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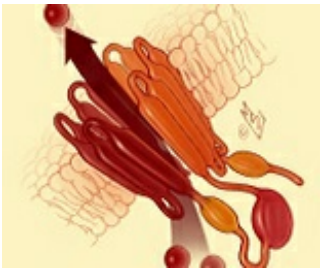

Understanding the Microbiology of the CF Lung

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In this Issue...

The airway microbiome in cystic fibrosis is generally more diverse and has more bacterial activity and interactions than in persons without CF, making identification of the infecting pathogen (and subsequent treatment) significantly more complicated.

In this issue, Dr. John J. LiPuma, professor of pediatrics at the University of Michigan, reviews the literature describing recent investigations into this critically important area.

LEARNING OBJECTIVES

- Describe the complexity of the CF airway microbiome.
- Summarize how the structure and activity of CF airway microbial communities affect lung disease progression.
- Differentiate between culture-based and culture-independent assessment of CF airway microbiology.

GUEST AUTHORS OF THE MONTH

Commentary & Reviews

Guest Faculty Disclosure

Dr. John LiPuma reports that he has served as a consultant for Raptor Pharma, Aradigm Corp, and CURx Pharma.

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Issue 3

Program Information

CME Information
Accreditation
Credit Designations
Intended Audience
Learning Objectives
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Length of Activity

1 hour Physicians
1 hour Nurses

Launch Date

February 25, 2016

Expiration Date

February 24, 2018

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Resources:

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Unlabeled/Unapproved uses

Dr. John LiPuma reports there will be no off-label or unapproved uses of any drugs.

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IN THIS ISSUE

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COMMENTARY

For the last half century, the approach to treating human infectious diseases has focused on: 1) identifying the infecting microbial species, most often by recovering viable organisms in cultures from the infected site; 2) determining the susceptibility of the recovered pathogen to antibiotics in vitro; and 3) providing therapy with appropriate antibiotics to eradicate the pathogen from the infected site.

Infection of the airways in persons with cystic fibrosis (CF) challenges each of these steps. First, it has become clear that, unlike in many other infectious diseases, airway infection in CF is typically polymicrobial, involving multiple bacterial species.[1] While a few of these species are considered typical human pathogens, most are opportunistic pathogens or commensal species that normally inhabit the upper airways. Thus, identifying the "infecting pathogen" responsible for causing disease is far from straightforward. Second, selecting antibiotic therapy based on susceptibility testing of one or more of the species recovered in culture of respiratory specimens has not been shown to predict treatment success.[2] Finally, apart from treating initial infection, antibiotic therapy is most often not effective in eradicating bacteria from the airways.[3]

Developing improved strategies to treat airway infection in CF, including pulmonary exacerbations, requires a deeper understanding of how and why infection of this site in this patient population differs from infection elsewhere. This involves gaining a better appreciation of the structure and activity of the complex microbial communities inhabiting the airways, a more sophisticated understanding of how bacteria adapt to the airway environment during chronic infection, and a clearer definition of the distinctive features of the CF airway environment that affect bacterial growth and efficacy of antibiotic therapy. Recently, several important studies have shed light on these issues.

The study by Jorth et al, reviewed in this issue, adds another dimension to the complexity of CF airway infection by demonstrating the degree to which *Pseudomonas aeruginosa* can diversify within severely damaged CF lungs. With a herculean effort, the investigators demonstrate that a single infecting *P. aeruginosa* strain can evolve in vivo, resulting in subpopulations whose virulence traits differ from one region of lung to another and, importantly, in antibiotic susceptibility. The study suggests that local conditions in lungs that are heterogeneously diseased could generate a multitude of specialized variants that together increase the ability of infecting bacteria to adapt to the constantly changing conditions of the lungs as disease progresses. Thus, CF lung disease may be considered a collection of regional infections, each involving bacteria with different virulence and resistance traits. In this regard, in vitro susceptibility testing of a single isolate recovered in culture would be limited in predicting the range of susceptibilities in the entire infecting population.

An important determinant of how effective many antibiotics are in killing bacteria is the growth rate of the targeted organisms. To have their greatest effect, many drugs require bacteria to double rapidly. The study by Kopf et al addresses a fundamental question: how rapidly do bacteria grow within CF airways? By labeling CF sputum with heavy water, the investigators found that the growth rate of *Staphylococcus aureus* was at least two orders of magnitude slower in sputum than when this species is grown in media in the laboratory. This study highlights the need to study bacteria under conditions that exist *in vivo* to gain insight into how bacteria survive, adapt, and resist killing by antibiotics.

