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Within-host evolution of *Pseudomonas aeruginosa* toward iron acquisition from hemoglobin in polymicrobial CF infections

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Bacterial pathogens require iron to survive and colonize a human host but their access to free iron is often limited by iron-withholding process where free iron is bound by proteins such as hemoglobin. Although most pathogens have developed tactics to acquire iron from host proteins, little is known about how evolutionary processes modulate bacterial iron acquisition systems in chronic, polymicrobial infections where interspecies competition for limited iron could be an evolutionary driver.

To begin to address this issue, we use chronic airway infections in patients with cystic fibrosis (CF) as a model to investigate evolutionary adaptation to an iron-limited environment in a polymicrobial context. Here, we investigate the within-host evolution of the transmissible *P. aeruginosa* DK2 lineage sampled from (CF) airway infections over a period of several decades.

We find a positive selection for promoter mutations in *P. aeruginosa* DK2 leading to increased expression of the *phu* (*Pseudomonas* heme utilization) system. By mimicking conditions of the CF airways *in vitro*, we experimentally demonstrate that increased expression of *phuR* confers a growth advantage in the presence of hemoglobin, thus suggesting that *P. aeruginosa* evolves towards iron acquisition from hemoglobin. We also find similar adaptive mutations in the genomes of two additional *P. aeruginosa* lineages ruling out the specificity of these mutations to this particular lineage. Furthermore, in all three lineages *phuR* promoter mutations coincide with the loss of pyoverdine production, suggesting that within-host adaptation towards heme utilization is coupled to the loss of pyoverdine production. We hypothesize that this particular adaptation in *P. aeruginosa* DK2 has an impact on interspecies interaction with other members of the CF polymicrobial community capable of heme utilization. We are currently testing this hypothesis by exploring competition for iron from hemoglobin between *P. aeruginosa* DK2 and *Staphylococcus aureus* that are frequently co-isolated from CF infections.