

Licensing Opportunity



A novel target and screen for endocrine signalling in insulin release

- Doc2b is required for whole body glucose homeostasis in mice
- Whole body glucose intolerance in Doc2b null mice is associated with impaired insulin secretion and peripheral insulin resistance in vivo, reminiscent of type II diabetes
- Pancreatic islets isolated lacking Doc2b mice are impaired in both phases of insulin secretion
- Skeletal muscle lacking Doc2b is impaired in insulin-induced incorporation of the glucose transporter GLUT4 despite a normal activation of the AKT signalling pathway
- As a novel key effector of insulin and GLUT4 exocytosis, Doc2b provides both a novel screen and a novel target

Doc2b | novel target | insulin resistance | type 2 diabetes | glucose homeostasis

2011

Background

Doc2b heterozygous and homozygous knockout mice were created to investigate the role of Doc2b in insulin granule exocytosis and insulin-stimulated GLUT4 vesicle translocation, culminating in a new in vivo model of glucose intolerance and insulin resistance. Doc2b protein levels were assessed in islets isolated from Doc2b^{+/-} and Doc2b^{-/-} mice, showing the expected loss of Doc2b protein levels compared with Doc2b^{+/+} islets. To determine the effects of Doc2b deficiency upon whole-body glucose tolerance, 4-6 month old Doc2b^{+/+}, Doc2b^{+/-} and Doc2b^{-/-} mice were subjected to intraperitoneal glucose tolerance tests (IPGTT). Glucose tolerance after either 18 h or 6 h fasting in Doc2b^{+/-} and Doc2b^{-/-} male mice was significantly impaired in comparison to WT mice.

The Technology

In vivo studies demonstrate key roles for Doc2b in multiple exocytotic processes relevant to the maintenance of whole body glucose homeostasis, including insulin secretion and peripheral glucose clearance. The requirement of Doc2b for both phases of insulin release and peripheral insulin sensitivity involves interactions with members of the SNARE protein complex via Munc18c, thus providing a stimulus-secretion coupling mechanism that regulates the secretion of insulin- or GLUT4-containing vesicles. Given that Doc2b is a soluble factor with discrete domain structure and that domains appear stable in isolation, novel reagents based upon Doc2b may carry promise as dual insulin-sensitizing/insulin secretion enhancement approaches to treating Type 2 diabetes.

Intellectual Property

METHODS OF SCREENING FOR THERAPEUTICS FOR MODULATING IMPAIRED GLUCOSE HOMEOSTASIS, US Provisional Patent Application No. 61/552,738, filed 10/28/2011.

Inventors

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Key publications

1. Ramalingam L., Oh E., Yoder S., Kalwat M., Verhage M., Groffen A., and Thurmond D. Doc2b is a Key Effector of Insulin Secretion and Skeletal Muscle Insulin Sensitivity. In press.