The study by Cowley et al similarly addresses a fundamental question, this time pertaining to the inorganic chemistry of CF sputum. Although much is known about the organic components of CF sputum, much less is understood about the chemistry of CF sputum that would likely have significant bearing on microbial growth in airways *in vivo*. The

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investigators studied freshly expectorated CF sputum samples using exquisitely sensitive methods to show that CF sputum is chemically dynamic and largely anoxic. The highly variable microenvironments in CF sputum suggested by this study predict that microbial communities inhabiting the airways must be metabolically versatile and as observed by Jorth et al able to diversify and adapt to changing conditions within the airways.

In addition to gaining a better appreciation of the CF airway environment and how this would be expected to affect microbial growth, virulence, and diversity, a number of studies have described microbe-microbe interactions and microbe-host interactions that also have potential to affect disease progression and response to antibiotic therapy. These are illustrated by the studies by Filkins et al and Mirkovic et al, reviewed in this issue. In the former study, the investigators employed an *in vitro* system of *P. aeruginosa* and *S. aureus* growing alone or in combination on cultured CF bronchial epithelial cells. They show that *P. aeruginosa* secretes products that drive *S. aureus* from aerobic respiration to anaerobic fermentation. This shift allows *P. aeruginosa* to outcompete *S. aureus*, leading to loss of *S. aureus* viability and/or promoting the emergence of antibiotic resistant *S. aureus* small colony variants. The study by Mirkovic et al provides evidence of a mechanism whereby anaerobic bacterial species that are commonly detected in CF airways could contribute to host inflammation in CF.

The studies reviewed in this issue highlight that airway infection in CF is complex and relatively poorly understood. While the regional heterogeneity of disease in CF lungs has been appreciated for many years,[4,5] the lack of utility of in vitro susceptibility testing in predicting clinical outcomes[2,6,7] and the diversity of bacteria involved in airway infection[1,8] are more recent observations. Studies such as those reviewed herein are helping us understand how these pieces of the puzzle fit together. We are beginning to appreciate how lung disease heterogeneity and variation in the chemical properties of CF sputum drive microbial diversification and adaptation. We are learning that the microenvironments of the CF lung and microbial interactions within these distinct niches could provide conditions that favor antibiotic resistance. These findings underscore the need to take these distinctive features of CF microbiology into account in future work to develop new strategies to treat airway infection in CF.

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PSEUDOMONAS AERUGINOSA DIVERSIFICATION AND REGIONAL ADAPTATION

Jorth P, Staudinger BJ, Wu X, et al. Regional isolation drives bacterial diversification within cystic fibrosis lungs. *Cell Host Microbe*. 2015;18:1-13.

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Chronic infection of the airways by *Pseudomonas aeruginosa* occurs in the majority of persons with CF. Previous studies have shown that this typically involves a single strain (ie, clone or lineage) of *P. aeruginosa*, rather than coinfection by multiple, distinct strains. A great deal of research has also detailed the ways in which *P. aeruginosa* adapts to the lung environment during prolonged infection, including, for example, by switching to a mucoid phenotype. More recent work has suggested that *P. aeruginosa* lineages can further diversify genetically and phenotypically during CF infections. However, the degree to which this occurs and the mechanisms driving diversification are not clear.

In this study, a group of investigators led by Pradeep Singh at the University of Washington characterized *P. aeruginosa* isolated from lungs removed from 10 patients with CF at the time of lung transplantation. Cultures were obtained from six sites in each set of lungs, and 200 *P. aeruginosa* colonies were isolated from each site (~1,200 *P. aeruginosa* colonies per patient were studied). Consistent with previous work, the investigators showed that all but one subject was infected with only a single strain of *P. aeruginosa*. However, they observed that within each lung — and within each region of lung — the recovered isolates differed in their expression of various virulence traits and in antibiotic resistance phenotypes. They also found that regions of the same lung differed with respect to the proportion of isolates expressing certain phenotypes. For instance, ~40% of isolates from the right upper lobe of subject 1 were ciprofloxacin resistant, whereas all isolates from the right lower lobe were susceptible. While the left lower lobe of this subject harbored mainly nonmotile isolates, the isolates in the left upper lobe were motile.

