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Review

Coupling metabolism and chemotaxis-dependent behaviours by energy taxis receptors

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Bacteria have evolved the ability to monitor changes in various physico-chemical parameters and to adapt their physiology and metabolism by implementing appropriate cellular responses to these changes. Energy taxis is a metabolism-dependent form of taxis and is the directed movement of motile bacteria in gradients of physico-chemical parameters that affect metabolism. Energy taxis has been described in diverse bacterial species and several dedicated energy sensors have been identified. The molecular mechanism of energy taxis has not been studied in as much detail as chemotaxis, but experimental evidence indicates that this behaviour differs from metabolism-independent taxis only by the presence of dedicated energy taxis receptors. Energy taxis receptors perceive changes in energy-related parameters, including signals related to the redox and/or intracellular energy status of the cell. The best-characterized energy taxis receptors are those that sense the redox state of the electron transport chain via non-covalently bound FAD cofactors. Other receptors shown to mediate energy taxis lack any recognizable redox cofactor or conserved energy-sensing motif, and some have been suggested to monitor changes in the proton motive force. The exact energy-sensing mechanism(s) involved are yet to be elucidated for most of these energy sensors. By monitoring changes in energy-related parameters, energy taxis receptors allow cells to couple motility behaviour with metabolism under diverse environmental conditions. Energy taxis receptors thus provide fruitful models to decipher how cells integrate sensory behaviours with metabolic activities.

Introduction

In order to survive and grow under changing environmental conditions, bacteria must constantly adjust their metabolism and behaviour. Nutrients such as amino acids, sugars and organic acids, terminal electron acceptors, light and temperature can affect metabolism and they may all act as signals. Sensing of specific cues is dependent on the presence of dedicated receptors, which are characterized by specificity and sensitivity for the signal detected. All receptors, regardless of the information-processing system that their sensory input regulates, consist of (at least) sensing and signalling/transducing regions (Zhulin, 2001; Mascher *et al.*, 2006; Hazelbauer *et al.*, 2008). Within a subfamily of receptors, most sequence diversity is seen in the sensing region of the protein, a feature that highlights the diverse set of cues that receptors can perceive (Mascher *et al.*, 2006). Characterizing the sensory specificity of receptors is expected to shed light on the potential abilities of an organism in coupling physiology and metabolism with behaviour. Dedicated signal-transduction systems are responsible for the information flow from sensing to response (Stock *et al.*, 2000; Wadhams & Armitage, 2004).

One of the best-characterized signal-transduction systems is the one that regulates bacterial chemotaxis. Chemotaxis is defined as the directed movement of motile cells in gradients of various physico-chemical parameters. The bacterial chemotaxis signal-transduction system has been best studied in *Escherichia coli* and *Salmonella typhimurium*, where it functions to regulate the probability of changes in the direction of rotation of the flagellar motors, which in turn affect the cellular swimming motility pattern. Rotation of the flagellar motor is driven by the transmembrane electrochemical gradient (proton motive force; PMF), and switches in the direction of flagellar motor rotation are controlled by the chemotaxis pathway (Berg, 2003; Wadhams & Armitage, 2004). At the molecular level, the chemotaxis signal-transduction system comprises a two-component signal-transduction pathway in which sensory information perceived by dedicated receptors is relayed to the flagellar motor(s) via a series of phosphorylation events initiated at the chemotaxis kinase CheA. CheA is coupled to the receptors via CheW and modulates the phosphorylation state of the CheY response regulator. Phospho-CheY has an increased affinity for binding to flagellar motor proteins, which results in a switch in the direction of flagellar rotation, probably via conformational spread, and a change in the direction of swimming (Wadhams & Armitage, 2004; Bai *et al.*, 2010). In addition to this excitation pathway, an adaptation pathway

functions to reset the receptors so that they remain sensitive to further changes in the background concentrations of chemostimuli. The chemotaxis adaptation pathway comprises the receptor-specific methylesterase CheB and the receptor-specific methyltransferase CheR. Both enzymes function to adjust the methylation status of receptors, but while CheR is constitutively active, CheB is activated upon phosphorylation from phospho-CheA. Changes in the methylation of receptors occur with a slight delay relative to the phosphorylation events. This notable feature of bacterial chemotaxis signal transduction is akin to a molecular 'memory' (Szurmant & Ordal, 2004; Hazelbauer *et al.*, 2008), and it endows the cells with the ability to navigate gradients by making temporal comparisons regarding chemoeffector concentration changes. The fundamental features of the chemotaxis signal-transduction pathway characterized for enteric organisms are conserved in most motile Archaea and Bacteria (Wuichet *et al.*, 2007).

Recent comparative analysis of completely sequenced genomes indicates that the greatest diversity in chemotaxis resides in the receptor repertoire, with the number of receptors per genome correlating with the genome size and the likely metabolic versatility of the organism (Alexandre *et al.*, 2004). For example, while *E. coli* K-12 possesses five chemotaxis receptors, *Rhizobium leguminosarum* has 27, *Vibrio cholerae* El Tor 45 and *Magnetospirillum magneticum* 61 ($MiST_2$ database; http://mistdb.com/; Ulrich & Zhulin, 2010). Variation in the number of receptors may even be seen in different strains of the same species; for example, *E. coli* (http://mistdb.com/). However, the greatest diversity remains within the sensory domain of receptors. At the molecular level, receptors may detect sensory stimuli by one of two mechanisms. Chemoeffectors may physically bind to the receptor, or to a specific periplasmic-binding protein that interacts with a receptor. Such receptors are referred to as chemoreceptors. Effectors may also be detected indirectly by the receptor, via their effects on intracellular energy levels, in particular the electron transport system (ETS). These receptors act as 'energy sensors' and are referred to as energy taxis receptors. This review focuses on energy taxis receptors, their diversity, sensory mechanisms and function in coupling energy metabolism with locomotor behaviours.

