ANGIOGENESIS REVISITED: ROLE AND (THERAPEUTIC) IMPLICATIONS OF ENDOTHELIAL METABOLISM

Carmeliet P, MD, PhD

Laboratory of Angiogenesis and Vascular Metabolism, VIB-KU Leuven Center for Cancer Biology (CCB), Department of Oncology KU Leuven, Leuven, Belgium

The past 40 years of research in the angiogenesis field have focused on identifying genetic signals such as VEGF and Notch, which determine vessel sprouting. However, the role and therapeutic potential of targeting endothelial cell (EC) metabolism have been largely overlooked. We have recently reported that ECs are glycolysis addicted and that glycolysis importantly co-determine vessel sprouting downstream of VEGF and other pro-angiogenic signals. In addition, we documented that ECs are rather unique in utilizing fatty acid-derived carbons for the de novo synthesis of deoxyribonucleotides for DNA synthesis during EC proliferation when vessels sprout. Moreover, targeting (blocking) glycolysis and fatty acid oxidation inhibit pathological angiogenesis and induce tumor vessel normalization (thereby reducing metastasis and improving chemotherapy), suggesting that these metabolic pathways are new targets for anti-angiogenic drug development without evoking systemic side effects. Furthermore, lymphatic ECs differ from other EC subtypes in their metabolic requirements for lymphangiogenesis. Since many of these metabolic targets are pharmacologically druggable, these metabolic pathways represent a new promising target for therapeutic anti-angiogenesis.

References

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