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meeting report

Sense and sensibility in bacteria

VIIIth International Conference on Bacterial Locomotion and Sensory Transduction

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The VIIIth International Conference on Bacterial Locomotion and Sensory Transduction (BLAST) was organized by R. Kadner, I. Kawagishi, P. O'Neill, J. Falke and J.S. Parkinson and was held in Boca Raton, FL, USA between 16 and 21 January 2005. This was the first BLAST Conference since the untimely death of Professor Robert Macnab of Yale University, one of the founders of the field of bacterial locomotion. We were delighted to inaugurate the first Bob Macnab prizes for poster presentations by young scientists. First prize went to Tatiana Besschetnova (Amherst, MA, USA; second on right), second prize to Collin Dyer (Santa Barbara, CA, USA; second on left), and third prize to Roger Alexander (Atlanta, GA, USA; far left). The winners received their awards from Bob's widow and co-researcher, May Kihara-Macnab (New Haven, CT, USA).

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Introduction

Two hundred bacterial researchers gathered in an unseasonably cold Boca Raton for the VIIIth Bacterial Locomotion and Sensory Transduction (BLAST) meeting. They quickly warmed to a programme that revealed several key themes. Bacterial flagellar motility and chemotaxis are relatively well understood, with studies increasingly moving to the structural level with contributions from crystallography and electron microscopy. At the same time, genomic data and new experimental models have allowed significant advances in understanding several types of non-flagellar gliding motility. The traditional two-component chemotactic systems are also being studied on a structural level, to determine how phosphosignalling from tactic receptor teams is achieved. Finally, recent work on alternative regulatory systems shows interactions between motility, synthetic, sensory and pathogenicity genes and confirms that bacterial regulatory pathways comprise a true network with many dynamic interactions between the components. These advances highlight the need for further in-depth understanding of the principles of bacterial cellular architecture and the determinants of cell polarity. Bacteria are spatially and sensorially highly organized, and this organization is very dynamic: they are so much more than just simple bags of enzymes.

Flagellar motility

Bacterial flagellar motility (Fig 1A) was a keystone of the meeting and is the best understood type of bacterial movement. The rotation of helical flagellar propellers is driven by the diffusion of ions, down an electrochemical gradient, through MotAB motor-stator proteins bound to the cytoplasmic membrane. These stator proteins interact with basal protein membrane-supramembrane (MS) and cytoplasmic (C) rings, which are rotor components of the motor that are attached to the cytoplasmic membrane. The interaction causes the rotation of the MS and C rings and of the flagellar filaments to which they are attached. Advances in flagellar rotation included the demonstration by Y. Sowa (A. Ishijima group, Nagoya, Japan) that ~12° steps in rotation can be visualized for flagella motors when they are manipulated to rotate slowly at low ion concentrations. This could be extrapolated to 30 steps per complete flagellar revolution.

