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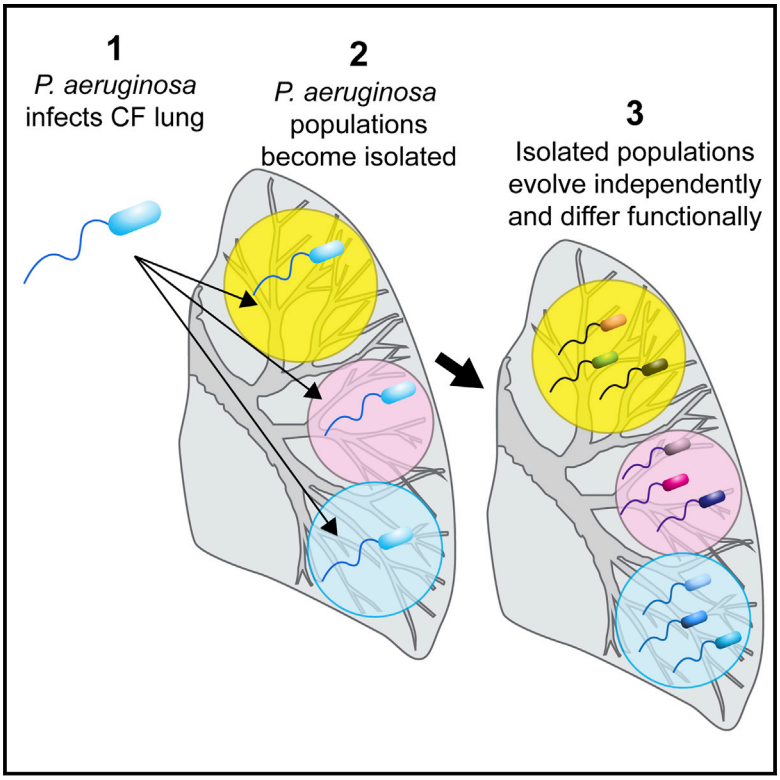
Regional Isolation Drives Bacterial Diversification within Cystic Fibrosis Lungs

Graphical Abstract



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In Brief

P. aeruginosa genetically diversifies during cystic fibrosis infections. However, the mechanisms producing diversification are unknown. Jorth et al. demonstrate that clonally related *P. aeruginosa* inhabiting different lung regions differ phenotypically and evolve divergently. Thus, isolation in different organ regions can contribute to pathogen genetic diversification within a human host.

Highlights

- Lungs from cystic fibrosis patients were dissected to obtain regional *P. aeruginosa*
- Clonally related *P. aeruginosa* from different lung regions differed phenotypically
- Phylogenetics shows regional bacteria evolve in isolation and mixing is limited
- Isolation drives divergent evolution of *P. aeruginosa* in cystic fibrosis infections

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Regional Isolation Drives Bacterial Diversification within Cystic Fibrosis Lungs

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SUMMARY

Bacterial lineages that chronically infect cystic fibrosis (CF) patients genetically diversify during infection. However, the mechanisms driving diversification are unknown. By dissecting ten CF lung pairs and studying ~12,000 regional isolates, we were able to investigate whether clonally related *Pseudomonas aeruginosa* inhabiting different lung regions evolve independently and differ functionally. Phylogenetic analysis of genome sequences showed that regional isolation of *P. aeruginosa* drives divergent evolution. We investigated the consequences of regional evolution by studying isolates from mildly and severely diseased lung regions and found evolved differences in bacterial nutritional requirements, host defense and antibiotic resistance, and virulence due to hyperactivity of the type 3 secretion system. These findings suggest that bacterial intermixing is limited in CF lungs and that regional selective pressures may markedly differ. The findings also may explain how specialized bacterial variants arise during infection and raise the possibility that pathogen diversification occurs in other chronic infections characterized by spatially heterogeneous conditions.

INTRODUCTION

Chronic infections involve long-term interactions between bacteria and their hosts, some lasting for decades. The chronic *Pseudomonas aeruginosa* infections that afflict cystic fibrosis (CF) patients are a prime example. Although host defenses, antibiotic treatment, and expectoration eliminate large numbers of organisms, bacterial replication keeps pace, enabling a single *P. aeruginosa* lineage to persist in a patient's lungs for life (Burns et al., 2001; Struelens et al., 1993). Landmark studies indicate that infecting *P. aeruginosa* evolve within CF lungs during infection (Smith et al., 2006; Yang et al., 2011). Furthermore, some common phenotypes are selected for in different strains infecting different patients, despite genetic differences in the strains and their hosts (Burns et al., 2001; Doggett et al., 1964; Huse et al., 2013; Smith et al., 2006).

Recent work also shows that infecting *P. aeruginosa* and *Burkholderia* lineages can genotypically and phenotypically diversify during CF infections (Ashish et al., 2013; Darch et al., 2015; Lieberman et al., 2014; Williams et al., 2015). Diversity likely enhances the pathogenic potential of bacterial populations by enabling rapid, adaptive responses to changes in host conditions including nutrient availability and immune and antibiotic pressure. However, the mechanisms producing diversification of infecting lineages and its consequences for disease remain unknown.

One possibility is that the genetic diversification of bacteria infecting CF lungs is driven by the isolation of organisms in different lung regions. Most CF lungs with established infection contain regions with very mild and very severe disease (Gurney et al., 1997). If regional populations were geographically isolated, they could evolve independently due to differing selective pressures and drift, a process termed genetic compartmentalization. A precedent for this mechanism exists in human infections. HIV populations infecting different body sites can be genetically compartmentalized, and compartmentalization is thought to be a key driver of viral diversification and disease progression (Heath et al., 2009; Pillai et al., 2006; Zárate et al., 2007).

However, organisms can also readily diversify in the absence of geographic isolation and spatial heterogeneity. The presence of varied nutrients or temporal fluctuations in conditions strongly promotes genetic diversification even in well-mixed and spatially homogenous environments (Jasmin and Kassen, 2007), and these factors are hallmarks of CF airway conditions.

In this study, we addressed two main questions. First, do clonally related isolates in different regions of chronically infected CF lungs differ functionally in ways that could affect their

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