Identification of Metabolic Pathways Essential for Fitness of Salmonella Typhimurium In Vivo - DTU Orbit (04/03/2019)

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Bacterial infections remain a threat to human and animal health worldwide, and there is an urgent need to find novel targets for intervention. In the current study we used a computer model of the metabolic network of *Salmonella enterica* serovar Typhimurium and identified pairs of reactions (cut sets) predicted to be required for growth in vivo. We termed such cut sets synthetic auxotrophic pairs. We tested whether these would reveal possible combined targets for new antibiotics by analyzing the performance of selected single and double mutants in systemic mouse infections. One hundred and two cut sets were identified. Sixty-three of these included only pathways encoded by fully annotated genes, and from this sub-set we selected five cut sets involved in amino acid or polyamine biosynthesis. One cut set (asnA/asnB) demonstrated redundancy in vitro and in vivo and showed that asparagine is essential for *S. Typhimurium* during infection. trpB/trpA as well as single mutants were attenuated for growth in vitro, while only the double mutant was a cut set in vivo, underlining previous observations that tryptophan is essential for successful outcome of infection. speB/speF,speC was not affected in vitro but was attenuated during infection showing that polyamines are essential for virulence apparently in a growth independent manner. The serA/glyA cut-set was found to be growth attenuated as predicted by the model. However, not only the double mutant, but also the glyA mutant, were found to be attenuated for virulence. This adds glycine production or conversion of glycine to THF to the list of essential reactions during infection. One pair (thrC/kbl) showed true redundancy in vitro but not in vivo demonstrating that threonine is available to the bacterium during infection. These data add to the existing knowledge of available nutrients in the intra-host environment, and have identified possible new targets for antibiotics.

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