Peculiarities of the regulation of the *Brucella* flagellum

The bacterial flagellum is involved in swimming motility and is exquisitely complex, with different structures comprising a basal body with different rings, a hook and a filament (Macnab, 1996). The biogenesis of the flagellum is a stepwise process that begins with building the basal body, followed by biogenesis of the hook and finally, extending the filament made of FliC protein subunits, which is an energetically costly process (McCarter, 2006). This process has been extensively investigated in *Escherichia coli* and *Salmonella* where there is a regulatory cascade at work involving three steps (class I–III genes) (Aldridge & Hughes, 2002; Soutourina & Bertin, 2003). In *E. coli*, the master regulator controlling the expression of class II genes is FlhDC. The products of the class II genes code for structural proteins and for two regulators. The class II structural proteins are FliF and FlgE, which are components of the basal body and the hook, respectively. The class II regulators in *E. coli* are FliA (an alternative sigma factor, also termed σ_{28}) and its anti-sigma, FlgM. When the hook is completed, the anti-sigma FlgM is secreted through its channel, allowing σ_{28} to activate the expression of the class III genes, including the FliC flagellin, hence completing the formation of the filament (Brown *et al.*, 2008; Chevance & Hughes, 2008). In the alphaproteobacterium *Caulobacter crescentus*, the flagellum biogenesis is even more complex, involving four hierarchical steps whereby the last genes (class IV) are under the post-transcriptional control of FlbT, a protein that binds to the flagellin mRNA, preventing its translation (Anderson & Gober, 2000). FlbT is antagonized by the transcription regulator FlaF, which represses the transcription of the *flbT* gene. In *Sinorhizobium meliloti*, another member of the order *Rhizobiales*, the regulation is even more complex and two-tiered, involving two different class II genes, class IIa and IIb (Sourjik *et al.*,

2000). Even though both *C. crescentus* and *S. meliloti* are alphaproteobacteria, in *Brucella melitensis*, another intracellular pathogen that is in the same order, the model described above is different, as demonstrated by Ferooz and colleagues in two articles published in this issue of *Microbiology* (Ferooz *et al.*, 2011a, b).

First, in this bacterium the production of the filament flagellin subunit FliC is not

subject to the completion of the basal body and the hook since mutants deficient in the FlgE (hook protein) and FliF (basal body) still produce the protein at wild-type level. *B. melitensis* produces a polar flagellum which characteristically has to be sheathed and to be produced only transiently at the end of the exponential phase of growth. In contrast with *C. crescentus*, the FlbT regulator in *B. melitensis* is needed for the production of the FliC flagellin, since a *flbT* mutant fails to produce FliC, while

Fig. 1. Regulation of flagellum biogenesis in *B. melitensis*. Regulators are shown in white on a black background, flagellar structural proteins are in black on a grey background. The genes are divided into classes I, II and III. Arrows represent a positive regulation while a blunt-ended line represents negative regulation.

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complementation with the regulator *in trans* restores the production of the flagellin, even in a mutant where the master regulator FtcR has been inactivated (Ferooz *et al.*, 2011a). FlaF, on the other hand, acts in the opposite direction, since FlaF downregulates the production of FliC. Interestingly, FlbT from *S. meliloti* could also restore the production of flagellin while the *C. crescentus* FlbT could not, confirming an opposite role for these two FlbT proteins. In their companion paper (Ferooz *et al.*, 2011b), these authors demonstrate that the alternative sigma factor RpoE1 represses the production of FlgE (hook protein) and FliC (flagellin) via activation of an unknown repressor, which in turn negatively regulates the expression of the master flagellar regulator FtcR, since expression of both *flaF* and *flbT* regulator genes was also found to be increased in the *rpoE1* mutant. A model combining and summarizing the two findings is presented in Fig. 1.

In conclusion, flagellar biogenesis shows interesting variations among different proteobacteria and even among members of the alphaproteobacteria. *Brucella* flagellar genes are required for the establishment of *in vivo* infection in mice and goats (Fretin *et al.*, 2005; Zygmunt *et al.*, 2006). However, the molecular basis

of the impact of the flagellum on virulence remains to be determined.

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