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A constraints-based systems approach to metabolic analysis of *Francisella tularensis* during infectionA. Raghunathan¹, S. Shin¹, S. Daefler¹¹Mount Sinai School of Medicine, Infectious Diseases, New York, United States

Francisella tularensis is an ill-characterized pathogen and a potential biowarfare agent necessitating a better understanding of its metabolism and virulence mechanisms. Genome scale constraints based metabolic models built for several microorganisms including *S. typhimurium* and *H. influenzae* provide a systems framework to study metabolism, infection and pathogenesis. We have developed a metabolic network reconstruction for *F. tularensis* using the current genome sequence annotation and biochemical legacy data. Mathematical techniques like Flux balance and flux variability analysis (FBA, FVA) were used to explore the metabolic capabilities of the *in silico* pathogen under *in vitro* and *in vivo* conditions. Gene expression, growth and physiological data were obtained experimentally and used as additional constraints in the model to compute and predict functional states of the pathogen. Integrating this data into the model as constraints allow us to reduce the solution space representing cell behavior and predict cellular function with more accuracy. *Francisella* was capable of growth with different specific growth rates on glucose and alternate carbon sources including glycerol, xylose, ribose, fructose and arabinose in a chemically defined medium with differential and preferential consumption of amino acids thus validating our model prediction that they can make up the bulk of the biomass. Gene expression of selected metabolic genes at specific time points of *francisella* during infection provide a snapshot and implicate certain metabolic pathways as critical to growth and survival in the host cell. Some observations include operation of TCA cycle in a branched mode; several functional amino acid pathways. Fatty acid gene transcript levels indicate their role as preferred gluconeogenic substrates during infection. Several gene transcripts detected in this data set were present in the optimal reactome calculated using FVA. Such an analysis provides insights into the lifestyle of the bacterium and the metabolic dependence on the host. Iterative model building can further help refine our understanding of the intracellular milieu encountered by the bacterium inside the host-cell and point towards genes essential in growth, survival and pathogenesis. Collectively, the results presented herein suggest an effective systems biology strategy of combining *in silico* modeling with experimental technologies to discover novel drugs and targets.