Ecological Niche Constrains Evolution of Metabolic Function in Pathobionts

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Abstract Text:

Pathogens pose a major global risk to human health, causing 43.7% of deaths in low-resource countries. While some pathogens are well characterized experimentally and computationally, we lack an understanding of lesser-known pathogens and pathobionts. Understanding the evolutionary relationship between pathobionts and their ecological niche will allow us to gain insight into the role isolate environment plays in differential pathobiont metabolic function. To address this question, we developed PATHGENN: a database of 914 genome scale metabolic network reconstructions (GENREs) for all known human bacterial pathobionts generated through an automated pipeline. To understand evolution of metabolic phenotypes across pathobionts, we generated pairwise genetic distances through 16s rRNA sequence alignment for all models. Secondly, we predicted essential genes via COBRApy essential gene analysis, and subsequently determined dissimilarity in essential gene profiles between pairs of pathobionts. The relationship between pairwise genetic distance and essential gene profiles suggests that for genetically similar pathobionts, small differences in relatedness correlate with large changes in metabolic functionality. Additionally, this implies that for related species, there is pressure to evolve different metabolic functions as new ecological niches are colonized. To explore the relationship between pathobiont metabolic niche and functional metabolism, we first performed flux balance analysis on all GENREs in PATHGENN. Dimensionality reduction of flux samples via t-SNE and subsequent visualization revealed clustering on isolation environment, suggesting there is a link between metabolic niche and functional metabolism. For example, we identified uniquely essential genes of stomach isolates. We identified two genes that are uniquely essential to the stomach (*tktA* and *fabF*), and subsequently determined existing drugs that could target these gene products. Using PATHGENN, we determined the relationship between evolution of metabolic phenotypes across pathobionts, the role of isolate environment in functional metabolic adaptation, and discovered antibiotic targets for stomach specific bacteria.