Profiling of changes in gene expression associated with epigenetic changes in peripheral blood cells under hyperinsulinemic euglycemic clamp condition

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Effects of supraphysiologic insulin action are very diverse, and further studies are required. And, epigenetic regulation of acute hyperinsulinemia on gene expression has not been studied a lot. In the present study, we evaluated DNA methylation and related changes of mRNA expression level in peripheral blood cells before and after hyperinsulinemic euglycemic clamp (HEC) condition in healthy adults. Through this, we investigated whether specific gene methylation induced by acute hyperinsulinemia cause a change in gene expression.

Two stage HEC (insulin infusion rate: 10 and 80 mU/m2/min) studies were performed in 5 non-diabetic subjects. Buffy coat sample was taken in each subject before and after the clamp study and RNA-seq and Methyl-seq were performed using blood cells before (0 min) and after hyperinsulinemia (200 mins). Differentially expressed genes (DEGs) were identified in RNA-seq data. Among DEGs that were identified, genes with a significant change in methylation of specific regions such as, promoter and gene body were selected based on Methyl-seq data.

Among 697 DEGs, 112 genes with a methylation change after HEC were identified and classified as "methyl-DEGs". And, in an analysis using MSigDB, among the 697 DEGs, 43 genes were involved in four major pathways (i.e., inflammation, insulin signaling, oxidative stress, and carbohydrate metabolism): we classified these genes as "phenotypic-DEGs". We performed a network analysis including Methyl-DEGs and Phenotypic-DEGs, as well as 26 INS/IGF-related genes. Among these, we found two genes (ESR1 and FGF4) that were highly correlated between changes in DNA methylation and changes in gene expression and were also associated with insulin response and diabetes.

Via combined analyses of RNA-seq and Methyl-seq data of human peripheral blood cells, we showed that a significant epigenetic regulation of two genes could occur in these cells after HEC, which may be important in the pathophysiology of hyperinsulinemia.