P46 – **Integrated multi-omic analysis of unique transgenic animal models uncovers the tissue omega-6/omega-3 fatty acid imbalance as a critical risk factor for chronic disease**

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An unbalanced increase in dietary omega-6 polyunsaturated fatty acids (PUFA) and decrease in omega-3 PUFA in our foods coincides with the global rise in preventable chronic diseases. However, whether omega-6 and omega-3 PUFA oppositely contribute to the development of chronic disease remains controversial; the clarification of this issue is challenging due to confounding factors of diet. In this study, we utilized unique transgenic mouse models in combination with multi-omics technologies to determine the impact of varying amounts of omega-6 and omega-3 PUFA and their ratio on metabolic conditions and disease development. The four mouse genotypes generated in this study – wild-type (incapable of producing essential fatty acids), *fat-1* transgenic (producing n-3 fatty acids), *fat-2* transgenic (producing only n-6 fatty acids), and *Omega* transgenic (producing both n-6 and n-3 fatty acids) – were fed an identical diet (high in saturated fat and carbohydrates and low in n-6 PUFA) to create four different tissue PUFA profiles. Multi-omics analysis showed that the mice with varying n-6/n-3 PUFA ratio exhibited distinct gut microbiome and metabolites, as well as susceptibilities to cancer and metabolic disorders (including metabolic endotoxemia, chronic low-grade inflammation, fatty liver, body weight gain, and insulin tolerance). In general, mice with similar PUFA ratios displayed similar phenotypes, indicating a determining role for n-6/n-3 PUFA ratio. In particular, *fat-2* mice with elevated n-6 PUFA levels and the highest n-6/n-3 PUFA ratio showed the most unfavourable metabolic conditions and the highest liver cancer rate, while these adverse health outcomes observed in the *fat-2* mice were largely prevented in *fat-1* and *Omega* mice, which can convert n-6 PUFA to n-3 PUFA and have a balanced n-6/n-3 PUFA ratio. This multi-omic study of host-microbiota interactions therefore demonstrate that n-6 PUFA may be harmful in excess and highlight the importance of n-3 PUFA and a balanced tissue n-6/n-3 PUFA ratio in lowering the risk for metabolic disease. This study also indicates that rising n-6 PUFA and declining n-3 PUFA consumption worldwide contribute to today's chronic disease epidemic.