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**Ludwig Institute for Cancer Research Ltd, Stockholm Branch
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Vascular Metabolomics -- gene regulation and role of VEGF-B in tissue fatty acid uptake

AKADEMISK AVHANDLING

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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 1 α (PGC-1 α) through coactivation of estrogen-related receptor α (ERR α). *Vegfb* was upregulated in parallel with *Pgc1 α* and mitochondrial genes upon nitric oxide simulation and serum deprivation in cells. ERR α , together with PGC-1 α , strongly activated the *Vegfb* promoter in luciferase assay. It is known that muscle creatine kinase PGC-1 α transgenic (MCK-PGC-1 α TG) mice become insulin resistant on a high-fat-diet (HFD). *Vegfb* deficiency in HFD-fed MCK-PGC-1 α 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-1 α and ERR α 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.