WISP2 – A Novel Adipokine Related to Obesity and Insulin Resistance

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs universitet kommer att försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborgs Universitet

Torsdagen den 19 mars 2015, kl. 9.00

av

John Grünberg

Fakultetsopponent: Professor Antonio Vidal-Puig,
Institute of Metabolic Science, University of Cambridge, United Kingdom

Avhandlingen baseras på följande arbeten:

I. Hammarstedt A, Hedjazifar S, Jenndahl L, Gogg S, Grünberg JR, Gustafson B, Klimcakova E, Stich V, Langin D, Laakso M, Smith U. **WISP2 regulates preadipocyte commitment and PPARγ activation by BMP4**
Proceedings of the National Academy of Sciences of the United States of America 2013; 110(7): 2563-2568

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**
Journal of Biological Chemistry 2014; 289(10), 6899-6907

III. Grünberg JR, Hoffmann JM, Hedjazifar S, Nerstedt A, Jenndahl L, Castellot J, Wei L, Movérare Skrtic S, Bäckhed F, Syed I, Saghetelian A, Kahn B, Hammarstedt A, Smith U. **Increased brown fat and insulin sensitivity in obese mice overexpressing WISP2 in the adipose tissue**
Manuscript

UNIVERSITY OF GOTHENBURG

Göteborg 2015

WISP2 – A Novel Adipokine Related to Obesity and Insulin Resistance

John Grünberg

The Lundberg Laboratory for Diabetes Research
The Sahlgrenska Academy at University of Gothenburg, Sweden

Type 2 diabetes mellitus (T2D) is increasing worldwide at an epidemic rate and is expected to reach 592 million inflicted 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 linage. 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 *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 to 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 *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 *WISP2* 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

ISBN: 978-91-628-9283-8 (print)
ISBN: 978-91-628-9323-1 (epub)
http://hdl.handle.net/2077/37992 Gothenburg 2015