A GENOME-SCALE METABOLIC RECONSTRUCTION OF HAEMOPHILUS INFLUENZAE REVEALS FABH AS A POTENTIAL TARGET FOR ANTIMICROBIAL THERAPEUTIC DEVELOPMENT

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Bacterial antibiotic resistance is a global health problem that requires urgent action. Haemophilus influenzae is an integral part of the human nasopharyngeal microbiota, but also an opportunistic pathogen whose increasing antibiotic resistance has driven its inclusion in the WHO list of bacteria for which new antibiotics are urgently needed.

We carried out a genome-scale metabolic reconstruction of H. influenzae Rd KW20, iNL630, based on publicly available genomic and physiological data. This manually curated reconstruction accounts 1,379 reactions, 630 genes and 1,156 metabolites. The model was thoroughly validated by predicting growth, metabolic fluxes, and essential genes with high accuracy. Furthermore, it was used to screen essential genes that could be used as new drug targets. These model-based analyses identified fabH, encoding for the β-Ketoacyl-ACP-synthase III, a key enzyme in the initiation module of FASII fatty acid biosynthesis. Exploitation of FabH as a drug target falls into the concept of antibacterial FASII inhibition based on the notion that lipid A biosynthesis requires a fully operating FASII pathway.

The antimicrobial effect of a synthetic molecule predicted to inhibit FabH activity by interacting with key residues at its catalytic site, was tested on a panel of H. influenzae clinical isolates where fabH allelic variation was detected. This molecule reduced bacterial viability in a dose-dependent manner, was bacteriostatic and did not generate resistance over time. Phenotypic variation among strains was observed, being unrelated to differences in fabH gene expression. Further work will allow us to fully characterize the potential of FASII inhibition against H. influenzae.