**The Interaction between Intestinal ACSL5 Expression and Gut Microbiota in Mice Fed a High Fat Diet**

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**Objectives:** A major contributor to the development of obesity is the excessive intake of calories and fat. Our preliminary data indicate that a critical step for the absorption of dietary fat is the acylation of FFA to acyl-CoA by enterocyte acyl-CoA long-chain synthetase 5 (ACSL5). In previous unpublished studies we demonstrated that mice with intestinal specific deficiency of ACSL5 ($ACSL5^{int-/-}$) fed a high-fat diet (HFD) were protected against diet-induced obesity (DIO) secondary to reduced HFD intake. Since the composition of the intestinal microbiome has been demonstrated to modulate DIO and metabolism, the objective of this project is to explore the relative role of reduced HFD intake versus intestinal deficiency of ACSL5 on the composition of the host microbiome.

**Methods:** The intestinal deficiency of ACSL5 mouse model ($ACSL5^{int-/-}$) and floxed littermates $ACSL5^{loxP/loxP}$ were fed either a low-fat diet (LFD, 4% fat) or a high-fat diet (HFD, 60% fat) for two weeks. Cecal contents were collected for 16S rDNA gene sequencing. For the pair-feeding study, one group of $ACSL5^{int-/-}$ mice and one group of $ACSL5^{loxP/loxP}$ mice received a HFD for 16 weeks *ad libitum*. At the same time, a second group of $ACSL5^{loxP/loxP}$ mice was pair-fed with the same amount of food ingested by $ACSL5^{int-/-}$ littermates.

**Results:** Our studies demonstrate that HFD fed $ACSL5^{int-/-}$ mice possess a significantly distinct microbiome structure compared to $ACSL5^{loxP/loxP}$ mice. Taxa analysis revealed that in 8 out of 11 $ACSL5^{int-/-}$ mice fed a HFD levels of *Akkermansia muciniphila* were present while it was not detected in any of the 8 $ACSL5^{loxP/loxP}$ mice. During pair-feeding, we observed that $ACSL5^{int-/-}$ mice consumed 20% less energy when fed a HFD and were protected against DIO and insulin resistance.

**Conclusions:** Reduced food intake resulting from intestine-specific deficiency of ACSL5 protects against the development of HFD-induced obesity and is associated with an altered microbial structure that is consistent with an improved metabolic profile. Ongoing studies using metagenomic sequencing will provide specific information on taxonomy at the species level, expression of genes and functional characterization of the microbiome of mice fed varying levels of high fat intake and intestinal ACSL5 deficiency.

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