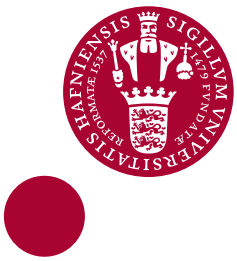

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Identification of Redundant Metabolic Pathways Essential for Virulence of *Salmonella* Typhimurium

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Abstract:
Metabolic pathways that are non-essential during infection because the bacterium has more than one alternative to perform the reaction are not well characterized. We hypothesised that such redundant pathways might be useful in control of infection, provided one could identify all components of the redundant pathways and block them in parallel. To test this hypothesis we developed a genome scale model of *Salmonella* Typhimurium containing 1165 reactions. After having curated the model, we performed damage analysis where all possible pairs of non-essential reaction were deleted from the model in order to identify synthetic lethal pairs. The model identified 63 fully annotated pairs of pathways, 32 of which involved only 2 or 3 genes. To test the validity of the predictions made by the model we selected 10 of these pairs and constructed single and double mutants and double mutants complemented in trans in the genes encoding the enzymes of these pathways. All strains were characterized for growth in LB, M9 and M9 with added glucose and amino acids (m9+ = the media used in the simulation study with the model). Despite the prediction, three pairs turned out to contain essential genes. Four of the pairs showed the expected phenotype when grown in M9+, i.e. growth in single-gene mutants but no growth in double mutants. Three pairs did not have a growth phenotype. The seven pairs where all mutants could be constructed were tested for virulence in mice. Only two pairs, encoded by 1) asnA/asnB) and 2) *spe*B/*spe*F+*spe*C) showed the expected outcome, i.e. double but no single mutants were attenuated. In conclusion, the genome scale model could be used to predict synthetic lethal pairs of pathways, but accuracy of prediction was below the expected.