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Title of the thesis: Study of the impact of gut microbial butyrate on RNA binding protein, AUF-1 on regulation of gastrointestinal physiology

ABSTRACT

The hepato-gastric metabolic function, immune function and the barrier function of a host body are regulated by the gut microbial metabolite, Short Chain Fatty Acids (SCFA), like propionate, butyrate, and acetate. In this thesis we aimed to dissect the "complex rules" by which gut microbial butyrate influences the cholesterol balance, barrier function and immune balance in hepato-gastrointestinal milieu in mice. Given butyrate causes anti- hypercholesterolemia, we have probed the mechanistic molecular details of butyrate action in maintaining cholesterol balance. Butyrate has the following consequences, as shown in the study: upregulation of RNA binding protein, AUF-1 isoforms, which resulted in Dicer-1 instability and reduced miR122 biosynthesis. The intracellular players placed in tandem establish a link as follows: butyrate-AUF-1-Dicer-1-mir122-cholesterol metabolic enzymes- serum cholesterol. To functionally validate decrease in cholesterol upon butyrate treatment we showed that butyrate increased membrane fluidity by disruption of cholesterol rich microdomains which resisted colonization of enteric pathogen.

We created a novel cell-penetrating morpholino-oligomer to selectively knock down AUF-1. Apart from hypercholesterolemia we showed AUF1 knockdown phenocopies colitis with increased barrier permeability, inflammation in the gut and reduced Th17 and Treg balance. We have shown AUF1 stabilizes occludin mRNA coding for Occludin, a tight junction protein and destabilizes claudin 2 mRNA which codes for a pore forming protein, Claudin 2 resulting into increase in barrier function. In a similar manner AUF1 regulates either positively or negatively the transcription factors, RORγt and FoxP3 respectively to influence Th17/Treg balance.

Together, these findings provide clear evidence that AUF1, upregulated by butyrate is an important protein which promotes gastrointestinal physiology by maintaining cholesterol balance, barrier function and immune function.

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