Genome sequence analysis of a subset of isolates from each lung indicated that the *P. aeruginosa* populations in each lung region evolved independently. This is characteristic of so-called “genetic compartmentalization,” a process by which regional populations of bacteria that are geographically isolated evolve independently due to differing selective pressures. In this case, differences in selective pressure likely result from regions of lung that are more or less diseased. The restricted trafficking of organisms between these regions drives spatially independent evolution of *P. aeruginosa* during chronic infection within individual patients.

These findings show how subpopulations of the same strain of *P. aeruginosa* can evolve independently in different areas of infected lungs to produce extensive diversity in virulence and resistance phenotypes. This raises the possibility that local conditions in infected lungs could generate a great number of specialized variant organisms, thereby increasing the ability of the infecting bacteria to adapt to changing conditions as lung disease progresses. Clearly, the variation observed in antibiotic resistance phenotype complicates approaches to effective antibiotic therapy.

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BACTERIAL GROWTH RATE IN CF SPUTUM AND THE IMPACT OF ANTIMICROBIAL THERAPY

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Kopf SH, Sessions AL, Cowley ES, et al. Trace incorporation of heavy water reveals slow and heterogeneous pathogen growth rates in cystic fibrosis sputum. *Proc Nat Acad Sci*. 2015;113:E110-E116.

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The efficacy of antibiotic therapy often depends on the growth rate of the targeted bacteria at the site of infection. Drugs that are active against a pathogen growing in laboratory culture may be less effective against that same pathogen during growth *in vivo*. Unfortunately, relatively little is known about in vivo growth rates of bacteria at specific sites during human infection.

In this study, investigators led by Dianne Newman at the California Institute of Technology sought to better understand microbial growth rates in CF sputum. This technically challenging question was addressed with a novel approach that involved labeling sputum with heavy water (^2H_2O) and using mass spectroscopy to measure ^2H incorporation into microbial-specific fatty acids. This technique provided a measure of biosynthetic turnover, which in turn allowed an estimation of bacterial growth rate. The study focused on *Staphylococcus aureus*; growth rate of this species was measured in 37 sputum samples from 16 patients. Although the calculated growth rates varied between patients and even between samples from a single patient, all values were two to 100 times lower than the rates typically observed when *S. aureus* is grown in the laboratory. In fact, while the doubling time of *S. aureus* in culture media in vitro is typically about an hour, the median doubling time observed in this study was a remarkable 2.1 days.

The authors were also interested in understanding if growth rates of *S. aureus* correlated with particular host characteristics or clinical features. They observed that growth rates, on average, were significantly lower when patients were receiving certain antibiotics. However, at the individual patient level, being on antistaphylococcal antibiotics at the time of sampling did not show a clear trend with respect to growth rate. Of interest, the growth rate of *S. aureus* slowed in some patients at the beginning of hospitalization, with a return to a faster rate before discontinuation of antibiotics. If this observation is confirmed with additional study, carefully executed longitudinal analyses will be required to elucidate the mechanism(s) driving this phenomenon.

These results of this study suggest that *S. aureus*, and likely other bacterial pathogens, experience significant constraints to growth within CF lungs. Although the specific constraints require definition, low oxygen penetration into sputum, inhibition by microbial competitors, the host immune system, and antibiotic treatment are all likely contributors. Understanding how the slow growth of microbes residing in the CF airways affects pathogen virulence and survival and the effects of treatment represents an important area of ongoing study.

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SURVIVAL OF OPPORTUNISTIC PATHOGENS IN THE CF LUNG ENVIROMENT

Cowley ES, Kopf SH, LaRiviere A, et al. Pediatric cystic fibrosis sputum can be chemically dynamic, anoxic, and extremely reduced due to hydrogen sulfide formation. *mBio.* 2015;6:e00767-15.

