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COMMENTARY

Sit and Stay a While: How BfiSR Controls Irreversible Attachment in *Pseudomonas aeruginosa* Biofilms[▽]

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The opportunistic pathogen *Pseudomonas aeruginosa* is an important example of the clinical relevance of microbial biofilms: the ability of this microbe to form sessile, multicellular communities is thought to play a major role in catheter infections, ventilator-associated pneumonia, and chronic lung infections in patients rendered susceptible by cystic fibrosis (11). Although early studies of this process focused largely on initial surface attachment, increasing evidence suggests that multiple points in this developmental process are regulated at both transcriptional and posttranscriptional levels. In this issue of *Journal of Bacteriology*, Petrova and Sauer dissect the role of the two-component system BfiSR in the transition between initial and irreversible attachment (10). This control occurs through transcriptional regulation of CafA (RNase G), which modulates levels of a small RNA (*rsmZ*) associated with multiple steps in biofilm formation. This elegant study mechanistically describes how *P. aeruginosa* biofilm formation is not a simple “switch” but instead a stepwise process in which external information is continually assimilated and translated as the organism transitions between various stages of biofilm development.

The initial attachment stages of *P. aeruginosa* biofilm formation are strongly influenced by the action of at least five two-component regulatory systems (TCSs). Three of these TCSs (GacS, RetS, and LadS) form a network that controls expression of small RNAs (*rsmY* and *rsmZ*) that in turn sequester the mRNA binding protein RsmA (2–4, 6, 12). RsmA directly binds and destabilizes certain target mRNAs; other targets appear stabilized by RsmA, although this may be indirect (1). Destabilized targets include *pel* and *psl* exopolysaccharides, which are both associated with initial stages of biofilm formation. An additional two TCSs regulate swimming and twitching motility, which are also implicated in this process (8).

In a previous work, Petrova and Sauer used metal oxide affinity chromatographic methods to identify phosphoproteins associated with specific stages of biofilm development (9). This earlier study demonstrated that three TCSs (BfiSR, BfmSR, and MifSR) are phosphorylated in a biofilm stage-specific manner and that deletion of each system arrests biofilm formation at the stage at which phosphorylation is observed. This

report provided support for a developmental model for biofilm formation, with stage-specific checkpoints under regulatory control (7), although how these TCSs are involved was not established.

In the study published in this issue of *Journal of Bacteriology*, Petrova and Sauer again demonstrate how proteomic approaches can shed new light on biofilm formation. In this report, they focus on BfiSR, a TCS required for the transition from initial to irreversible attachment. Comparison of wild-type and $\Delta bfiS$ mutant proteomes from cells grown under biofilm conditions suggested a regulatory overlap with the Gac/Rsm system; consistent with this observation, the authors demonstrate that the levels of *rsmYZ* are significantly higher in $\Delta bfiS$ biofilms than in their wild-type counterparts. Notably, this difference is not observed in planktonic cells, suggesting that loss of BfiS specifically disrupts the reduction of *rsmYZ* levels that occurs in wild-type cells after surface attachment. This observation is confirmed by overexpression of these small RNAs: overexpression of *rsmZ* in a wild-type background results in biofilms that resemble those formed by the $\Delta bfiS$ mutant (*rsmY*-overexpressing cells, in contrast, form biofilms with a wild-type morphology). This result is important for two reasons: first, it shows that BfiS-dependent repression of *rsmZ* is a critical postattachment step in biofilm formation (note that earlier studies have associated upregulation of this small RNA with initial attachment [3]), and second, it suggests that overexpression of *rsmZ* and *rsmY* have distinct phenotypic consequences.

To determine how the BfiSR TCS modulates *rsmZ* levels, the authors next use chromatin immunoprecipitation to identify the DNA targets of the response regulator BfiR. The majority of sequences identified were located upstream of *cafA*, the gene encoding RNase G. This and other results described in the article further differentiate *rsmZ* from *rsmY* (turnover of the former, but not the latter, is *cafA* dependent) and suggest that this RNase has considerable target specificity. Further, *rsmZ* emerges as a target of impressive coordination: signals from at least three sensor kinases (GacS, RetS, LadS) appear to regulate this 127-nucleotide RNA at the transcriptional level, and a fourth (BfiS) further modulates its steady-state levels via CafA.

The TCS-dependent developmental model proposed by Petrova and Sauer, described in an earlier report and significantly extended here (10), is attractive for several reasons. First, it suggests that a series of identifiable (and potentially disruptable) checkpoints govern biofilm formation in clinically

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and industrially important settings. Second, this model implies that these checkpoints, though distinct, can include central “barometers” such as *rsmZ*, whose levels can increase to activate one stage of biofilm formation and decrease to activate the next. Identification and careful characterization of such proteins (or in this case, small RNAs) can provide clues to other inputs and outputs of the network. Third, the model implies that integration of multiple TCSs may be a common theme in controlling complex processes in bacteria. In this respect, the roles of TCS-associated accessory proteins (5) in coordinating TCS functions may be underappreciated.

Although the model proposed is appealing, this report raises several critical questions. Specifically, how does CafA target *rsmZ* and how does the BfiSR TCS control *rsmY* levels in a CafA-independent manner? Further, why is BfiSR (or down-regulation of *rsmZ*) required for the transition from initial to irreversible attachment? More generally, this study raises a further “call to arms” to develop methods to identify ligands for two-component sensor kinases. Without an understanding of the ligands that likely signal the transitions between stages of biofilm formation, it will be difficult to complete a picture of this (or any other) TCS-dependent developmental process in microbes. Perhaps the same multidisciplinary approach demonstrated in the report highlighted here will be useful in these efforts.

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