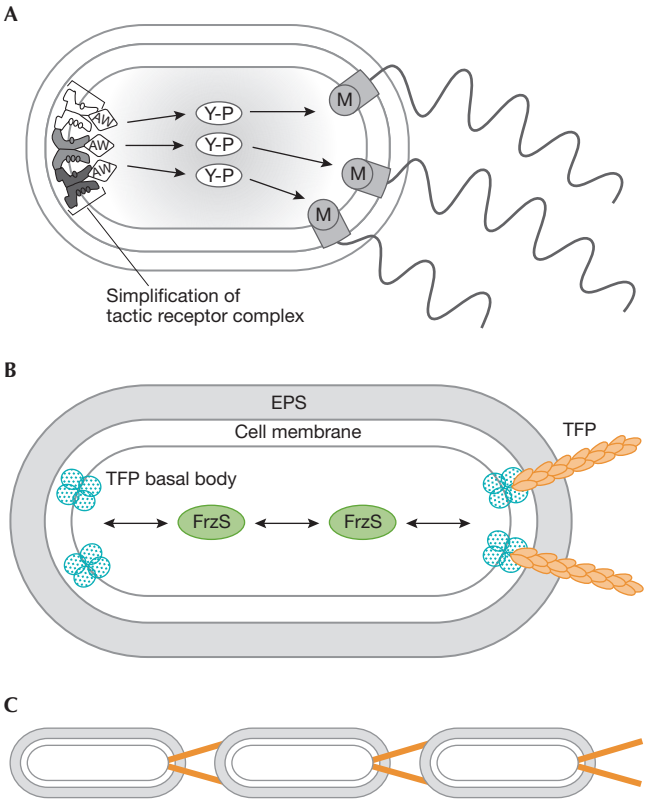

Fig 1 | Simplified diagrams of bacterial motility systems. (**A**) Schematic overview of simplified chemotactic signalling in flagellate *Escherichia coli*. Clusters of receptor–CheA kinase–CheW complexes signal chemotactic receptor occupancy by changing the phosphorylation state of cytoplasmic CheY signalling proteins, shifting the CheY conformational equilibrium towards the active conformation. The CheY-P proteins tactically modulate flagellar rotational behaviour by interaction with FliM switch proteins, located at the basal C ring of the flagellar motor. (Fig 2 shows a detailed atomic model of the receptor clusters shown in outline in this schematic). (**B**) Schematic overview of social 'S' gliding motility in *Myxococcus xanthus*. This type of motility depends on cell–cell contact and involves the interaction of type IV pili (Tfp) with extracellular polysaccharide layers (EPS) on adjacent cells (see part C). Movement is achieved by Tfp retraction after attachment. The FrzS protein moves dynamically between poles concomitant with reversals in Tfp-mediated S motility. (**C**) Schematic overview of Tfp–EPS contact in *M. xanthus* cells during social 'S' gliding motility.

Using mutagenesis studies of the MotAB proteins, which channel ions to the motor, E. Hosking (M. Manson group, College Station, TX, USA) proposed that a periplasmic MotB domain forms a lid over an adjacent MotA protein to restrict ion entry until motors are assembled. Y. Toshiharu (from the groups of M. Homma, Nagoya, Japan, and D. Blair, Salt Lake City, UT, USA) further probed how dynamic interactions between MotAB proteins lead to conformational changes in the flagellar motor and hence rotation. D. Thomas (Waltham, MA, USA) used image reconstruction of electron micrographs to show how the matching symmetries of the flagellar MS ring and the inner domain of the C ring suggest how they might interact in motor rotation. However, many bacteria actively glide over surfaces using processes that do not involve flagella (McBride, 2001), and the meeting advanced our understanding of the mechanisms underlying this gliding motility.

Myxococcus xanthus: adventurous and social motility

Myxococcus xanthus has two gliding motility systems: the S system, which operates on the surfaces of cells within contact distance of each other (Fig 1B,C); and the A system, which operates in single cells (Sogaard-Andersen, 2004). S motility depends on type IV pili (Tfp). W. Shi (Los Angeles, CA, USA) reported that S motility relies on the following sequence of events: assembly of Tfp at the pole of a cell, Tfp attachment to the polysaccharide portion of the extracellular matrix on a nearby cell, the retraction of Tfp and, consequently, the forward movement of the Tfp-containing cell (Fig 1B,C).

The mechanism underlying A motility in *M. xanthus* is enigmatic. The current model states that slime secretion from polar-localized nozzle-like structures generates the motive force. P. Hartzell (Moscow, ID, USA) reported findings to suggest that slime secretion may only be part of the A motility mechanism. The cytoplasmic MglA protein, a member of the Ras/Rab/Rho superfamily of small eukaryotic GTPases, interacts with the membrane-bound tyrosine kinase MasK to regulate S motility, and interacts with the AglZ protein to regulate A motility. AglZ contains a myosin-like carboxy-terminal coiled-coil domain, and immunofluorescence and AglZ–green fluorescent protein (GFP) visualization show that AlgZ forms a helical filament in the cytoplasm *in vivo* (Yang *et al*, 2004). Whether this helix forms a structural skeleton that contributes to the movement of the bacteria awaits further investigation.

