Microbial Metabolites in Cystic Fibrosis: A Target for Future Therapy?

Cystic fibrosis (CF) is a recessively inherited genetic disease that affects approximately 1:2,500 live births in the United States and 1:8,000–10,000 in European Caucasian populations (1). Life expectancy for individuals with CF is greatly reduced, with a median survival of 40 years (2010/USA) (1). CF is caused by the presence of one out of >1,600 potential mutations in the CFTR (cystic fibrosis transmembrane regulator) gene. Clinical phenotypes vary with genetic background and cover pulmonary, gastrointestinal, and urogenital symptoms in a systemic fashion. In the airways, CFTR deficiency results in mucus thickening and defective mucociliary clearance of inhaled microbiota, which leads to recurrent and chronic infections by a complex microbiota (2, 3). Such polymicrobial infections trigger pulmonary exacerbations through recruitment of inflammatory immune cells, which in turn provokes lung remodeling and irreversible lung function decline. Treatment intervention is usually conducted *post hoc*, after the patient presents with acute infection, and is targeted to the most abundant, cultivable pathogens, such as Staphylococcus *aureus*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae* (4). However, pathogen control is not easily achieved, and sequencing surveys indicate long-term persistence despite the use of various treatment regimens (5). Over time, the chronic microbiota adapts to the pulmonary microenvironment, showing altered virulence factor profiles, organization into mucoid biofilms, and the accumulation of functional genetic mutations (1). In addition, plastic changes in the microbial metabolism have recently been reported. In the deep mucus, for example, low oxygen availability limits ATP production for survival, and competition for alternative terminal electron acceptors such as phenazines, nitrate, and fumarate drives metabolic adaptations (6, 7).

To exploit microbial metabolic requirements as therapeutic targets to prevent exacerbations, and to develop early-onset markers for disease aggravation, we need to identify predictable metabolic shifts during pathogen adaptation. In this light, the study by Gabryszewski and coworkers (pp. 185–197) in this issue of the *Journal* represents an important step forward in defining metabolic adaptations of methicillin-resistant *Staphylococcus aureus* (MRSA) (8), one of the most prevalent CF pathogens (9). The research team collected sequential samples from subjects with CF and studied adjustments in metabolic activity, immunogenicity, and genetics during chronic infection with MRSA. Using whole-genome sequencing, they detected that the genetic mutations mostly affected metabolic and transporter genes, and no global difference in immunogenicity was observed to support the aggravation of the clinical phenotype. The presented results indicate that the key to understanding the observed disease dynamics is the significant change in central carbon metabolism and the exaggerated production of fumarate. The host-adapted strains showed increased avidity for sugars, including trehalose, maltose, and sorbitol, as well as for pyruvate, a central metabolite in sugar turnover. Although it was not shown directly, this also points to increased fermentation activity of adapted MRSA, likely due to pronounced anoxic conditions in later stages of disease or in dense biofilm. Analysis of the transcriptome revealed a dramatic increase in expression of the tricarboxylic acid enzyme fumarate hydratase (fumC), which resulted in remarkable fumarate levels. By using mouse infection models, the authors associated fumC expression with the induction of proinflammatory cytokines and a stronger pneumonia phenotype, and linked fumarate levels to biofilm formation. Importantly, fumarate may be used as an alternative terminal electron acceptor by MRSA, *Escherichia*, *Fusobacterium*, and *Haemophilus* in anoxic sputum (7), and can provide a competitive advantage for cross-feeders in the microbial community.

Microbial consortia emerge in a context-dependent manner in the CF lung (10) and can persist in mixed-species biofilms or secluded parts of the diseased lung (11). For example, the pathogens *S. aureus* and *P. aeruginosa* form such temporary interacting consortia. In coculture experiments, it has been shown that *P. aeruginosa* alters *S. aureus* expression profiles and enhances resistance to antimicrobial substances, oxidative stress, and immune clearance by triggering biofilm formation (12, 13). One important limitation to the study by Gabryszewski and colleagues is that they focused on a single pathogenic organism, thereby disregarding the context dependency of metabolic adaptations within a microbial community that is typically present in the lungs of patients with CF. It appears that the immune environment and the pulmonary niche select for robust evasion strategies through metabolic plasticity of the microbiota. A number of recurrent signal molecules have been identified in this context that connect the redox state of the organisms (e.g., oxygen availability and carbon usage) with biofilm formation and virulence (14). Such adaptive processes reflect microbial metabolism, pulmonary inflammation, and the stage of disease. The small number of patients studied in the current work prevented the authors from explicitly distinguishing between different disease stages. Scaling up and including well-defined patient cohorts will deepen our mechanistic understanding of microbial metabolic processes and provide relevant molecular triggers as promising drug targets that we are eager to explore. ■

Supported by Austrian Science Fund (FWF) V 585-B31 (S.W.).

Author disclosures are available with the text of this article at www.atsjournals.org.

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