**Potential therapeutic implications of histidine catabolism by the gut microbiota in NAFLD patients with morbid obesity**

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**Presenter: Chin-Chun Lin                    Date and Time: 2023.9.14, 16:00-1700**

**Commentator: Chu-An Wang, PhD  Location: Room 601, Med**

**Background:**

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent metabolic disorders, affecting one-third of the global population. It is characterized by excessive fat accumulation in the liver, accompanied by mild inflammation and insulin resistance, which can lead to fibrosis, ultimately resulting in irreversible liver cirrhosis or liver cancer.

The liver is a central organ in coordinating amino acid metabolism, and alterations in these metabolites are associated with type 2 diabetes and NAFLD. Various medical conditions such as obesity, chronic kidney disease, and heart failure are linked to decreased histidine levels. Histidine possesses multiple beneficial effects, including antioxidant, anti-inflammatory, anti-glycation, and chelation properties. Previous studies have shown that histidine supplementation is beneficial in ethanol-induced mouse liver injury models and may improve obesity and blood sugar control, but its impact on liver function remains unclear. The gut microbiota plays a crucial role in regulating the biological utilization of dietary histidine and is involved in hepatic changes leading to NAFLD. However, it is currently unclear whether there is an association between gut microbiota, histidine metabolism, and NAFLD.

**Objective:**

The authors evaluated the relationship between histamine metabolism and NAFLD using plasma metabolomics, fecal metagenomics, liver transcriptomics, and fecal microbiota transplantation. And use different animal models to understand the effectiveness of histamine as a treatment strategy for NAFLD and the impact of gut microbes on histamine.

**Results:**

HAA (histidine, serine, carnosine, and cysteine) supplementation in diet-induced NAFLD mouse models increased hepatic histidine levels, leading to a significant reduction in NAFLD features. Similar effects were observed in other NAFLD animal models and studies on human primary liver cells, where histidine therapy decreased total lipid content or TG levels and downregulated genes associated with de novo lipogenesis, albeit with variable effects on β-oxidation and fatty acid transport. This suggests that histidine promotes the metabolism of free fatty acids, thereby reducing lipid accumulation. Histidine serves as an important carbon, nitrogen, and/or energy source for many bacteria, particularly those from the phylum Proteobacteria. Microbiota analysis revealed a negative correlation between plasma histidine levels and several bacterial families increased in NAFLD, especially those from the phylum Proteobacteria. Patients with higher degrees of hepatic steatosis showed higher histidine degradation metabolism by the gut microbiota, explaining the lower plasma histidine levels in these patients. Results from fecal microbiota transplantation (FMT) further supported the role of histidine in NAFLD. Compared to mice receiving microbiota from donors with high histidine levels, those receiving microbiota from donors with low histidine levels exhibited higher liver TG accumulation. Consistently, mono-colonized with *E. cloacae* (a member of the Proteobacteria) in flies resulted in TG accumulation and increased AST and ALT activity. However, with increasing histidine doses, the TG accumulation gradually decreased, suggesting that Proteobacteria partially prevented its absorption by consuming histidine in the culture medium.