Forkhead genes in adipocytes and podocytes

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten

   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.

    Walum E, Enerbäck S, and Cao Y. FOXC2 controls Ang-2 expression and modulates angiogenesis,
    vascular patterning, remodeling, and functions in adipose tissue.

    Overexpression of Foxf2 in adipose tissue is associated with lower levels of IRS1 and decreased
    glucose uptake in vivo.

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