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Robustness and Plasticity of Metabolic Pathway Flux among Uropathogenic Isolates of *Pseudomonas aeruginosa*

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Abstract:

Pseudomonas aeruginosa is a human pathogen that frequently causes urinary tract and catheter-associated urinary tract infections. Here, using 13C-metabolic flux analysis, we conducted quantitative analysis of metabolic fluxes in the model strain P. aeruginosa PA01 and 17 clinical isolates. All P. aeruginosa strains catabolized glucose through the Entner-Doudoroff pathway with fully respiratory metabolism and no overflow. Together with other NADPH supplying reactions, this high-flux pathway provided by far more NADPH than needed for anabolism: a benefit for the pathogen to counteract oxidative stress imposed by the host. P. aeruginosa recruited the pentose phosphate pathway exclusively for biosynthesis. In contrast to glycolytic metabolism, which was conserved among all isolates, the flux through pyruvate metabolism, the tricarboxylic acid cycle, and the glyoxylate shunt was highly variable, likely caused by adaptive processes in individual strains during infection. This aspect of metabolism was niche-specific with respect to the corresponding flux because strains isolated from the urinary tract clustered separately from those originating from catheter-associated infections. Interestingly, most glucosegrown strains exhibited significant flux through the glyoxylate shunt. Projection into the theoretical flux space, which was computed using elementary flux-mode analysis, indicated that P. aeruginosa metabolism is optimized for efficient growth and exhibits significant potential for increasing NADPH supply to drive oxidative stress response.

Keywords: Pseudomonas aeruginosa, metabolic pathways, oxidative stress, flux-mode analysis, urinary tract infection, C-metabolic flux analysis