（様式4）（Form4）

学 位 論 文 の 内 容 の 要 旨

Dissertation Abstract

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（学位論文のタイトル） Title

CD11c-dependent ablation of the Protein Tyrosine Phosphatase Shp1 improves insulin resistance

プロテインチロシンホスファターゼ Shp1 の CD11c 依存性除去はインスリン抵抗性を改善する

（「論文目録（様式3）」の主論文の部分を記載する。英文の場合は和訳をつける。）

For English paper, Japanese title is necessary.

（学位論文の要旨）2,000字程度、A4判 （approx. 800 Words in English /A4 size）

Obesity is a well-known risk factor for insulin resistance and type 2 diabetes (T2D). It is associated with chronic low grade visceral adipose tissue inflammation secondary to immune dysregulation and immune cells' infiltration and activation. In this study, we analyzed the influence of Shp1, the protein tyrosine phosphatase, in dendritic cells (DCs) over type 2 diabetes. Shp1 is highly expressed in hematopoietic cells including DCs, and has negative role in signaling pathways. For this reason, we generated Shp1 conditional knockout mice (Shp1 CKO) that lack Shp1 in specifically $CD11c^+$ cells, and found splenic $CD4^+$ T cells from Shp1 CKO are prone to differentiate into Th1 cells and are more susceptible to glomerulonephritis. Therefore, we aim to clarify the contribution of the depletion of Shp1 in CD11c positive cell to the development of obesity induced T2D.

Diet-induced obesity model was induced in Shp1 CKO by feeding high fat diet (HFD). Gain of body weight over 16 weeks of HFD was similar between CKO and control mice. Glucose and insulin tolerant tests at 12 weeks after HFD result in improved glucose tolerance and insulin sensitivity respectively in Shp1 CKO mice compared to control. Shp1 CKO showed decreased serum insulin levels compared to control but blood glucose levels were similar. Homeostatic Model Assessment of Insulin resistance (HOMA-IR), also showed lower score in CKO mice. These metabolic tests indicate that Shp1 deletion in CD11c improves glucose tolerance and protects mice from HFD-induced insulin resistance.

As diet induced obesity is typically accompanied by dyslipidemia, the levels of lipid parameters such as cholesterol,

triglycerides and non-esterified fatty acid (NEFA) were measured. These lipid profiles were lower in the serum of Shp1 CKO compared to control indicating that there is more lipid metabolism in Shp1 CKO unlike in control mice. Serum leptin level is abnormally higher in HFD control mice than that of mutant mice, which might have worsened insulin resistance in control HFD. However, adiponectin level is comparable between the control and Shp1 CKO group. The grade of steatosis was lower in Shp1 CKO on as visualized by H&E stain was milder in Shp1 CKO. Also, lipid droplet was decreased in liver of Shp1 CKO confirmed by Oil red O staining. These findings indicate that Shp1 in DCs has a role not only in glucose homeostasis but also in lipid homeostasis.

Lean body mass was significantly increased in Shp1 CKO after 24 weeks of HFD as shown by CT scan. Also, gross examination of the mice revealed massive splenomegaly with significantly higher cellularity in Shp1 CKO. The glucose uptake in splenocytes in vitro was analyzed by incubating the splenocytes 2-NBDG. The analysis of *in-vitro* glucose uptake revealed increased incorporation of sugar analog into spleen cells of Shp1 CKO, therefore, the spleen of HFD-fed Shp1 CKO is the dominant site for glucose uptake and metabolism. Collectively, ameliorated insulin resistance in HFD-fed Shp1 CKO could be attributable to splenomegaly of Shp1 CKO. The levels of type 1 cytokine IFN-γ, IL-6 and TNF-α in serum were upregulated in Shp-1 CKO and control, showing no statistical significance; however, anti-inflammatory cytokine IL-10 was increased in HFD-fed Shp1 CKO. We assume that a marked rise in the levels of serum IL-10 could contribute to the improved glucose tolerance in Shp1 CKO.

In conclusion, Shp1 in $CD11c^{+}$ cells negatively control insulin sensitivity through the upregulated IL-10 production and increased glucose uptake into splenocytes.