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COMBESITY (Combat obesity) - von Willebrand factor A domain-containing protein 8 as a target for obesity and diabetes treatment

Almost 60 % of the European Union population is overweight, with around 25 % obese people. Increased body mass index (BMI) is a major risk factor for disorders such as type 2 diabetes, hypertension and cardiovascular diseases. Treatment of obesity mostly relies on active approaches (dietary changes, physical activity, bariatric surgery) that cannot be achieved in all individuals. Thus, therapies aimed at the conversion of white adipocytes into thermogenic beige adipocytes (a process called “browning”) represent approaches that might be useful for a larger group of individuals. Mitochondria and their dynamics (fusion and fission) participate in the browning process, but how they control it is not clear. We found that an uncharacterized mitochondrial protein, called von Willebrand factor A domain-containing protein 8 (Vwa8) associates with the key mitochondrial shape regulator Opa1 and is upregulated in high BMI individuals from a cohort of BMI-discordant homozygotic twins. We generated a mouse model where Vwa8 was deleted and found that surprisingly, the lack of Vwa8 led to browning of subcutaneous adipose tissue, improved insulin sensitivity, increased lean mass upon high fat diet and licensed mitochondrial fatty acid oxidation (FAO) in ad hoc generated cell models. Based on our preliminary results, we propose to understand whether and how adipose tissue Vwa8 favors obesity. We will explore how Vwa8 influences differentiation of mesenchymal cells into white or beige adipocytes. In parallel, we will study how Vwa8 modulates mitochondrial substrate preference and how its absence favors FAO. Finally, we will study whether Vwa8 inhibition can be beneficial against obesity.