M. xanthus cells regularly reverse their gliding direction, possibly due to a coordinated switch in the polarity of the two gliding engines. Elegant immunolabelling and *in vivo* analyses of FrzS–GFP fusions by T. Mignot (D. Zusman group, Berkeley, CA, USA) showed that the FrzS protein may have a critical role in switching the polarity of Tfp. FrzS is localized to both cell poles, but localization is highly dynamic with a 'package' of FrzS being dispatched from the FrzS cluster at the leading pole of a cell to the cluster at the lagging end (Fig 1B). A cell reversal coincides with the arrival of an FrzS package at the lagging pole. Simultaneously, a package of FrzS is dispatched from the new leading pole to the lagging pole. It remains to be shown whether FrzS triggers reversals or relocalizes after reversals. Nonetheless, FrzS dynamics suggest mechanisms that generate cell polarity to control the direction of motility.

Mycoplasma and 'dead cells gliding'

Mycoplasma cells also glide, but apparently without flagella, pili or slime secretion. The flask-shaped *Mycoplasma* cells move in the direction of the tapered end. Recently, spike structures, which protrude from the membrane and attach to the substratum, were implicated in gliding motility in *Mycoplasma mobile* (Miyata & Petersen, 2004). A. Uenoyama (M. Miyata group, Osaka, Japan) defined the positions of key gliding proteins within spikes or at their cell anchors and related these to the effects of mutations in the corresponding genes on gliding motility. To analyse the energy source for gliding motility, a 'ghost' cell model was established in which cells were permeabilized and killed by detergent treatment. Intriguingly, the addition of ATP to the ghost cells resulted in the movement of ghosts with the same characteristics as live cells, whereas uncleavable ATP analogues inhibited motility. These data suggest that the ghosts harbour an intact gliding apparatus and that the energy source for gliding motility is ATP.

Flavobacterium: staying on track?

Flavobacterium johnsoniae, a third gliding model system, lacks flagella, pili and other surface structures that could be involved in gliding motility. These bacteria can propel latex spheres along their surface, a phenomenon that has been connected to gliding motility (McBride, 2001). T. Braun (M. McBride group, Milwaukee, WI, USA) reported that the GldJ outer-membrane lipoprotein is required for gliding motility and forms a helical structure in the cell envelope. It remains to be shown whether this helical structure is dynamic and whether it constitutes part of the conveyor belt that propels latex spheres across the cell surface.

Regulatory crosstalk between systems

New regulatory links between motility genes and other systems were also reported at the meeting. Q. Wang (Austin, TX, USA) showed that for multi-flagellate bacteria swarming on surfaces, mutations in the chemotaxis genes alter hydration of the bacterial colonies, which affects the secretion of the flagellar-regulatory anti-s28-σ factor FlgM and, consequently, the length of flagella produced (Wang *et al*, 2005). K.A. Syed (K. Klose group, San Antonio, TX, USA) reminded us that mutants of the human gut pathogen *Vibrio cholerae* that lack flagella not only show a decrease in intestinal colonization, but also produce high levels of exopolysaccharides, which are important for biofilm formation on intestinal surfaces (Watnick *et al*, 2001). Syed investigated this regulatory connection by analysing global gene expression in flagellar mutants, and found upregulation not only in cell adhesion genes but also in many virulence genes. Interestingly, he also found that two GGDEF domain proteins, which have potential diguanylate cyclase activity, were under the control of the flagellar σ-subunit s28. Mutants that lacked one of these potential diguanylate cyclases showed upregulated haemolysis and haemagglutination behaviour. These results support the suggestion (Tischler & Camilli, 2004) that the second messenger cyclic diguanosine monophosphate (c-diGMP) controls virulence determinants in *V. cholerae*. In *M. xanthus*, Z. Yang (Blacksburg, VA, USA) showed that Tfp may act as a sensor to appropriately induce the synthesis of the extracellular matrix polysaccharides that are required for gliding motility (Yang & Li, 2005).

Molecular detail of *Escherichia coli*'s chemosensory 'nose'

Bacterial chemotactic signalling starts with the detection of a chemical gradient by the binding of attractant or repellent molecules to the extracellular portion of a protein receptor complex located at the cell pole. These complexes contain several thousand copies each of different transmembrane receptor dimers, the cytoplasmic kinase CheA and the scaffold protein CheW. Receptor occupancy regulates autophosphorylation of the CheA kinase. Subsequent transfer of phosphoryl groups to the freely diffusible response regulator CheY activates it to bind at the flagellar switch and to mediate a chemotactic response (Fig 1A).

