Novel animal model for Obesity related disorders and Diabetes

Lead compound selection and optimization through this relevant animal model enabling identification of drug target genes in vivo

Technology

LSD1 levels are dramatically induced in white adipose tissue after cold exposure and transgenic expression of LSD1 is sufficient to promote the formation of functional beige fat islets within white fat pads in mice.

Our data demonstrate that LSD1+/- mice (less LSD1 than +/+) show lower oxidative capacities compared to their control littermates, which leads them to obesity when challenged with a high fat diet. Importantly, treatment of control mice with a β3-adrenergic agonist increases LSD1 levels in white fat tissue and in 3T3-L1 cells, resulting in upregulation of thermogenic genes.

Together, our data establish that LSD1 is a key regulator of beige fat biogenesis. Consequently, targeting LSD1 may be a promising strategy to treat obesity related disorders.

=> For overview of LSD1 effects on white adipocytes, therapy potentials & applications of mouse model => see p. 2

Innovation

- Potential for better treatment of obesity & type-2 diabetes
- By modulation of LSD1 activity
- Related mouse model available

Application

- Therapy: better treatment options
- Mouse Model: test new anti-obesity compounds

Developmental Status

- LSD1 is a key regulator of beige fat biogenesis
- Proof of Principal: first active inhibitor of LSD1 blocks thermogenesis in fat

  ➢ Duteil et al., Nat. Comm. (2014)

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Novel animal model

Patent Status

Filed (PRD) Oct 31th 2012

PCT filed Oct 31th 2013
(Pub No.: WO2014/068033)

PCT-US patent application pending
PCT-EP granted, validation under progress

Reference Number

ZEE20110427

Status: Sept. 2018

CTF – The R&D Company of the
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Loss of LSD1 has a dual action in white adipocytes:

- in precursor cells, knock-out (KO) or knock-down of LSD1 or treatment with an LSD1 inhibitor impair adipogenesis
- in differentiated adipocytes, KO or knock-down of LSD1 or treatment with an LSD1 inhibitors lead to obesity and type 2 diabetes via a loss of thermogenic and oxidative capacities

Overexpression (OE) of LSD1 has a different effect in white adipocytes:

- in precursor cells, LSD1 OE commits white adipocytes into beige adipocytes that are thermogenetically more active
- in differentiated adipocytes, LSD1 OE increases the oxidative capacities of white fat cells

In term of therapy:

- a LSD1 inhibitor could be applied on patients after liposuction to prevent the formation of new adipocytes
- LSD1 could be applied in liposomes on abdominal fat to make it thermogenetically more active
- LSD1 activity could be chemically enhanced

How to use the mouse models?

- LSD1 KO mice are more prone to obesity than control mice. They can therefore be used as a model system to test new anti-obesity compounds
- LSD1 OE mice can be used as a positive control for mice treated with the LSD1 molecule in liposomes

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