TITLE: Kombucha-associated Microbes Remodel Host Pathways to Promote Metabolic Health
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ABSTRACT:
The ancient, probiotic-rich beverage Kombucha Tea (KT) has surged in popularity partially due to its purported health benefits that include lowered blood pressure, protection against metabolic disease, and hepatoprotective activity; however, none of these claims have been rigorously tested. Moreover, the mechanistic interactions between the microbial components of KT and the consumer remains unexplored. It is difficult to deconvolute how a small community of microbes might impact human health as humans eat a complex diet already have trillions of microbes colonizing their gastrointestinal tract and many experiments are not feasible with human subject. *C. elegans* a well-established model system for studying metabolism offers a unique opportunity to explore mechanisms of probiotic action, as these nematodes are bacterivorous with a simple body plan. We have established a standardized method to maintain *C. elegans* on a diet exclusively consisting of Kombucha Tea-associated microbes (KTM), which is equivalent to the microbial community found in the fermenting culture. Animals consuming a KTM diet have an established gut microbiome and display normal development and fecundity. Intriguingly, *C. elegans* consuming KTMs are markedly devoid of lipid stores and exhibit reduced lipid droplet size, which is consistent with some of the purported human health benefits of KT consumption (*i.e.*, protection against diabetes, obesity and metabolic disease). While decreased fat storage can be a consequence of reduced caloric intake, worms fed KTMs have similar food intake and increased growth rates compared to animals fed a traditional *E. coli* diet, suggesting that dietary restriction does not account for the metabolic changes observed in KTM-fed animals. Additionally, growing KTMs separately and combining them before ad libitum feeding (KTM-Mix) does not promote lipid utilization, suggesting there is something unique about the established fully-fermented KT culture that confers metabolic rewiring of the host. In addition to these physiological phenotypes, we found that KTM consumption triggers widespread transcriptional changes within core metabolic pathways. Of particular note, when animal consume a KTM, but not KTMmix diet, several lysosomal lipase genes induced during lipophagy are up-regulated (*lipl-1*, *lipl-2* and *lipl-3*) and *dgat-2*, which encodes a conserved diacylglycerol acyltransferase involved in lipid droplet expansion, is down-regulated. Consistently, increased lipid accumulation was observed in lysosomal lipase-deficient animals consuming a KTM diet as well as in animals with constitutively active *dgat-2*(GOF). Together, these findings suggest that KTM consumption is reconfiguring host metabolism through the induction of conserved metabolic programs, like lipophagy, to trigger a fasting-like metabolic state even in the presence of sufficient nutrients. Investigating the host metabolic response to KTM consumption using *C. elegans* will provide unprecedented insight into how this popular beverage may be impacting human health, provide a roadmap for future studies in other animal model systems, and ultimately inform its use in complementary health care approaches.