Understanding how these complexes are spatially arranged will clarify how receptor dimers communicate with each other, and should account for several fundamental properties of chemotaxis, such as its extraordinary sensitivity and its ability to integrate information from different receptor types. Towards this end, P. Wolanin (J. Stock group, Princeton, NJ, USA) presented an atomic model based on an extensive collection of electron microscopy images of a complex containing the receptor-cytoplasmic domain, CheA and CheW (Francis *et al*, 2004). Modelling the atomic structures of the protein components into the elongated, bi-lobed, microscopic image reconstruction (Fig 2) showed receptor dimers to be arranged in asymmetrical groups of three, with the long coiled-coil regions extending roughly parallel to each other with their ends interacting with CheA and CheW. Additionally, S. Subramaniam (Bethesda, MD, USA) showed that engineered *Escherichia coli* overproduced receptors in microcrystalline hexagonal arrays, consistent with dimers clustering in fundamental units of three (Zhang *et al*, 2004). This grouping agrees with the 'trimer of dimers' arrangement observed in the crystal packing of purified receptor-cytoplasmic domains (Kim *et al*, 1999), but the nature of the interactions differs between the dimeric hairpin ends in a symmetrical trimer.

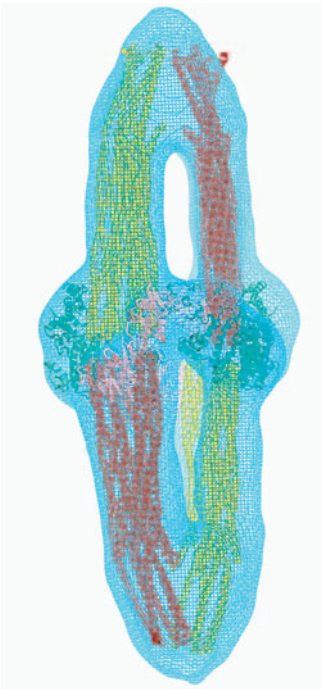

Fig 2 | Modelling of the density map derived from electron microscopic images of a soluble receptor/CheA/CheW complex (blue mesh) with atomic structures of the individual protein components (presented by P. Wolanin and described in more detail in Francis *et al*, 2004). The atomic structures are displayed in ribbon format and are CheA (cyan), CheW (magenta), and the cytoplasmic domain of the chemoreceptor (yellow and red).

Several labs presented genetic and biochemical work in support of the functional relevance of these inter-dimer interactions. R. Alexander (I. Zhulin group, Atlanta, GA, USA) compared 1,250 receptor protein sequences from 75 bacterial and archaeal genomes, and found high sequence conservation in residues predicted to be involved in inter-dimer contacts. P. Ames (Salt Lake City, UT, USA) found that genetic suppressors to defective receptors, with mutations in regions of predicted inter-dimer contacts in the trimer, all contained amino-acid substitutions in the predicted trimer contact region of a different type of receptor. This probably restores activity by correcting inter-dimer geometry in the trimer. A. Miller (J. Falke group, Boulder, CO, USA) probed the inter-protein interactions in the receptor–CheA–CheW complexes by assessing the ability of a bulky sulphydryl-reacting reagent to inhibit complex formation *in vitro* for CheA mutants with different surface cysteine

substitutions. S.-Y. Park (B. Crane group, Ithaca, NY, USA) used an electron spin resonance method to determine the distances between spin labels located on either protein in the stable CheA–CheW complex. Complementing the structural approaches, C. Studdert (Mar del Plata, Argentina) showed that the exchange of newly formed receptor dimers into established trimers *in vivo* was highly dynamic in the absence, but not in the presence, of CheA and CheW (Studdert & Parkinson, 2004). It is now clear that there is extensive collaborative signalling by bacterial chemoreceptors, with teams of mixed receptors being formed by triplets of receptor dimers (Parkinson *et al*, 2005). The challenge now is to understand how closely the atomic models of subunit interactions from *in vitro* studies mirror the dynamic associations between receptor–CheA–CheW proteins that allow *in vivo* signalling.

