Therapeutic targeting of PC1/3 deficiency: from obesity to gastrointestinal disorders

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Proprotein convertase 1/3 (PC1/3), encoded by the PCSK1 gene, is an enzyme that belongs to the family of seven highly conserved subtilisin-like serine proteases. PC1/3 is expressed in neuronal and endocrine cells, including endocrine cells in the gut, the β cells in the pancreas and in hypothalamic nuclei (POMC and AgRP neurons) known to function as centres for energy homeostasis. Loss-of-function mutations in PCSK1 cause an autosomal recessive disorder characterized by childhood obesity, malabsorptive diarrhea and other endocrinopathies. The gastrointestinal complications start immediately after birth and causes chronic diarrhea, weight loss, dehydration and metabolic acidosis which can lead to death in early childhood. After hospitalization and parental nutrition these PCSK1 null patients are reported with severe early onset obesity and postprandial hypoglycaemia. PC1/3 is highly expressed in the enteroendocrine cells of the small intestine and co-localizes with gut hormones like cholecystokinin (CCK), glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1,2 (GLP-1 and GLP-2). Remarkably however, the gastrointestinal tract has a (near-)normal histology and no chronic infection. How PC1/3 deficiency leads to chronic diarrhea is still unclear. Because of the appearance of the idiopathic chronic diarrhea in the PCSK1 null patients, has caused a shift in the clinical paradigm of PC1/3 deficiency and highlighted the current lack of understanding the role of PC1/3 in the gastrointestinal tract. Given the role of enteroendocrine factors secreted by gastrointestinal cells in energy and blood glucose homeostasis, a better understanding of this phenotypical aspect is dearly needed. Therefore we characterize the novel Pcsk1-/- mouse model, which is a representative mouse model to study the metabolic disorder of PC1/3 deficiency because of the duel phenotype: the obesity and gastrointestinal phenotype.

Biography

Laetitia Aerts is a biochemist and biotechnologist and ending PhD at the laboratory for biochemical neuroendocrinology at the centre for human genetics at KU Leuven. She won several scientific awards as poster and presentation awards (ref Science battle, Diabetes Liga). Beside her role as an assistant teacher and supervisor of master students, she started a new thematic program metabolic diseases in the doctoral school of biomedical sciences at KU Leuven. She obtained numerous certificates of statics, laboratory animal science, the floor is yours training, strategic management in pharmacological sector.