Cell polarity/motility in bacteria: closer to eukaryotes than expected?

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The Gram-negative bacterium *Myxococcus xanthus* glides on solid surfaces and periodically reverses the direction of movement. Work published in this issue of *The EMBO Journal* (Leonardy *et al*, 2010) reports on the small GTPase MglA that ensures the correct polarity of the motility engines through its GTP/GDP cycle in conjunction with its cognate GAP, MglB. MglA has also been shown to interact with the actin-like protein MreB in eukaryotic-like motility complexes. Altogether, the data suggest that compelling similarities exist between the mechanisms of motility and establishment of cell polarity in *M. xanthus* and eukaryotes.

M. xanthus moves through the synergistic activity of two genetically, functionally and structurally different motility engines (Hodgkin and Kaiser, 1979). The first motility system, Social (S) motility, functions through the extension and retraction of polar Type IV Pili (Sun *et al*, 2000), whereas the second motility system, Adventurous (A) motility, is powered by distributed motors that assemble at the leading cell pole. These motors behave similarly to the eukaryotic focal adhesion complexes observed in apicomplexan parasites (Mignot *et al*, 2007). *M. xanthus* cells periodically reverse the direction of their movement by switching the polarity of the A and S engines at a frequency that is modulated by the Frz chemosensory system (Zusman *et al*, 2007) (Figure 1). Recently, evidence indicates the fact that similar mechanisms are shared by *M. xanthus* and eukaryotic cells regarding the way in which motility functions and cell polarity are established. In particular, the featured paper from the Sogaard-Andersen laboratory describes the importance of

a small GTPase, MglA and its GTP/GDP cycle in the regulation of cell polarity in *M. xanthus* (Leonardy *et al*, 2010). The GTPases of the Ras superfamily perform a broad range of functions in eukaryotic cells including transport, signal transduction and cell migration (Charest and Firtel, 2007). The gene encoding MglA was first reported by Hodgkin and Kaiser (1979) and annotated as *mutual gliding A (mglA)* mutant, because its deletion caused defects in both A and S motility (Hodgkin and Kaiser, 1979). Some years later, Hartzell (1997) showed that MglA belongs to the Ras superfamily of small eukaryotic GTPases. In fact, the expression of the yeast Ras family protein SAR1 in *mglA* cells that were unable to sporulate rescued sporulation (Hartzell, 1997). Mauriello

Figure 1 The core of the Frz system, such as chemotaxis pathways in enteric bacteria, consists of a receptor, FrzCD, a histidine kinase, FrzE, a CheW-like coupling protein FrzA and a dual response regulator protein, FrzZ (Zusman *et al*, 2007). MglA and MglB are downstream of the Frz pathway. The Frz pathway might act as a direct or indirect GEF of MglA and mediate the accumulation of GTP-bound MglA at the leading pole. MglB, acting as a GAP, inhibits MglA localization at the lagging pole by keeping the concentration of GTP-bound MglA very low at this site. The MglA GTPase activity is essential to establish the correct polar localization of RomR and PilT, but not AglZ. Mauriello *et al* (2010) showed that in the absence of MglA, AglZ and FrzS are mislocalized (AglZ also signals directly to FrzCD). In the absence of MglA, activity cells still reverse, suggesting the presence of a yet unproved regulatory activity of the Frz pathway on MglA (dashed line) and the existence of an intrinsic reversal clock.

et al (2010) first showed that MglA is able to slowly hydrolyse GTP *in vitro* and represents a polarity factor in *M. xanthus* as it (i) localizes mostly at the leading cell pole (also along the cell, in positions occupied by the A motility machineries); (ii) establishes the polar localization of motility proteins using mechanisms that might also involve the actin-like protein, MreB (Mauriello *et al*, 2010).

In their recent work, Leonardy *et al* (2010) conducted elegant biochemical analyses to assign MglB, the small protein produced by the first gene of the *mglBA* operon, the function of the cognate GAP of MglA. The authors, in fact, showed that MglB specifically recognizes, binds to and stabilizes the GTP-bound form of MglA, significantly enhancing the hydrolysis of GTP. The GTPase activity, but not the ability to bind GTP, is lost when MglA carries a G to V substitution that locks the protein in the GTP-bound state. Subsequent *in vivo* analyses revealed the biological significance of the MglA-MglB combined activity and the function of the GTP/GDP cycle in the establishment of cell polarity in *M. xanthus*. Although *mglA* mutant cells appear to be completely non-motile, *mglA*^{G21V} and *mglB* mutant cells show a hyper-reversing phenotype. This suggests that while the complete absence of MglA causes a lack of cell movement, the lack of only the GTPase activity leads to an unregulated reversal frequency and switch of polarity. Double mutants and phenotypic analyses show that the Frz chemosensory system signals, directly or indirectly, to MglA to control the reversal frequency (Figure 1). The result represents an additional point of similarity with eukaryotic organisms, such as *Dictyostelium discoideum* in which small GTPases work in concert with chemoreceptors to polarize the cell and determine directional movement during chemotaxis.

On the basis of localization studies, the authors hypothesize how MglB exerts its function as a GAP of MglA and

propose that the establishment of cell polarity depends on the equilibrium between GTP and GDP-bound MglA. First of all, the authors show that GTP-bound MglA (YFP-MglA and YFP-MglA^{G21V}) predominantly localizes at the leading cell pole and switches its polar localization upon cell reversals. Conversely, GDP-bound MglA (YFP-MglA^{T26/27N}) is diffused in the cytoplasm. MglB-YFP localizes at the opposite pole with respect to MglA. YFP-MglA localization is affected in *mglB* mutant cells in which the protein localizes at both cell poles. The authors propose that the Frz pathway acts as a direct or indirect GEF as it favours the accumulation of GTP-bound MglA at the leading pole. At the opposite pole, MglB keeps the concentration of GTP-bound MglA very low by promoting GTP hydrolysis. A reversal occurs when GTP-bound MglA reaches a concentration high enough to form a cluster at the lagging pole. By an as of yet unknown mechanism, MglB then relocates the old leading pole and a new reversal cycle begins. Patryn *et al* (2010) proposed, based on immunofluorescence microscopy studies, that the relocation of MglA from pole to pole occurs in a helical manner further reinforcing the hypothesis that MglA and MreB work in concert (Mauriello *et al*, 2010; Patryn *et al*, 2010).

Interestingly, in the absence of MglA GTPase activity, cells are still able to reverse suggesting the existence in *M. xanthus* cells of a yet uncharacterized intrinsic reversal clock.

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Conflict of interest

The author declares that she has no conflict of interest.

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