Title: THE HUMAN GUT METABOLOME MODULATES Salmoenella enterica INTERACTIONS WITH HOST CELLS

Authors
ALVES, E.S.¹; PINA, L.C.²; LOBO, L.A.¹; FERREIRA, R.B.R.¹; DOMINGUES, R.M.C.P.¹; ANTUNES, L.C.M.²

Institution
¹UFRJ - UNIVERSIDADE FEDERAL DO RIO DE JANEIRO (AVENIDA CARLOS CHAGAS FILHO, 373 - RIO DE JANEIRO, RJ), ²FIOCRUZ - FUNDAÇÃO OSWALDO CRUZ (ESTRADA DA CURICICA, 2000 - RIO DE JANEIRO, RJ)

Abstract: The human gastrointestinal microbiota is an intricate assembly of microorganisms that coexist peacefully with their host and have critical functions for the maintenance of host health. Current knowledge of the relationship between the microbiota and the host suggests that this microbial community affects various aspects such as host resistance or susceptibility to invasion by exogenous pathogens. Recently, our group demonstrated that a specific metabolite from the gut metabolome, 3,4-dimethylbenzoic acid (DMB), inhibits host cell invasion by Salmonella. Further analysis by RNA sequencing of Salmonella grown in the presence of DMB showed that the expression of many other genes is affected by this compound. Among these genes was the operon ssrAB, which encodes an important virulence regulator, and was significantly repressed by DMB. SsrAB is one of the most important two-component regulatory systems of Salmonella, which directly regulates the expression of the Salmonella Pathogenicity Island 2 (SPI-2) and the ability of Salmonella to survive inside host phagocytic cells, such as macrophages. In the current work, we studied the effect of DMB on SPI-2 gene regulation and its impact on Salmonella interactions with host macrophages. We were able to confirm the RNAseq results through gene expression analysis of ssrA by Real-Time PCR, which indicated that the effect of DMB is consistent and can be reproduced. In order to determine the effect of DMB on macrophages, we performed a viability assay with bone marrow derived macrophages (BMDM) as well as immortalized RAW 264.7 macrophages. Preliminary results showed that DMB has no effect on macrophage viability. In order to expand our understanding of the effect of this metabolite on Salmonella-host interactions, in this study we intend to address the following questions: (1) Does DMB affect the expression of SsrA-controlled genes?; (2) Does DMB affect Salmonella entry into, survival and replication within macrophages?; (3) Does DMB affect the production of inflammatory mediators by infected macrophages? Our preliminary results clearly show that the interaction between Salmonella and RAW 264.7 macrophages is significantly affected by DMB. Answers to these questions will provide a better understanding of the role of small molecules produced by the human gut microbiome and may provide a framework for the study of other small molecules involved in microbiota-pathogen interactions.

Keywords: Salmonella enterica, signaling, microbiota, small-molecules, macrophages.

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