WISP2 – A Novel Adipokine Related to Obesity and Insulin Resistance

Akademisk avhandling

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av

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II. Grünberg JR, Hammarstedt A, Hedjazifar S, Smith U. The novel secreted adipokine WNT1-inducible signaling pathway protein 2 (WISP2) is a mesenchymal cell activator of canonical WNT
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Type 2 diabetes mellitus (T2D) is increasing worldwide at an epidemic rate and is expected to reach 592 million afflicted individuals by 2035 as compared to 382 million in 2013. Obesity is a major risk factor for insulin resistance, defined as an impaired cellular effect of insulin, and this precedes the development of T2D. Around 85% of subjects with T2D are overweight or obese. However, the obesity-associated insulin resistance is not a direct consequence of an increased fat mass per se but rather a reduced ability to recruit new subcutaneous adipose cells following weight gain and the associated dysregulated, inflamed and insulin-resistant adipose tissue characterized by enlarged adipose cells (hypertrophic obesity).

The adipogenic potential of human pre-adipocytes differs between donors and this is related to cell size and maintained activation of WNT-signaling in precursor cells. The canonical WNT pathway allows the mesenchymal stem cells to proliferate and prevents them from committing to the adipocyte lineage. We identified a novel secreted “adipokine” induced by WNT activation, WNT1 inducible signaling pathway protein 2 (WISP2). WISP2 is preferentially expressed in mesenchymal precursor cells and links hypertrophic obesity with canonical WNT-signaling. We found transcriptional activation of \textit{WISP}-2 in the subcutaneous adipose tissue to be a marker of the obesity-associated metabolic complications including degree of insulin resistance, ectopic fat accumulation and hypertrophic obesity. Mechanistically, we found canonical WNT signaling/WISP2 to regulate adipogenic commitment and differentiation in two different ways; - intracellular WISP2 retains the PPARγ transcriptional activator ZFP423 in a cytosolic complex which, when dissociated by BMP4, allows nuclear entry of ZFP423, induction of PPARγ and commitment into the adipose lineage and; - as a secreted molecule, WISP2 enhances cell proliferation and inhibits adipocyte differentiation by activating canonical WNT signaling and, thereby, inhibiting PPARγ activation.

To investigate the effect of WISP2 in vivo, we generated a transgenic mouse model overexpressing WISP2 in the adipose tissue under the aP2-promoter. We found WISP2 to be secreted by the adipose tissue and present in serum. The mice had a similar body weight but were characterized by improved insulin sensitivity, increased circulating levels of adiponectin and the novel FAHFA lipids and increased \textit{Glut4} in both adipose tissue and skeletal muscle. They were also characterized by markers of increased mesenchymal stem cell growth and development with a markedly expanded BAT, a “healthy” hyperplastic subcutaneous adipose tissue and increased lean body mass. Serum from the Tg mice also increased the proliferation of both brown adipose precursor cells and the mesenchymal stem-like CH3T101/2 cells and this was inhibited by adding specific anti-WISP2 monoclonal antibodies to the serum.

Taken together, WISP2 is a novel secreted autocrine/endocrine regulator of mesenchymal stem cell growth and proliferation as well as their adipogenic commitment. There is important cross-talk between WISP2 and BMP4 in the regulation of adipogenic commitment and differentiation and BMP4 is also a regulator of \textit{WISP} transcriptional activation. WISP2 is a novel target in hypertrophic obesity and the Metabolic Syndrome.

**Keywords:** Adipose tissue; BMP4; Canonical WNT pathway; Insulin Resistance; Obesity; PPARγ; Type 2 Diabetes; WISP2

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