論　文　概　要

論 文 題 目 MafB is important for pancreatic β-cell maintenance under a MafA deficient condition

(MafBはMafA欠損下において膵β細胞維持に重要な役割をもつ)

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目　　的：Lifelong expression of MAFB in human pancreatic β-cells implies its involvement in maintaining mature β-cell function. However, as a preferred mammalian model for biomedical research to understand how humans function, mouse does not express MafB in adult pancreatic β-cells. Interestingly, Re-expression of MafB in the β-cells of adult MafA deficient mice was detected in the previous study, which implies potential role of MafB in mature β-cells under curtain pathological condition in mice. Therefore, purpose of this study is to investigate whether MafB can take part in adult mouse β-cell activity under MafA-deficient condition by generating MafA and MafB double knockout (A0B0) mice.

対象と方法: Using C57BL/6J mice strain, I generated MafA and MafB double knockout (A0B0) mice, in which MafB was specifically deleted from the pancreatic β-cells, and compared their phenotype with those of A0 and WT mice under normal diet and high fat diet (HFD) condition. To compare the glucose metabolism of each mice group, fasting blood glucose level measurement, i.p. glucose tolerance test and plasma insulin level measurements were conducted at certain time points. To compare the islet morphology of the mice from different genotypes, immunohistochemistry (IHC) and hematoxylin and eosin (HE) staining were performed together with the cell counting. Quantitative real-time PCR experiment was also done using islet derived cDNA to check gene expression.

結　　果： Several main observations on pancreatic function and islet morphology are reported here. First, A0B0 adult mice displayed more severely impaired glucose tolerance compared to A0B2 mice. This phenomenon was further aggravated with

HFD treatment, which caused diabetes in the A0B0 mice. Second, deficiency of MafA has a destructive effect on normal islet structure, and moreover, this abnormality becomes more significant with the deletion of MafB. Third, a notable reduction in islets, islet cell numbers together with increase of β-cell apoptosis were detected in HFD feeding A0B0 mice. Therefore, those findings provided evidence for a functional role of MafB on maintaining mature β-cell features in some specific pathological conditions.

考　　察： Deletion of MafA and MafB together aggravated the metabolic phenotype resulting from MafA single knock-out mice. Under a normal diet condition, relatively more impaired glucose intolerance in A0B0 mice than A0B2 mice was observed. Although plasma insulin level of A0B0 mice at ipGTT was comparable with that of A0B2 mice, *in vitro* glucose stimulated insulin secretion (GSIS) test need to be carried out to confirm whether the insulin secretion abilities of β-cell were comparable between A0B2 and A0B0 groups. Besides, the α-cell to β-cell ratio became remarkably higher in the A0B0 islets compared to the A0B2 islets. Impaired islet structure is one of the significant phenotypes of MafA-deficient mice, but the molecular mechanisms leading to this structural abnormality have not been clarified. Since this abnormality became more remarkable in the A0B0 group, I assume this could be related to the relatively more impaired glucose tolerance in A0B0 mice than in A0B2 mice under normal diet conditions.

Under HFD condition, insulin^{+} cell numbers showed a dramatic reduction in A0B0 islets, while plasma insulin level of A0B0 mice was comparable with A0B2 mice,

indicating critically damaged insulin production ability of β-cells can be a reason for A0B0 mice to become extremely glucose intolerant and developed diabetes. Nevertheless, their insulin content and GSIS needs to be measured to confirm this conclusion.

In addition to that, total islet numbers were notably reduced and islet size failed to properly expand in the A0B0 pancreas. In insulin resistance disorders caused by adiposity or gestation, the β-cell mass increases to adapt to the body's increased requirements for insulin, which results in enlarged islets and increased islet numbers. Deficiency of MafA in an HFD condition is harmful enough to cause insulin insensitivity in the body. I speculate removing MafB from β-cells will further inhibit the β-cell mass from expending itself by increasing the islet number and islet size. The drastic reduction in insulin^{+} β-cells in A0B0 mice supports my hypothesis. However, I failed to detect and compare the β-cell proliferation in the islets of WT, A0B2 and A0B0 mice with 5-month HFD treatment. This is probably because of adaptive β-cell expansion was already completed by the time of 5-month HFD feeding, which was reported to start within the first week of HFD treatment. On the other hand, I clearly detected increase of β-cell apoptosis in A0B0 islets. Although it was an unexpected result, it may be reasonable because MafB is known as a regulator to prevent apoptosis in macrophages under specific condition as reported previously. Therefore, this finding provides a whole new prospective towards MafB function in pancreatic β-cells.

結　　論：A0B0 mice became more susceptible to diabetes under HFD conditions with impaired islet morphology and decreased insulin-expressing cell numbers because of apoptosis, indicating MafB is important for pancreatic β-cell maintenance under specific pathological conditions. So far, this is the first study to show role of MafB in mature pancreatic β-cells in a certain pathological state using MafA and MafB (MafB is specifically deleted in β-cell) double knock-out mouse. Moreover, this finding can apply for human case to understand diabetic disease process and prevent the disease by using MAFB as a possible target factor to improve body's response to metabolic stress.