論　文　概　要

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RNA-sequencing analysis of paternal low-protein diet-induced gene expression change in mouse offspring adipocytes

(父親への低タンパク質餌による次世代マウス脂肪細胞での遺伝子発現変化のＲＮＡシーケンシング解析)

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Abstract

Purpose

Increasing evidence indicates that parental diet affects the metabolism and health of offspring. It is reported that paternal low-protein diet (pLPD) induces glucose intolerance and the expression of genes involved in cholesterol biosynthesis in mouse offspring liver. The aim of the present study was to determine the effect of a pLPD on gene expression in offspring white adipose tissue (WAT), another important tissue for the regulation of metabolism. We also compared gene expression pattern with liver and with progenitor generation and with liver to characterize the difference between generations and tissues.

Methods

To determine the effects of a pLPD on gene expression in offspring WAT, we used essentially the same feeding regimen reported by Carone *et al*. [15]. In brief, after weaning at 3 weeks of age, male F0 mice were fed the CD or LPD, then mated with female F0 mice which were fed the CD to produce F1 offspring. Transcriptomic profile of inguinal white adipose tissue (iWAT) from male F1 offspring at 5 weeks of age were analysed by RNA-seq. To see whether the alteration in gene expression pattern in F1 offspring iWAT mimicked that in their male parents, we performed transcriptome profiling of F0 iWAT in 10–12-week-old male mice fed the LPD or CD and compared transcriptome profiles in iWAT between two generations. Finally, to understand how pLPD-induced differences in gene expression in the iWAT and liver of the offspring contribute to the glucose intolerance that was previously reported [16], we also compared the transcriptome between 2 tissues, using the DEGs in F1 liver, which was previously analyzed following a similar feeding study [15].

Results

pLPD up- and down-regulated 54 and 274 genes, respectively, in offspring WAT. The down-regulated genes contained numerous representatives from metabolic pathways, such as fatty acid biosynthesis and glycolysis.

The expression of carbohydrate response element-binding protein β (ChREBP-β), an important lipogenic transcription factor, was markedly reduced in pLPD offspring. pLPD reduced the amount of ChREBP, presumably ChREBP-α, binding to the promoter of ChREBP-β, leading to a reduction in the expression of ChREBP-β. Moreover, Igfbp2 was among most up-regulated genes, which may inhibit glycolysis, leading to suppression of the nuclear translocation of ChREBPα.

Furthermore, the analysis of the DEGs of F0 iWAT showed that lipolysis is up-regulated in F0 iWAT. Only 12 genes showed overlapping differential expression among the 274 and 334 down-regulated genes in the F1 and F0 iWAT, respectively.

Comparison of the DEGs in F1 iWAT and liver showed almost no overlap, with only one and five genes overlapping among the up- and down-regulated lists, respectively.

Discussion

Carone *et al*. demonstrated that pLPD increased the expression of many cholesterol biosynthesis-regulating genes in offspring live. Using the same diet and feeding regimen, we found that pLPD down-regulates multiple lipogenic genes in offspring iWAT. Both of these opposite effects on lipogenesis of liver and WAT would be expected to cause insulin resistance. It is as yet unclear how a pLPD might differentially affect the expression of genes in these two offspring tissues. LPD may induce an epigenetic change, such as histone modification or RNA induction, in the TGCs, which may be transmitted to the mature sperm. Because differentiation into tissues such as liver

and WAT occurs in the post-blastocyst embryo, such changes in the early embryo would be expected to affect gene expression in the embryo at a later stage. A LPD up-regulates the expression of lipid oxidation genes in the iWAT of F0 mice. Differences in gene expression in offspring WAT may be the result of epigenetic changes in the TGCs of their male progenitors. Further analysis is required to dissect the mechanism underlying the differential effects of a pLPD on the expression of genes in iWAT and liver.

Conclusion

The mRNA expression of many genes involved in lipogenesis was down-regulated by pLPD feeding in white adipose tissue, which may contribute to glucose intolerance. The expression of ChREBP-β was also significantly lower in the WAT of pLPD offspring, which may have mediated the down-regulation of the lipogenic genes. By contrast, the LPD did not affect the expression of lipogenic genes in the WAT of the male progenitor, but increased the expression of lipid oxidation genes.