Right on the Nose: IL-17C and Nasal Host Defense

Pseudomonas aeruginosa is a ubiquitous environmental organism, so common that many of us inhale this bacterium aerosolized in our daily shower. The healthy sinonasal cavity is highly resistant to infection by *P. aeruginosa.* When innate epithelial defenses are impaired, for example in cystic fibrosis or primary ciliary dyskinesia, *P. aeruginosa* is the most common organism causing chronic rhinosinusitis, a near-universal complication of both diseases. Infection of the sinonasal cavity by environmental bacterial strains may be the initiating site of respiratory infection in cystic fibrosis, and after lung transplantation, *P. aeruginosa* resident in the sinonasal cavity may seed the allograft. Despite the likelihood that the sinonasal cavity plays a prominent role in the establishment of chronic lower respiratory infections, relatively little is known regarding the epithelial response to gram-negative pathogens in the nose as compared with the lung. A better understanding of innate defenses against gram-negative pathogens in the sinonasal cavity would help us better target prevention and early eradication strategies for *P. aeruginosa* in cystic fibrosis and ciliary diseases.

In this issue of the *Journal*, Jeon and colleagues (pp. 95–103) describe a nasal epithelial cell–*P. aeruginosa* coculture model (1). Using this model, they show that IL-17C is highly induced in the nasal epithelial cells by *P. aeruginosa.* The epithelial IL-17C response contributes to the clearance of *P. aeruginosa* in the model and also leads to upregulated expression of lipocalin-2 (LCN2), which sequesters some classes of bacterial siderophores, thereby decreasing bacterial iron uptake. IL-17C is a functionally distinct member of the IL-17 family, which signals in an autocrine/paracrine fashion in epithelium-rich tissue through the IL17-RA/IL17-RE receptor complex. In bronchial epithelial cells, polyinosinic:polycytidylic acid, flagellin, LPS, and intact bacteria, including *P. aeruginosa,* potently stimulate IL-17C production (2, 3). Increased expression of IL-17C in the bronchial epithelium is seen in a variety of disease states, including cystic fibrosis (3). Nasal epithelial production of IL-17C was previously demonstrated in a mouse model of eosinophilic rhinosinusitis, and increased IL-17C expression was seen in nasal mucosal samples from individuals with chronic rhinosinusitis compared with control subjects; however, the roles of IL-17C in nasal defense are poorly understood (4, 5). When either IL-17C or the receptor IL-17RE was silenced by Jeon and colleagues, increased growth of *P. aeruginosa* was seen in the coculture model. Pretreatment with recombinant IL-17C restricted *P. aeruginosa* growth. Interestingly, the authors show induction of LCN2 in the coculture, which is lost with silencing of IL-17C. LCN2 is produced by multiple cell types, including epithelial and myeloid cells, and is upregulated by numerous cytokines, including IL-17A, IL-22, and IL-1β; thus, additional regulatory mechanisms may exist when myeloid-derived cells are present. LCN2 has roles in different biologic processes, including host defense and iron metabolism.

One main function of LCN2 is to limit bacterial access to iron. Iron is possibly the single most growth-limiting nutrient during chronic lung infections with *P. aeruginosa.* Thus, there is ongoing competition between the human host and the bacterium for iron, with defenses and counterdefenses on both sides of the battle. Bacterial siderophores are secreted small molecules that bind iron with high affinity and are taken back up by the bacterium. LCN2 can sequester some siderophores, thereby preventing bacterial reuptake. Siderophores are structurally diverse, and LCN2 mainly binds the catecholate class of siderophores, including enterobactin. The main siderophores of *P. aeruginosa*, pyoverdine and pyochelin, are so-called "stealth" siderophores because they are not bound by lipocalin, which makes it more difficult for the host to sequester these molecules (6). Beyond pyoverdine and pyochelin, *P. aeruginosa* can obtain iron by importing siderophores produced by other bacterial species, and it can incorporate both free iron and heme. Understanding the full role of LCN2 specifically in containing *P. aeruginosa* requires substantial additional work due to the production of stealth siderophores that are resistant to LCN2, as well as the redundancy in bacterial iron uptake systems. However, beyond LCN2, IL-17C regulates a broader host response through secretion of antimicrobial peptides and cytokines that could also play a role in protection against *P. aeruginosa* nasal colonization. The iron uptake systems of *P. aeruginosa* are exquisitely regulated, and it may be that a secreted host factor is leading to downregulation of bacterial siderophore secretion. In addition to iron, the nutritional environment in the nasal epithelial coculture model is likely zinc limited. The gene PA4834, induced in this coculture model, is part of the metallophore pseudopaline operon (*cntOLMI* or *zrmABCD*), which is a key factor in zinc uptake in chelating environments (7, 8). Zinc limitation via calprotectin modulates interbacterial interactions between *P. aeruginosa* and *Staphylococcus aureus*, two common coinfecting organisms in cystic fibrosis–associated chronic rhinosinusitis (9). Additional rigorous studies to examine the role of the immune response and metal limitation in the nose should be conducted to define mechanisms that lead to increased nasal bacterial colonization in specific patient populations.

Our understanding of the initial steps in gram-negative bacterial airway colonization in human respiratory disease states has been limited by the availability of model systems. Immune responses differ with regard to airway location (paranasal sinuses vs. conducting airway), between species (human vs. mouse), between primary cell culture and cell lines, and according to whether bacterial products or live organisms are used. In addition, the innate immune response may differ between the nose and paranasal sinuses, although this remains poorly understood. The use of a

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primary human nasal epithelial–*P. aeruginosa* coculture model system and the use of polarized and well-differentiated primary nasal epithelial cells are strengths of the study by Jeon and colleagues. In these cocultures, bacterial communities were observed to adhere to a densely ciliated epithelium and appeared to exhibit features of biofilm formation, such as those seen in coculture models using lower respiratory airway epithelial cells (10). The validation of a nasal epithelial *P. aeruginosa* coculture model is a useful contribution to our understanding of sinonasal biology, and this model could be adapted to study disease-specific issues such as the roles of CFTR function in sinonasal epithelial defenses and nasal biofilm pathophysiology, and the impact of viral infections on nasal bacterial colonization. ■

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