Genome-scale model of Rothia mucilaginosa predicts gene essentialities and reveals metabolic capabilities

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Abstract

Cystic fibrosis (CF), an inherited genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator gene, results in sticky and thick mucosal fluids. This environment facilitates the colonization of various microorganisms, some of which can cause acute and chronic lung infections, while others may positively impact the disease. Rothia mucilaginosa, an oral commensal, is relatively abundant in the lungs of CF patients. Recent studies have unveiled its anti-inflammatory properties using in vitro three-dimensional lung epithelial cell cultures and in vivo mouse models relevant to chronic lung diseases. Apart from this, R. mucilaginosa has been associated with severe infections. However, its metabolic capabilities and genotype-phenotype relationships remain largely unknown. To gain insights into its cellular metabolism and genetic content, we developed the first manually curated genome-scale metabolic model, iRM23NL. Through growth kinetics and high-throughput phenotypic microarray testings, we defined its complete catabolic phenome. Subsequently, we assessed the model's effectiveness in accurately predicting growth behaviors and utilizing multiple substrates. We used constraint-based modeling techniques to formulate novel hypotheses that could expedite the development of antimicrobial strategies. More specifically, we detected putative essential genes and assessed their effect on metabolism under varying nutritional conditions. These predictions could offer novel potential antimicrobial targets without laborious large-scale screening of knockouts and mutant transposon libraries. Overall, iRM23NL demonstrates a solid capability to predict cellular phenotypes and holds immense potential as a valuable resource for accurate predictions in advancing antimicrobial therapies. Moreover, it can guide metabolic engineering to tailor R. mucilaginosa's metabolism for desired performance.