

Foxf2 and Foxc2, two transcription factors that regulate adipocyte metabolism

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- I. **Westergren R**, Nilsson D, Heglind M, Arani Z, Grande M, Cederberg A, Ahrén B, Enerback S. Overexpression of Foxf2 in adipose tissue is associated with lower levels of IRS1 and decreased glucose uptake in vivo. *Am J Physiol Endocrinol Metab.* 2010 Mar; 298(3): E548-54
- II. Kim JK, Kim HJ, Park SY, Cederberg A, **Westergren R**, Nilsson D, Higashimori T, Cho YR, Liu ZX, Dong J, Cline GW, Enerback S, Shulman GI. Development 132:2623-2632. Adipocyte-specific overexpression of FOXC2 prevents diet-induced increases in intramuscular fatty acyl CoA and insulin resistance. *Diabetes.* 2005 Jun; 54(6):1657-63
- III. Xue Y, Cao R, Nilsson D, Chen S, **Westergren R**, Hedlund EM, Martijn C, Rondahl L, Krauli P, Walum E, Enerback S, Cao Y. FOXC2 controls Ang-2 expression and modulates angiogenesis, vascular patterning, remodelling, and functions in adipose tissue. *Proc Natl Acad Sci U S A.* 2008 Jul 22; 105(29): 10167-72.



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Foxf2 and Foxc2, two transcription factors that regulate adipocyte metabolism

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Abstract

Type 2 diabetes is the most common metabolic disorder today and has reached epidemic proportions in many countries. Diet-induced insulin resistance plays a central role in the development of type 2 diabetes. Studies included in this thesis describe findings regarding two forkhead genes, *Foxf2* and *Foxc2*, and their involvement in the development of insulin resistance. We produced a mouse in which the forkhead factor FOXF2 is overexpressed in an adipose tissue-restricted fashion, such mice display induced insulin secretion in response to an intravenous glucose load. In addition we could demonstrate that adipocytes from FOXF2 transgenic mice have an impaired insulin-mediated glucose uptake. We argue this to be, at least in part, due to lower expression of insulin receptor substrate 1. Mice overexpressing forkhead factor FOXC2 in adipose tissue have previously been shown to be protected from diet-induced obesity and glucose intolerance. In hyperinsulinemic-euglycemic clamp experiments, we demonstrated that FOXC2 transgenic mice are protected from diet-induced insulin resistance in liver and skeletal muscle. Furthermore, on high-fat diet, FOXC2 transgenic mice displayed decreased intramuscular levels of fatty acyl CoA compared with wild-type littermates. Expansion and regression of adipose tissue requires continuous remodelling of the vasculature in order to meet demands of metabolism. We have shown that the adipose tissue of FOXC2 transgenic mice exhibit a higher vascular density and altered patterning of vascular smooth muscle cells and pericytes. Furthermore, we could show this, at least in part, to be dependent on the role of FOXC2 as a direct regulator of Angiopoietin 2.

Keywords: forkhead genes, *Foxc2*, *Foxf2*, *Irs1*, insulin signaling, glucose metabolism, insulin resistance, Ang-2, adipose tissue, angiogenesis.

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