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Technology Offer

FFA2 (GPR43) and FFA3 (GPR41) as novel targets for antidiabetic therapies

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A double KO, a conditional KO as well as single KO mouse models for FFA2 and FFA3 (free fatty acid receptors 2 and 3), novel targets for diabetes therapies.

Background

Diabetes is a major health problem worldwide, and one of its key features is the inability of elevated glucose to stimulate the release of sufficient amounts of insulin from pancreatic beta cells to maintain normal blood glucose levels. In addition to glucose and amino acids from diet, fatty acids are an essential energy source. Furthermore, free fatty acids (FFA) act as signaling molecules through binding G-protein-coupled receptors named free fatty acid receptors (FFAR) which are widely expressed in the human body and regulate the metabolic, endocrine, immune and other systems to maintain homeostasis under changing dietary conditions. The FFAR subtypes 2 and 3, also known as GPR43 and GPR41, respectively, are activated by short chain fatty acids including acetate, and evidence has been provided that FFA2 and FFA3 expressed in mouse and human pancreatic beta cells play an essential role in the regulation of insulin secretion in particular under diabetic conditions. However, studies on the metabolic function of FFA2 and FFA3 using single deficient mice have so far yielded conflicting data. These controversial results may be due to the close proximity of both genes leading to compensatory phenomena in mice deficient in only one receptor. In addition, the overlapping spectrum of endogenous ligands and very similar expression pattern of both receptors may result in partial redundancy.

Technology

Scientists from the MPI for Heart and Lung Research in Bad Nauheim have generated the following mouse models to comprehensively study the function of both receptors in vivo. These encompass a double KO, a conditional KO as well as single KO mouse models for *Ffar2* and/or *Ffar3*. Reporter mouse lines expressing monomeric red fluorescent protein (mRFP) under the control of the mouse *Ffar2* and *Ffar3* promoter allow to follow their expression in vivo on a single cell level.

Mouse models:

- *Ffar2-/-*;*Ffar3-/-* (double KO mouse model)
- *Ffar2flox/flox*;*Ffar3-/-* (conditional KO of *Ffar2* possible)
- *Ffar2*-deficient mice
- *Ffar3*-deficient mice

Reporter mouse lines:

- Ffar2-mRFP
- Ffar3-mRFP

Max-Planck-Innovation GmbH
Amalienstr. 33
80799 München
www.max-planck-innovation.de

Scientists showed that FFA2 and FFA3 are expressed in mouse and human pancreatic beta cells and mediate an inhibition of insulin secretion. Furthermore, they provided evidence that mice with dietary-induced obesity and type 2 diabetes, compared to non-obese control mice, have increased local formation by pancreatic islets of acetate, an endogenous agonist of FFA2 and FFA3, as well as increased systemic levels. This elevation may contribute to the insufficient capacity of beta cells to respond to hyperglycemia in obese states. Scientists demonstrated that genetic deletion of both receptors, either on the whole-body level or specifically in pancreatic beta cells, leads to greater insulin secretion and a profound improvement of glucose tolerance when mice are on a high-fat diet compared to controls.

In summary, FFA2 and FFA3 are suggested as new targets for antidiabetic strategies. As an FFA2 and FFA3 antagonist is expected to be efficacious only in diabetic persons with increased glucose levels, it would not affect insulin secretion in normoglycemic healthy subjects or diabetes patients with normalized glucose plasma levels, thereby decreasing the risk of hypoglycemia.

We are now looking for a licensing partner for above mentioned mouse models. We will be very pleased to share further information and scientific data.

Publications

Cong Tang, Kashan Ahmed, Andreas Gille, Shun Lu, Hermann-Josef Gröne, Sorin Tunaru, Stefan Offermanns Loss of FFA2 and FFA3 increases insulin secretion and improves glucose tolerance in type 2 diabetes. Nature Medicine 21:173-177 (2015).

Contact

Dr Ingrid Kapser-Fischer
Patent- & License Manager
Nutritionist, M.Sc.
Phone: +49 89 / 29 09 19-19
Email: kapser-fischer@max-planck-innovation.de

Max-Planck-Innovation GmbH
Amalienstr. 33
80799 München
www.max-planck-innovation.de