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Forkhead genes in adipocytes and podocytes

Akademisk avhandling

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av

Daniel Nilsson

Fakultetsopponent: Professor Eva Degerman
Lunds universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. Kim JK, Kim HJ, Park SY, Cederberg A, Westergren R, Nilsson D, Higashimori T, Cho YR, Liu ZX, Dong J, Cline GW, Enerback S, and Shulman GI. Adipocyte-specific overexpression of FOXC2 prevents diet-induced increases in intramuscular fatty acyl CoA and insulin resistance. *Diabetes* 2005;54:1657-1663.

II. Xue Y, Cao R, Nilsson D, Chen S, Westergren R, Hedlund EM, Martijn C, Rondahl L, Krauli P, Walum E, Enerbäck S, and Cao Y. FOXC2 controls Ang-2 expression and modulates angiogenesis, vascular patterning, remodeling, and functions in adipose tissue. *Proc Natl Acad Sci U S A* 2008;105:10167-10172.

III. Westergren R, Nilsson D, Heglind M, Arani Z, Grände M, Cederberg A, Ahrén B, and Enerbäck 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;298:E548-554.

IV. Nilsson D, Heglind M, Arani Z, and Enerbäck S. Foxc2 is essential for proper podocyte function. *Manuscript*.

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Forkhead genes in adipocytes and podocytes

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Abstract

Forkhead genes are a family of transcription factors with important functions in development and metabolism. This thesis addresses tissue-specific functions of the two forkhead genes, *FOXC2* and *FOXF2*, using transgenic mouse models. Overexpression of either *FOXC2* or *FOXF2* in adipocytes resulted in opposing phenotypes in terms of insulin sensitivity. Induction of *FOXC2* increased insulin sensitivity and protected the mice against diet-induced insulin resistance based on results from hyperinsulinemic-euglycemic clamp. In addition, *FOXC2* induced the expression of ANGPT2, an angiogenic factor which in turn increased the vascular density in the adipose tissue and supported the adipocyte with increased capacity for energy supply and waste disposal. *FOXF2*, on the other hand, appeared to block insulin signaling in adipocytes by decreasing the expression of IRS1, an important component in the transduction of insulin signaling. Consistently, these mice displayed decreased insulin sensitivity in glucose and insulin tolerance tests. Finally, we generated mice with conditional deletion of *Foxc2* in podocytes and found that such deletion lead to severe proteinuria and kidney failure shortly after birth. Ultrastructural analyses revealed that the podocytes had lost their unique architecture of interdigitated foot processes, and instead, had developed microvilli structures that projected into the urinary space. In conclusion, these studies demonstrate important roles of *FOXC2* and *FOXF2* in insulin sensitivity and kidney function, roles that might also be relevant to human disease conditions.

Keywords: FOXC2, FOXF2, forkhead, transgenic animal, adipocyte, insulin signaling, insulin resistance, lipotoxicity, angiogenesis, ANGPT2, podocyte, proteinuria

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