Ludwig Institute for Cancer Research Ltd. Stockholm branch
och Institutionen för Cell- och Molekylärbiologi
Karolinska Institutet, Stockholm, Sverige

Vascular Metabolomics –

Role of VEGF-B in fatty acid uptake and metabolic disease

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid
Karolinska Institutet offentligen försvaras i Hörsal Hillarp
Retziusväg 8

Fredagen den 15 april 2011 klockan 9.30

av

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Stockholm 2011

ABSTRACT

The incidence of type 2 diabetes and the metabolic syndrome is rapidly increasing among both adults and children worldwide. Type 2 diabetes is strongly associated with obesity and ectopic lipid accumulation. Recent research has shown that peripheral insulin sensitivity is directly impaired by excessive lipid deposition within tissues. Therefore, it would be highly beneficial to be able to control lipid uptake and accumulation in organs prone to developing insulin resistance. The role of the vasculature as a controlling barrier for FA uptake has not previously been explored in detail.

In **Paper I**, we describe an unexpected role for Vascular Endothelial Growth Factor B (VEGF-B) in the control and endothelial targeting of fatty acids to heart and muscle. VEGF-B signals in a paracrine fashion through its receptors present on vascular endothelial cells. We show that the expression of *Vegfb* is tightly co-regulated with the expression of nuclear-encoded mitochondrial genes. VEGF-B signalling to the endothelium upregulates the mRNA and protein levels of Fatty Acid Transport Proteins (FATPs). Increased vascular FATP-levels leads to subsequent uptake and transport of long chain fatty acids across the endothelium. Mice lacking VEGF-B, or its receptors, have lower endothelial expression of FATPs and show less accumulation of lipid droplets within peripheral tissues. We conclude that VEGF-B is part of a novel regulatory mechanism, whereby endothelial lipid uptake and mitochondrial lipid usage is tightly coordinated.

In **Paper II**, we show that inhibition of VEGF-B signalling protects against the development of insulin resistance in the *db*/*db* mouse model of type 2 diabetes. Genetic deletion of either one, or both, copies of *Vegfb* in *db*/*db* mice significantly reduces cardiac lipid deposition and leads to increased glucose usage. The *db*/*db*//*vegfb*$^{-/-}$ mice are protected against the development of hyperglycaemia, glucose intolerance and triglyceridemia. Pre-diabetic *db*/*db* mice receiving neutralising anti-VEGF-B antibodies similarly do not develop hyperglycaemia or triglyceridemia. Anti-VEGF-B treatment of mice with established diabetes prevents a further increase in blood glucose levels. The study shows that the endothelium can act as an efficient barrier against excessive nutrient uptake, even in a pathological context. Based on these results, we propose that targeting VEGF-B could be a future approach for treating peripheral insulin resistance and type 2 diabetes.

ISBN 978-91-7457-271-1