Title: THE EFFECT OF HUMAN GASTROINTESTINAL METABOLITES ON *SALMONELLA ENTERICA* VIRULENCE

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Abstract:

The gastrointestinal microbiota is commonly described as an intricate complex of microorganisms, estimated to contain over 1000 species, that has critical functions for the maintenance of host health. Current knowledge of the gastrointestinal microbiota and its relationship with the host suggests that complex interactions between different microbial species as well as between microbes and host cells occur in this environment. Such interactions have the ability to affect not just the relationship between the cells involved, but may also impinge on host resistance or susceptibility to invasion by exogenous pathogens. In order to better understand the interactions between microbiota, pathogen and host in the gastrointestinal tract, we studied the effect of metabolites from the gastrointestinal microbiota on the virulence of *Salmonella enterica* serovar Typhimurium. Initially, the effect of a crude extract of human feces on *Salmonella* growth and gene expression was studied. This revealed that *Salmonella* readily responds to the presence of fecal small molecules; expression of genes involved in host cell invasion was highly affected. We then characterized this crude extract using standard purification methods coupled with mass spectrometry and found that active fractions contained various aromatic hydrocarbons. Some of these small molecules were then obtained from commercial sources and tested with regards to their ability to modulate invasion gene expression. One of these molecules, 3,4-dimethylbenzoic acid, showed significant activity, repressing *Salmonella* virulence gene expression as well as host cell invasion in a tissue culture infection model. This study, together with previous observations, shows that the human gastrointestinal tract is rich in molecular diversity, and that some of the small molecules present have a significant impact on the microbe-microbe and microbe-host interactions established in this environment. The present work deepens our previous knowledge of the roles of the human gut microbiota and provides a framework for the study of other small molecules involved in microbiota-pathogen interactions.

Keywords: Microbiota, small molecules, signalling, *Salmonella*

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