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Chemotaxis: Communication strategies from bacteria to humans

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Signal transduction in bacterial chemotaxis

We explore signal transduction strategies using chemotaxis of the bacteria *Escherichia coli* and *Salmonella typhimurium* as a model. Bacterial chemotaxis is a sophisticated system that integrates many different signals into a common output - a change in the direction of flagellar rotation. Our goal is to understand how CheY - a messenger protein that shuttles back and forth between the receptor supramolecular complex and the flagellar-motor supramolecular complex (Fig. 1) - brings about changes in the direction of flagellar rotation. We found that phosphorylation of CheY increases its binding to the switch protein FliM with a consequent increased probability of clockwise rotation, we identified the reciprocal binding domains on FliM and CheY, and we further found that CheY phosphorylation also regulates the termination of the signal by controlling the activity of a specific phosphatase, CheZ. Recently we investigated the correlation between the fraction of FliM molecules that are occupied by CheY and the probability of clockwise rotation. We found that this probability increases only when most of the FliM molecules are occupied by CheY, and then the change is very steep. Furthermore, the change in clockwise probability upon an increase in the occupancy level of FliM is not the inverse of the probability change upon a decrease in the occupancy, suggesting the involvement of hysteresis in the function of the switch within the flagellar-motor supramolecular complex. Such a situation of hysteresis, which involves a difference between the thresholds for clockwise rotation when the occupancy increases and decreases, might reflect a damping mechanism, which prevents a situation in which fluctuations in the phosphorylation level of CheY throw the switch from one direction of rotation to the other (Fig. 2).

A number of lines of evidence indicate that the signal transduction circuit, as currently known in chemotaxis (Fig. 1), is not complete. In a search for missing steps, we found a few additional players: (a) We found that phosphorylation is not the only chemical modification of CheY and not the only one that activates the protein. We found that CheY also undergoes specific acetylation at lysine residues, mediated by the enzyme acetyl-CoA synthetase (Acs), and that the consequence of this acetylation is a large increase in CheY activity. Recently we

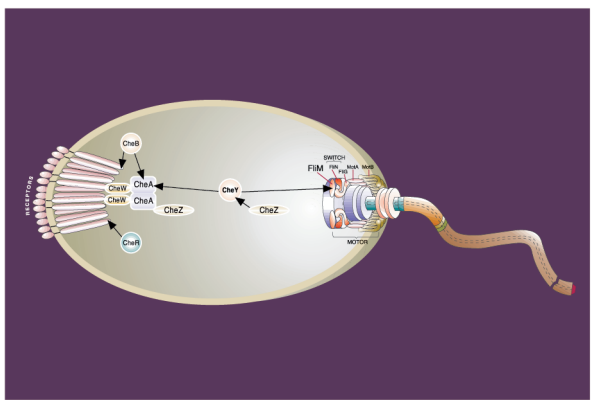

Fig. 1 *Simplified scheme of signal transduction in bacterial chemotaxis of E. coli and S. typhimurium. Black arrows stand for regulated protein-protein interactions. CheY is a response regulator, CheA is a histidine kinase, and CheZ is a phosphatase.*

provided evidence that CheY acetylation also occurs in vivo and that, in the absence of Acs, chemotaxis is defective. (b) We found another component, fumarate, which modulates the probability of clockwise rotation. It does so by interacting with the switch and lowering the standard free energy difference between its clockwise and counterclockwise states. (c) We demonstrated that *E. coli* probably possesses an additional signal transduction pathway, different from the conventional pathway. Currently we are trying to understand why two modes of signal activation (one by phosphorylation and one by acetylation) are needed, to identify the roles of CheY acetylation and fumarate action, and to reveal the molecular mechanism underlying the additional signaling pathway.

Mammalian sperm chemotaxis

Observations made in our laboratory suggest that, in humans, the egg and sperm communicate prior to fertilization by way of chemotaxis. This process is mediated by a chemoattractant(s) secreted from the egg or its surrounding cells and detected by the sperm cells. We demonstrated that only a small fraction of the sperm population is chemotactically responsive at any given time, and that spermatozoa acquire this responsiveness as part of capacitation process. They lose this responsiveness when

the capacitated state is terminated. Based on our observations that a human sperm cell can remain capacitated for no more than 4 hours (at least in vitro) and that the capacitated cells within a sperm population are continuously replaced, we suggested that this situation results in extended availability of capacitated cells following mating, and that this is a mechanism, which was evolved in humans, to compensate for the lack of linkage between sperm entry and ovulation. Recently, in collaboration with the group of L.C. Giojalas in Argentina, we put this hypothesis to test by examining the timing and length of the sperm's capacitated stage in the rabbit, where ovulation is not periodical but rather induced by mating. The situation in the rabbit was indeed found to be different, and the time window of the capacitated state was found to be perfectly synchronized with the time window, at which an egg can be found in the rabbit's oviduct. We are currently trying to identify the chemoattractants as a first step towards revealing the molecular mechanism of sperm chemotaxis in mammals.

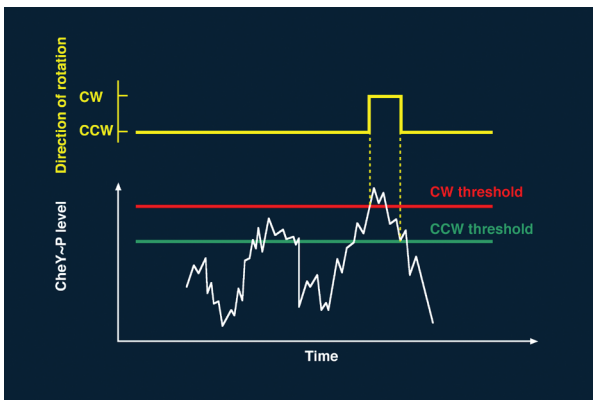

Fig. 2 *Schematic presentation of the potential role of the different thresholds of CheY~P for clockwise (CW) and counterclockwise (CCW) rotation. Lower panel, hypothetical random fluctuations in CheY~P levels. Upper panel, direction of flagellar rotation.*

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For additional information see:

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