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In another study headed by Dianne Newman's research group at the California Institute of Technology, the chemical composition of CF sputum was investigated in detail. Although previous studies have characterized the organic components of CF sputum (eg, mucin and DNA), much less is known about the inorganic chemistry that would be expected to have bearing on microbial growth *in vivo*. The investigators paid particular attention to oxygen and sulfide concentrations, as well as to pH and oxidation reduction potentials. A total of 48 sputum samples from 22 children with CF were studied. Oxygen concentrations at various depths within sputum samples were painstakingly measured using microsensors capable of detecting ultralow (as low as 2 nM) levels of oxygen. In all samples, oxygen was depleted rapidly within the first few millimeters below the sputum-air interface. Sputum beneath this sharp oxygen gradient (the main volume of expectorated sputum) was anoxic. Oxidation reduction potentials measured in 28 samples varied, with some samples having positive and other samples having negative redox potentials (ie, oxidized or reduced microenvironments, respectively), suggesting a fair degree of chemical variability in sputum both within and between patients. The highly reduced samples were found to contain hydrogen sulfide and had a low pH, ranging from 2.9 to 6.5.

Recognizing that chemical measurements on freshly expectorated sputum are limited in characterizing the microenvironment of sputum in human airways *in vivo*, the investigators modeled oxygen dynamics, taking into account variables such as oxygen diffusion through mucus layers of different thicknesses and oxygen consumption rates by microbial communities of various densities. The models, informed by the experimental measurements on expectorated sputum, predict that sputum in CF airways is spatially heterogeneous, spanning an oxygen-replete layer located at and just beneath the air-sputum interface, a thin hypoxic zone with a steep oxygen gradient, and entirely anoxic microenvironments that dominate the majority of the sputum below. The modeling suggests that the extent of hypoxia vs anoxia depends on the local geometry of and microbial density in the airways.

These findings have important implications for the microbiology of the CF airways. Besides providing a microenvironment suitable for the growth of anaerobic bacterial species, hypoxia and anoxia would favor typically aerobic species that can generate energy in the absence of oxygen. This is, in fact, a trait shared by essentially all major CF pathogens, including *Pseudomonas aeruginosa, Staphylococcus aureus, Stenotrophomonas maltophilia, Burkholderia spp*, and *Achromobacter* spp. Some species (eg, *S. aureus*) are more resistant to certain antibiotics at low pH. The chemical heterogeneity of sputum also likely reflects physiologic adaptation by metabolically versatile microbial communities. Determining how microbes adapt and survive in these different environments is an important consideration when studying CF pathogens in the laboratory.

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MICROBIAL INTERACTIONS AND ANTIBIOTIC RESPONSE

Filkins LM, Graber JA, Olson DG, et al. Coculture of *Staphylococcus aureus* with *Pseudomonas aeruginosa* drives *S. aureus* towards fermentative metabolism and reduced viability in a cystic fibrosis model. *J Bacteriol*. 2015;197:225222-64.

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It is becoming increasingly accepted that airway infection in CF in vivo involves complex communities of bacteria living in close proximity in a variety of microenvironments. It is also generally believed that microbes interact in myriad ways when occupying the same niche. However, the precise nature of these interactions and the mechanisms driving them require further elucidation. A research group headed by George O'Toole at the Geisel School of Medicine at Dartmouth sought to understand how two common CF pathogens, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, might interact to affect their respective growth and survival *in vivo*.

The investigators developed a dual-bacterium, in vitro coculture system of *P. aeruginosa* and *S. aureus* growing on monolayers of human bronchial epithelial cells homozygous for F508del *CFTR* mutation. A distinctive feature of this system is that it allows the formation of a dual-species biofilm on CF airway epithelium. Using this system, the investigators show that *P. aeruginosa* and *S. aureus* initially coexist for several hours. In fact, while *P. aeruginosa* appeared little affected by the presence or absence of *S. aureus*, a significant increase in the planktonic (ie, nonbiofilm) population of *S. aureus* was noted within the first few hours of coculture. Between 10 and 16 hours of coculture, a rapid decline in the *S. aureus* population was observed. This apparent killing of *S. aureus* by *P. aeruginosa* was observed with multiple strains of both species and was noted to occur in both biofilm and planktonic populations of bacteria.

To understand the mechanism of this interaction, the research team profiled gene expression in each species when grown alone and when grown in coculture. While *P. aeruginosa* gene expression was only minimally affected by the presence of *S. aureus*, a significant change in the expression of many genes in *S. aureus* were observed in the presence of *P aeruginosa*. Most striking was an up-regulation of *S. aureus* fermentation pathway genes. In other words, it appears that *P. aeruginosa* drives *S. aureus* from aerobic respiration to anaerobic fermentation. Further analysis indicted that this shift in *S. aureus* metabolism was mediated by the production of specific *P. aeruginosa* metabolites, including a quinolone referred to as HQNO, and iron-scavenging siderophores.

