Vascular Metabolomics
-- gene regulation and role of VEGF-B in tissue fatty acid uptake

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ABSTRACT

Vascular endothelial growth factor B (VEGF-B) belongs to the VEGF family, which constitutes of five mammalian members. VEGFs exert pivotal roles in the formation, development and maintenance of the vascular and lymphatic vessels. Unlike VEGF-A, the first VEGF discovered and a close homologue, VEGF-B is poorly angiogenic in most tissues and not regulated by hypoxia. Gene regulation and physiological function of VEGF-B remained obscure for more than a decade after its discovery.

We identified an unexpected high correlation of expression of Vegfb with a large cluster of nuclear-encoded mitochondrial genes. This high correlation is not shared by any other VEGF gene. Based on this finding, we were able to answer two fundamental questions in VEGF-B biology in this thesis work: gene regulation and role of VEGF-B.

In Paper I, we identified an unexpected role of VEGF-B in tissue fatty acid (FA) uptake. VEGF-B induces endothelial FA uptake through upregulation of two fatty acid transporter proteins (FATPs), namely FATP3 and FATP4. This regulation is dependent on the two known receptors for VEGF-B, VEGF receptor 1 (VEGFR1) and neuropilin 1 (NRP1), and it is unique among the three VEGFR1 ligands. Genetically modified mouse models that are deficient in VEGF-B signaling showed reduced lipid accumulation in peripheral tissues. In Vegfb knockout mice, FA uptake capacity in heart, skeletal muscle and brown adipose tissue was reduced. The resulted excess FA was diverted to white adipose tissue for storage. As a consequence, the glucose uptake capacity in the heart was drastically increased in Vegfb knockout mice.

In Paper II, we demonstrated that Vegfb is regulated by peroxisome proliferator activated receptor coactivator 1α (PGC-1α) through coactivation of estrogen-related receptor α (ERRα). Vegfb was upregulated in parallel with Pgc1α and mitochondrial genes upon nitric oxide simulation and serum deprivation in cells. ERRα, together with PGC-1α, strongly activated the Vegfb promoter in luciferase assay. It is known that muscle creatine kinase PGC-1α transgenic (MCK-PGC-1α TG) mice become insulin resistant on a high-fat-diet (HFD). Vegfb deficiency in HFD-fed MCK-PGC-1α TG mice greatly improved insulin sensitivity as well as other metabolic parameters. This improvement may be attributed to the reduction in muscular lipid accumulation.

PGC-1α and ERRα are known major regulators of mitochondrial biogenesis. In this thesis, we have elucidated that they also regulate VEGF-B expression and hence endothelial FA uptake in parallel. The two pathways are tightly coordinated to maintain a balance of FA β-oxidation and lipid homeostasis in the body. These findings have opened up new horizons for finding therapeutic targets in treating metabolic disorders such as type 2 diabetes.

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