PYRIMIDINE DE NOVO SYNTHESIS IN ENDOTHELIAL CELLS: AN OVERLOOKED TARGET?

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Tumors stimulate angiogenesis, generation of new blood vessels, to gain essential oxygen and nutrients. Angiogenesis is initiated by endothelial cells (ECs) that form the inner lining of blood vessels. In tumor vasculature, ECs rewire their metabolism to upregulate pyrimidine de novo synthesis. Whether this metabolic rewiring in tumor ECs supports angiogenesis or promotes tumor formation in any other way is unknown. For this reason, we disabled dihydroorotate dehydrogenase (DHODH), an enzyme essential for de novo pyrimidine synthesis and a target of anticancer therapy, in ECs in vitro and in vivo. DHODH deficiency in ECs decreased their angiogenic capacity in vitro and inducible DHODH ablation in the mouse endothelium reduced physiological angiogenesis in vivo, suggesting that pyrimidine synthesis in ECs supports angiogenesis. Surprisingly, despite reduced angiogenesis expected to compromise tumorigenicity, the endothelial DHODH deficiency accelerated the growth of syngeneic murine orthotopic lung tumors. Single cell transcriptomics and flow cytometry revealed major changes in the immune cell compartment of tumors from EC-specific DHODH KO mice. This suggests that anticancer therapies directed at DHODH may indirectly stimulate tumorigenesis via their impact on the ECs. We are currently in the process of identifying mechanism by which endothelial deficiency of pyrimidine synthesis affects immune landscape of tumors.