The investigators propose a model whereby lactate produced by *S. aureus* fermentation is preferentially consumed by *P. aeruginosa.* This gives *P. aeruginosa* an advantage in competing with *S. aureus* for oxygen at the same time *S. aureus* is disadvantaged by the lower energy production afforded by fermentation. This affects not only the viability of *S. aureus*, it is also believed to promote the development of antibiotic-resistant *S. aureus* small colony variants (SCVs). Thus, the selection of *S. aureus* SCVs in the presence of *P. aeruginosa* could allow the persistence of an antibiotic resistant subpopulation of *S. aureus* in the CF lung.

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THE ROLE OF ANAEROBIC SPECIES IN CF AIRWAY INFLAMMATION AND DISEASE

Mirkovic B, Murray M, Lavelle G, et al. The role of short chain fatty acids, produced by anaerobic bacteria, in the cystic fibrosis airway. *Am J Resp Crit Care Med*. 2015;192:1314-1324.

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The increasing appreciation that bacterial species other than the typical CF pathogens likely inhabit the CF airways not only raises questions about how these species may interact with each other *in vivo*, but also how these species affect the host, either singly or in combination. In this study, a research team led by Noel McElvaney at the Royal College of Surgeons in Ireland investigated the role that anaerobic bacteria may play in contributing to airway inflammation in CF. As a first step, the investigators used anaerobic culture to assess 80 sputum and 29 bronchoalveolar lavage (BAL) samples from 109 persons with CF. Consistent with results of several previous reports, they recovered anaerobic bacteria from the majority of samples. They next analyzed representative strains from the most prevalent species by using gas chromatography and showed that all strains secrete copious amounts of short chain fatty acids (SCFAs) when grown in vitro. Analysis of BAL samples by gas chromatography revealed the presence of micromolar concentrations of several of the same SCFAs that had been detected in the bacterial culture supernatants. Of note, SCFA levels were higher in BAL samples from adults than in those from children.

Treating epithelial cells grown in vitro with culture supernatants from representative anaerobic species resulted in a dose dependent increase in the release of IL-8, the key proinflammatory mediator in CF lungs, from the epithelial cells. This effect was more pronounced in CF epithelial cells than in normal bronchial epithelial cells and was also observed when cells were treated with nontoxic concentrations of purified SCFAs alone.

To better understand the mechanism by which SCFAs trigger a proinflammatory response from respiratory epithelial cells, the investigators focused on SCFA receptors previously identified on human bronchial epithelial cells. They observed that G protein-coupled receptor 41 (GPR41) expression was increased in CF cells compared to normal cells. Targeting GPR41 by using small interfering RNA (siRNA) technology resulted in a marked reduction in SCFA-mediated IL-8 production from epithelial cells. The investigators speculated that the increased expression of GPR41 on CF epithelial cells, relative to normal cells, was associated with CFTR dysregulation and/or endoplasmic reticulum stress. This hypothesis was supported by experiments in which normal bronchial epithelial cells treated with agents that inhibit CFTR or induce endoplasmic reticulum stress showed up-regulated GPR41 expression on their cell surfaces in vitro.

In summary, this study shows that anaerobic bacteria commonly found in CF respiratory secretions produce SCFAs *in vitro* and *in vivo*. By acting through a SCFA receptor that appears to be over-expressed on CF epithelial cells, SCFAs mediate IL-8 release. This suggests a mechanism by which anaerobic bacteria may contribute significantly to the inflammatory environment in CF airways.

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KEY TAKEAWAYS

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- Although airway infection in CF is typically polymicrobial, nearly all patients are infected with only a single strain of *P. aeruginosa*. However, the single infecting *P. aeruginosa* strain can evolve into subpopulations that differ from one region of the lung to another in virulence traits and in antibiotic resistance phenotypes.
- Microbe-microbe interactions (ie *P. aeruginosa* and *Staphylococcus aureus*) as well as microbe-host interactions also have the potential to affect disease progression and response to antibiotic therapy. Further, anaerobic bacteria may contribute significantly to the inflammatory environment in CF airways.
- Therefore, *in vitro* susceptibility testing of a single isolate recovered in culture from expectorated CF sputum samples would be limited in predicting the range of susceptibilities in the entire infecting population.

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