Terminating the chemotactic signal

In chemotaxis, the lifetime of the signalling molecule CheY-P must be brief for the cell to respond continuously to a rapidly changing environment. In *E. coli*, but not all bacteria, efficient dephosphorylation of CheY-P is accomplished by the CheZ phosphatase. Identification of alternative phosphatases had been lacking in other bacteria until phosphatase activity was shown for CheC and FliY from *Bacillus subtilis* (Szurmant *et al*, 2004). Building on this, T. Muff (G. Ordal group, Champaign-Urbana, IL, USA) showed that FliY and CheC are members of a family of homologous proteins that also contains CheX (a putative phosphatase) and FliM, the component of the flagellar switch to which CheY-P binds (Fig 1A). Expanding the new phosphatase story, B. Crane (Ithaca, NY, USA) presented X-ray crystal structures of both CheX and CheC (Park *et al*, 2004). As predicted by sequence similarity, the two structures had similar folds, but CheX forms a dimer whereas CheC is monomeric. Both CheC and CheX show phosphatase activity towards CheY-P *in vitro*. To examine the phosphatase mechanism, Crane's group focused on pairs of conserved residues located on consecutive turns of an α-helix, reminiscent of the catalytic region of *E. coli* CheZ. Mutagenesis studies have highlighted the functional importance of the conserved pairs but have not yet shown conclusively whether the new phosphatases behave similarly to CheZ or have a novel phosphatase mechanism.

Bacterial cellular architecture

Several presentations highlighted a recent paradigm shift in microbiology: bacterial cells are highly organized spatially and this organization is highly dynamic. The advent of cell biology methods in the analysis of signal transduction in bacteria has supported this view and continues to provide stunning detail of the intricacies of bacterial cell structure. Both Hartzell and Braun showed the importance of membrane-associated helical protein filaments in gliding motility. Mignot's eye-catching demonstration of dynamic FrzS polar localization, which is correlated with the direction of gliding, exemplifies how protein localization may be transformed into morphogenetic cell movements. Also, U. Jenal (Basel, Switzerland) reported the polar sequestration of the PleD response regulator, which dynamically localizes to the differentiating *Caulobacter crescentus* cell pole as a function of its phosphorylation status. The observation that activation and subcellular localization of a regulatory protein are coupled argues that a spatially restricted readout of specific signal-transduction pathways might be necessary to control cell morphogenesis (Paul *et al*, 2004).

S. Thompson and G. Wadhams (J. Armitage group, Oxford, UK) both addressed the spatial organization of distinct flagellar chemotaxis machineries in *Rhodobacter sphaeroides* by studying a membrane-bound cheOp2 chemosensory apparatus, localized at the cell pole, and a soluble cheOp3 apparatus found in a defined cluster in the bacterial cytoplasm. The cheOp3 cluster is segregated actively during cell division in a process requiring PpfA, a protein homologue of the DNA-partitioning factor ParA. This suggests that bacterial cells have evolved specialized machineries for the active segregation not only of DNA but also of proteins or protein complexes during cell division. The molecular detail of how proteins reach distinct cellular addresses and how positional information is signalled to sensory networks is yet to be discovered.

New signalling insights for two-component systems

As mentioned above, the 'two-component' chemotaxis system in *E. coli* signals through phosphorylation of the response regulator CheY. It has been proposed that CheY, even when unphosphorylated, exists in an equilibrium between the inactive and active conformational states and that phosphorylation stabilizes the active conformation. C. Dyer (R. Dahlquist group, Santa Barbara, CA, USA) presented nuclear magnetic resonance (NMR) chemical shift evidence in direct support of this model, showing that the conformational equilibrium for a functionally activated mutant of CheY is shifted towards the active conformation relative to wild-type CheY. A. Toro (A. Stock group, Piscataway, NJ, USA) proposed a general mechanism for the activation of the OmpR/PhoB subfamily of response regulators. Members of this group are two-domain proteins, with a regulatory domain that receives the phosphoryl group and a DNA-binding output domain that acts as a transcriptional regulator. Considering structural, NMR chemical shift and biochemical data derived from several members of this subfamily, Toro proposed that phosphorylation of the regulatory domain induces rotation of conserved threonine and aromatic residues, causing surface changes that induce the formation of a rotationally symmetrical dimer of the regulatory domains. This dimerization liberates the DNA-binding domains for proper alignment to bind to a tandem repeat of DNA.

