Histone methylase MLL attenuates insulin secretion by reducing glucose sensitivity in mouse pancreas

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Background: Myeloid / Lymphoid or Mixed-lineage leukemia gene (MLL) is translocated to chromosome 11 long arm q23 region (11q23) and the MLL fusion gene expressed as a result of translocation reconstruction plays an important role in MLL-related leukemia development. It has also been reported that MLL and MLL protein play an important role in tumor development as a Menin-binding protein in Multiple Endocrine Neoplasia Type I (MEN1). More recently, normal MLL protein has been shown to have histone H3 lysine 4-methylation (H3K4-HMT) activity and to be an epigenetic transcriptional regulator. In addition, the function of MLL protein as a histone methylase has been reported in the gene region involved in metabolism regions. Here, we analyzed the involvement of MLL in glucose metabolism in the pancreas using MLL knockout mice.

Methods: Glucose metabolism in MLL knockout mice and the function of MLL in cultured cells were analyzed. Result: Since the homozygotes of MLL knockout mice are embryonic lethal, we analyzed them using Heterozygous mice. MLL heterozygous mice showed significantly weight loss compared to the wild type mice. MLL heterozygous mice showed no difference in food intake compared to wild type mice. IPGTT showed impaired glucose tolerance in MLL heterozygous mice. However, ITT showed no insulin resistance and decreased insulin secretion during glucose loading. In GSIS tests, Islets isolated from heterozygous mice pancreas have been observed to decrease insulin secretion in the response to glucose stimulation. In comprehensive gene analysis using Microarray analysis of mRNA extracted from mice islet, the gene expression changes related insulin secretion and apoptosis have been revealed in MLL heterozygous mice. Histological search showed no decrease in β-cell number, and immunohistological search showed no difference in insulin, glucagon, and TUNEL staining between heterozygous and wild type mice. And also, MLL knockdown was performed in a cultured cell line. Insulin secretion was decreased to glucose stimulation in MLL knockdown cell line same as in MLL knockout mice. In addition, RNA microarrays were performed to these cell lines, several same genes that have confirmed in MLL mouse islets were observed in MLL knockdown cell. In common to both MLL knockout mice and MLL knockdown cell line, the expression levels of GLUT1 and GLUT2 were decreased. In conclusion, MLL knockout mice showed decreased insulin secretion. It was suggested that MLL may be involved in insulin secretion through decreased expression of the GULT1 gene and GLUT2 genes in islets.

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