Early-life Fungal Colonization Mediates Obesity Development and White Adipose Tissue Inflammation in Mice

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Background: Obesity is a growing issue in our society, especially during childhood, where the effects can persist long term and increase the risk of metabolic disease. The microbiome is known to play a central role in human health, including obesity development. While recent research has begun to include fungi in microbiome studies of obesity, this has focused only on adults, leaving our understanding of how the fungal microbiome (mycobiome) impacts the development of childhood obesity unknown.

Methods: In a longitudinal birth cohort study of Canadian infants, we identified correlations between the abundance of specific fungal species in stool samples (*Candida albicans*, *Rhodotorula mucilaginosa* and *Malassezia restricta*) and body mass index up to 5 years of age. These findings have been translated in a mouse model of diet-induced obesity to determine causality of the human findings. Germ-free mice were colonized from birth with twelve mouse-derived bacteria (Oligo-MM12) alone or in combination with the identified fungi and weaned onto a high-fat-high-sugar diet or standard chow until twelve weeks of age.

Results: Our results showed all three fungal species differentially influenced obesity development and adipose tissue inflammation, a major determinant of metabolic dysfunction. Mice colonized by *C. albicans* were lean and resistant to diet-induced obesity, accompanied by enhanced adipose tissue inflammation, which may hinder energy storage. In contrast, *R. mucilaginosa* colonization was associated with enhanced development of metabolic disease and obesogenic alterations to the adipose tissue immune landscape. Lastly, *M. restricta* colonized mice displayed increased adiposity without any markers of metabolic disease and reduced adipose tissue inflammation, suggesting an enhanced ability to expand fat tissue in a controlled manner.

Discussion: This work revealed that three common fungal colonizers have distinct and striking consequences for obesity development and metabolic inflammation and prompts for the inclusion of fungi in microbiome studies on host metabolism.