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 σ28) and its anti-sigma, FlgM. When the hook is completed, the anti-sigma FlgM is secreted through its channel, allowing σ28 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 FliT, 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 twotiered, 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.](image-url)
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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