Form 3

Report for Joint/usage program for Endocrine/Metabolism

Date 2014/April/10

To: Fumikazu Okajima
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Name of Principal Researcher: Yong-soo Lee
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（Program No: 13009 ）

1. Research title	The role of hypothalamic ATF3 in the regulation of energy metabolism
2. Objective of the research	Activating transcription factor 3 (ATF3) is an adaptive response transcription factor and is known to regulate metabolism in various organs. However, the role of ATF3 in the hypothalamus remains unknown. So, in this study we will generate and analyze hypothalamic neuron specific ATF3 knockout mice to elucidate the physiological role of ATF3 in vivo.
3. Period	2013/April/1 ～ 2014/March/31

4. Project organization

Name	Affiliation	Position
(Principal applicant)	Hormone Research Center, Chonnam National University	Research Professor
(Co-applicant)		

5. Name of Researcher in IMCR	Laboratory	Metabolic Signal	Name	Tadahiro Kitamura

※ Please summarize items 1-5 in 1 page.

（Program No. 13009 ）

6. Research plans:

We crossed the mice bearing floxed ATF3 alleles with Pdx1-cre mice, in which cre is specifically expressed in the pancreas and hypothalamus, and analyzed metabolic parameters, pancreatic morphology, food intake, energy expenditure and sympathetic activity in the adipose tissue. We also investigated the molecular mechanism by which ATF3 regulates agouti-related protein (Agrp) transcription using hypothalamic cell line N-41 cells.

7. Research results:

We succeeded to generate pancreas- and hypothalamus-specific ATF3 knockout (PHT-ATF3-KO) mice. Although PHT-ATF3-KO mice displayed better glucose tolerance, neither plasma glucagon nor insulin level was altered in these mice. However, these mice exhibited higher insulin sensitivity, which was accompanied by leaner phenotype due to decreased food intake and increased energy expenditure.

We also observed decreased hypothalamic *Agrp* expression in PHT-ATF3-KO mice. Importantly, ATF3 expression is induced by fasting or low glucose in the hypothalamus. We also found that ATF3 interacts with FoxO1 on the *Agrp* promoter and activates *Agrp* transcription.

We concluded that ATF3 plays an important role in the control of glucose and energy metabolism by regulating *Agrp*.

8. Publications and/or Presentations made through this collaboration

1. Lee Y-S, Sasaki T, Kobayashi M, Kikuchi O, Kim H-J, Yokota-Hashimoto H, Shimpuku M, Susanti V-Y, Ido-Kitamura Y, Kimura K, Inoue H, Tanaka-Okamoto M, Ishizaki H, Miyoshi J, Ohya S, Tanaka Y, Kitajima S and *Kitamura T. Hypothalamic ATF3 is involved in regulating glucose and energy metabolism. ***Diabetologia*** 56: 1383-1393. 2013.

2. Lee Y-S, Kobayashi M, Kikuchi O, Sasaki T, Kim H-J, Yokota-Hashimoto H, Susanti V-Y, Ido-Kitamura Y and *Kitamura T. ATF3 expression is induced by low glucose in pancreatic alpha and beta cells and regulates glucagon but not insulin gene transcription. ***Endocr J*** 61: 85-90. 2014.

※ Please summarize items 6-8 in page 2