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# Olfactomedin 4 negatively regulates glucose-stimulated insulin secretion through inhibition of mitochondrial complex I activity

**Wenli Liu, Hongzhen Li, Oksana Gavrilova, Shalini Jain** and **Griffin P Rodgers**
National Institute of Health, USA

Olfactomedin 4 (*Olfm4*) is a member of olfactomeidn glycoprotein family, which plays important roles in innate immunity against bacterial infection, gastrointestinal inflammation and carcinogenesis. Several recent genome-wide association studies (GWAS) have linked polymorphisms in *Olfm4* with childhood obesity. This prompted us to study the potential role of *Olfm4* in pancreatic β-cells, which regulate glucose metabolism and energy balance. In this study, we have identified *Olfm4* is expressed in pancreatic β-cells and further investigated its potential roles in glucose homeostasis and pathogenesis of type 2 diabetes using *Olfm4* deficient mouse models. Compared with wild-type mouse, *Olfm4* deficient mouse did not show any difference in body weight, chow and fasting glucose level and insulin level. However, the *Olfm4* deficient mouse showed improved glucose tolerance and this effect was accompanied with increased serum insulin levels following high glucose challenge. *In vitro*, islets from *Olfm4* deficient mouse secreted more insulin than those in wild-type mouse after high glucose stimulation. Mitochondrial adenosine triphosphate (ATP) production in *Olfm4* deficient mouse islets was also significantly higher than wild-type mouse islets. We also investigated the effect of *Olfm4* overexpression on insulin secretion in Min6 cells. *Olfm4* overexpression in Min6 cells lowers basal insulin level and glucose stimulated insulin level. Accordingly, the ATP production and complex I activity in *Olfm4* overexpressed Min6 cells were significantly decreased compared with control Min6 cells. Under high-fat diet conditions, glucose stimulated insulin secretion increase fold was significantly higher in *Olfm4* deficient mice than in WT mice. The impaired glucose tolerance in high-fat diet-fed mice was improved by deletion of *Olfm4*. When *Olfm4* was deleted in ob/ob mouse, the fasting glucose level in these mice was significantly lower than those in the ob/ob mice. These studies established that *Olfm4* negatively regulates glucose-stimulated insulin secretion through inhibition ATP production and complex I activity. *Olfm4* may become a potential therapeutic target for impaired glucose tolerance and type-2 diabetes patients.

## Biography

Wenli Liu is currently a Staff Scientist at Molecular and Clinical Hematology Branch, National Heart, Lung and Blood Institute, National Institutes of Health, USA. He received his MD at Medical School of Qingdao University, China in 1988 and MSc at Dalian Medical University, China in 1991. After graduation, he had worked in the Department of Dermatology, the First Affiliated Hospital of Dalian Medical University for Several Years. He worked as a Research Associate at the Center for Endocrinology and Metabolism, Northwestern University Medical School, USA for 3 years. He joined National Institutes of Health in 2002, first as a Research Follow and later a Staff Scientist since 2007. His research interests include Hematology, Endocrinology, Cancer Research and Immunology. He has published 35 papers in peer-reviewed journals and 1 US patent. He first cloned and characterized the *olfactomedin 4 (Olfm4)* gene from human myeloid cells. He has published 12 *Olfm4* related research papers which show that *Olfm4* plays important roles in a variety of biological functions including innate immunity, inflammation and cancer.

wenlil@nhlbi.nih.gov

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