Q and VEGFR2S1100F mutants in human melanoma cells. Seahorse experiments revealed that the expression of inactive VEGFR2 induces to changes in energy metabolism. Moreover, metabolomics analyses on tumor xenografts of melanoma cells expressing wild-type and mutated VEGFR2 highlighted alterations in one-carbon metabolism. Transcriptomic analyses and qPCR confirmed the differential regulation of SHMT1, SHMT2, TYMS, ATIC and MTHFD2 in this metabolic pathway. Preliminary results indicate that serine supplementation promotes the proliferation and migration of cells expressing both VEGFR2R1032Q and VEGFR2S1100F mutants. Building upon these findings, we utilized SHIN1 as a potent inhibitor of Serine hydroxymethyltransferase. The inhibition of SHMT decrease the proliferation and migration of the Sk-Mel-31 cells expressing inactive VEGFR2 mutants. This study underscore serine-glycine-one-carbon metabolism as a downstream target of VEGFR2 dysregulation in melanoma cells, suggesting its involvement in tumor progression and positioning it as a promising therapeutic target.