BACTERIAL PATHOGENESIS

Divide and conquer

“ surface colonization triggers asymmetrical divisions, which generate specialized cell types — a ‘spreader’ for dissemination of the pathogen and a ‘striker’ that causes tissue damage ”

Adhesion of the opportunistic pathogen *Pseudomonas aeruginosa* to host epithelia is mediated by type IV pili (T4P) and host adhesins; however, the initial phases of bacterial colonization and how T4P are regulated during this process are not fully understood. Previous work suggested that surface sensing and the production of the second messenger cyclic di-GMP (c-di-GMP) regulates T4P biogenesis, consolidates attachment and stimulates virulence gene expression. Now, Laventie et al. report that when *P. aeruginosa* contacts host cell surfaces, it rapidly activates a c-di-GMP-dependent surface programme that promotes the biogenesis of adherent T4P. They also find that surface colonization triggers asymmetrical divisions, which generate specialized cell types — a ‘spreader’ for dissemination of the pathogen and a ‘striker’ that causes tissue damage.

As the authors hypothesized that c-di-GMP may be involved in the initial stages of *P. aeruginosa* colonization, they screened for c-di-GMP-binding proteins using capture compound technology

and mass spectrometry, and then investigated these hits further using fluorescence microscopy. They identified FimW (also known as PA4958) as a high-affinity binder of c-di-GMP and showed that this protein rapidly localizes to cell poles during surface contact in a c-di-GMP-dependent manner.

Next, the authors investigated potential sensors that trigger FimW relocalization and found that MotAB — a flagellar motor stator complex that is required for swimming in liquid — is necessary for relocalization and that artificially increasing c-di-GMP in a ΔmotAB strain rescued the polar localization. To identify diguanylate cyclases and phosphodiesterases that facilitate surface-dependent FimW activation, the authors screened a library of transposon insertions within genes encoding c-di-GMP-related enzymes and found that a number of specific members of the diguanylate cyclase family activate FimW. These data suggest that *P. aeruginosa* senses surfaces through its rotary motors, and in response increases c-di-GMP levels, resulting in FimW relocalization.

The authors observed that FimW is crucial for piliation and for surface attachment — cells expressing a variant of FimW that cannot bind c-di-GMP are unable to attach to surfaces. Furthermore, FimW is required for walking motility, enabling cells to adopt a vertical position to explore the surrounding environment.

Next, the authors observed newly attached *P. aeruginosa* cells during the first cellular divisions. They tracked >200 cell lineages and found that approximately two-thirds of divisions were asymmetrical; after dividing, FimW remained polar in one daughter cell while reverting to a

cytoplasmic distribution in the other cell. Remarkably, cells with a cytoplasmic distribution were found to be in an unstable state that leads to either their detachment from surfaces or the development of polar FimW distributions. By contrast, cells with a polar FimW distribution were stable and never detached or altered their FimW distribution. The authors posit that this asymmetry is driven by differences in distribution of c-di-GMP after division. In agreement with this, Pch (a phosphodiesterase that degrades c-di-GMP and causes heterogeneity in c-di-GMP after cell division) and FimW localized to opposite poles.

The authors hypothesized that the observed asymmetry promotes colonization and the virulence of *P. aeruginosa*. In infection experiments, in which A549 lung epithelial cells were infected at a low multiplicity of infection, wild-type bacteria homogeneously colonized the epithelium. By contrast, a Δpch mutant formed compact microcolonies and caused local cell death. Co-inoculation of wild-type and Δpch bacteria on microscopy slides designed to assess colonization over long ranges showed that wild-type cells had an advantage in colonizing distant sites, suggesting that asymmetrical division promotes the colonization of surfaces.

Altogether, these data led the authors to propose a ‘touch-seed-and-go’ model for *P. aeruginosa* surface colonization that creates phenotypic diversity to enhance spread and virulence.

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