Novel signalling pathways elucidated

The crystal structure of *C. crescentus* PleD, an unorthodox member of the response regulator family, was discussed by Jenal (Chan *et al*, 2004). PleD consists of two regulatory CheY-like receiver domains arranged in tandem and a C-terminal output GGDEF domain that converts GTP into c-diGMP (Paul *et al*, 2004). By contrast to the OmpR/PhoB subfamily, phosphorylation is proposed to remodel the interaction surface between the two receiver domains of a PleD monomer, causing dimerization of PleD and activation of the diguanylate cyclase (DGC) domain. In addition to, and overriding the control by, phosphorylation, the DGC activity of PleD is subject to tight product inhibition through the binding of two c-diGMP molecules to a distinct conserved allosteric site of the DGC output domain. This may constitute a general mechanism that helps to restrain the synthesis of this secondary messenger.

M. Galperin (Bethesda, MD, USA) reported that genome sequencing shows the GGDEF domain to be a universal bacterial signalling domain, sometimes incorporated as modules in both

one- and two-component bacterial signal-transduction systems (Galperin, 2004). Bacterial cells may use GGDEF domain proteins and c-diGMP to make a 'should I stay or should I go' decision about inducing motility (Simm *et al*, 2004). Generally, increased cellular levels of c-diGMP negatively modulate several forms of cell motility, whereas cell adhesiveness and biofilm formation are promoted under these conditions (Jenal, 2004). Consistent with this view, A. Wolfe and K. Visick (Chicago, IL, USA) used an elegant genetic screen and found a novel, membrane-bound one-component signal-transduction protein with a GGDEF output domain, which is involved in the control of motility in the squid light-organ symbiont *Vibrio fischeri*. In the absence of Mg^{2+}, synthesis of c-diGMP might block flagellar motility and promote the adhesion required for light-organ colonization after successful host entry.

T. Murray (B. Kazmierczak group, New Haven, CT, USA) showed the importance of c-diGMP in controlling other forms of motility. FimX is a GGDEF domain protein required for Tfp-based twitching motility in *Pseudomonas aeruginosa*. Although the role of FimX in pilus assembly and function is not known, proteins that interact with FimX include two components of an ATP-hydrolysing modular (ABC) transporter and FlhF, a regulator of flagellar assembly. Both FlhF and FimX localize to the same cell pole, which means that flagellar- and pilus-based motility in *P. aeruginosa* might be coordinately regulated through the interaction with GGDEF domain proteins at the pole. How the signalling molecules and other physico-chemical parameters control membrane-embedded bacterial motors could be analysed using a new method from S. Rainville (H. Berg group, Boston, MA, USA), which uses localized femtosecond laser pulses to punch submicrometre-sized holes in the bacterial cell envelope. Cells punctured at one end could then be attached to an artificial membrane and a new cytoplasm could be artificially constituted from one side, allowing the motor to be manipulated from 'inside' the cell.

Future perspectives

This conference was both multi-dimensional and dynamic in terms of discussing signalling protein complexes and bacterial cellular architecture. Genome sequences show the complexity of the signalling networks that control the 'lifestyle choices' of even a single bacterium. The full molecular details of how even the relatively simple network of *E. coli* chemotaxis proteins interacts within super-complexes on the bacterial membrane are only now being revealed. Building on this foundation, we are now beginning to explore the pathological and environmental consequences and molecular details of adaptive signalling in bacteria with networks of tenfold complexity. With new techniques for visualizing protein architecture and interactions, and new microscopic methods for following the routes that signalling proteins take within the landscape of bacterial cells, the next BLAST meeting in January 2007 promises to be every bit as enthralling as this one.

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