Chemotaxis receptors provide sensory input for tactic behaviours: structure and architecture of receptor signalling complexes

In the model organism *E. coli*, stimuli from the environment are sensed by an array of membrane-associated receptor homodimers assembled as trimers-of-dimers in localized patches at one or both cell poles. These membrane-associated receptor arrays cluster with CheA and CheW to form functional ternary signalling complexes (Ames *et al.*, 2002; Studdert & Parkinson, 2004; Sourjik & Berg, 2004; Lai *et al.*, 2005; Kentner *et al.*, 2006; Hazelbauer *et al.*, 2008). A similar organization of receptors and chemotaxis proteins as membrane-associated polar clusters has been observed in phylogenetically diverse Bacteria and Archaea (Gestwicki *et al.*, 2000; Briegel *et al.*, 2009). Another defining feature of chemotaxis that directly results from the ternary complex assembly described above is that sensory information is processed into a single signalling output (directional switch of the flagellar motors) from multiple interacting receptors of diverse sensory specificity (Hazelbauer *et al.*, 2008). This architecture of the receptor–CheA–CheW ternary signalling complex as higher-order arrays contributes to the signal amplification and broad dynamic range of the chemotactic response that allows for detection of, and response to, differences in minute amounts of stimuli (Bray *et al.*, 1998; Ames *et al.*, 2002; Lai *et al.*, 2005; Hazelbauer *et al.*, 2008).

Prototypical receptors (such as *E. coli* Tsr) span the cytoplasmic membrane and consist of three structurally and functionally distinct regions: sensing, signal conversion and kinase control modules (Hazelbauer *et al.*, 2008). The sensing module is at the N terminus and it may be localized in the cytoplasm or, more typically, it may be periplasmic and flanked by two transmembrane regions that anchor it to the membrane. Periplasmic sensory modules are likely to detect environmental cues external to the cell, while cytoplasmic sensory modules may detect signals that can cross the cytoplasmic membrane or that are generated in the cytoplasm. The signal conversion module corresponds to the conserved HAMP (present in histidine kinases, adenylyl kinases, methyl-accepting chemotaxis proteins and phosphatases) domain and it has been identified in most membrane-anchored receptors (Aravind & Pontig, 1999). The kinase control module is archetypal for receptors, because it comprises a conserved region for interaction and regulation of CheA kinase activity as well as adaptation regions, which include residues specifically modified by CheB and CheR (Szurmant & Ordal, 2004).

Analysis of the sensory domains of receptors has revealed conservation with the sensory domains of other signal-transducing proteins, including histidine kinases and diguanylate cyclases (Zhulin, 2001; Mascher *et al.*, 2006). Such domain conservation may suggest the type of environmental cue(s) detected by the receptor, providing that a representative domain has been characterized. Additional clues regarding the sensory specificity of receptors may be obtained from a combination of genomic context, analysis of gene expression patterns and/or conservation patterns. However, in most cases, the specificity of these N-terminal sensory domains remains unknown.

Energy taxis is a metabolism-dependent behaviour

In *E. coli* chemotaxis, most stimuli are detected via a metabolism-independent mechanism, where binding of the ligand to the periplasmic domain (or a periplasmic-binding protein) of a dedicated chemoreceptor triggers a conformational change that is transduced through the

chemoreceptor array and modulates CheA activity (Wadhams & Armitage, 2004; Szurmant & Ordal, 2004). Experimental evidence for metabolism-independent sensing of chemoeffectors is obtained by demonstrating that non-metabolizable analogues trigger a response and/or that mutants affected in the metabolism of a compound respond chemotactically to a challenge with this compound. Given that the majority of receptors identified in completely sequenced genomes possess a putative periplasmic sensing domain (Zhulin, 2001), most receptors are expected to function as chemoreceptors.

Metabolism-dependent behaviour has also been described in diverse bacteria, including *E. coli* (Taylor *et al.*, 1999; Alexandre *et al.*, 2004; Schweinitzer & Josenhans, 2010). This behaviour is referred to as energy taxis when motile cells respond tactically to direct effect(s) of the stimulus on energy-generating processes or to effects resulting from the metabolism of the chemoeffector. Energy taxis shares most features of prototypical chemotaxis, but is distinct in terms of the way in which the sensory stimulus is perceived by the signal-transduction pathway. It follows that energy taxis behaviour will involve specific energy sensors that detect signals related to the redox and/or intracellular energy status of the cell. An appropriate step-up or step-down in energy levels (rate of electron transport, PMF, redox, etc.) will be detected as a signal (Taylor *et al.*, 1999). Effectors for energy taxis include terminal electron acceptors, light, redox-active compounds and metabolizable substrates that act as donors of reducing equivalents to the ETS. For example, light or terminal electron acceptors affect the flow of electrons through the ETS and can cause energy taxis. Weak acids, which can permeate the cytoplasmic membrane, may lower the cytoplasmic pH and therefore the PMF. Redox-active compounds, such as oxidized quinones, with a redox potential sufficient to interfere with electron flow within the respiratory chains, may also be sensed as energy taxis stimuli since they can affect the redox and energy output of the cell. Effectors for energy taxis may affect the PMF and thus can directly affect the rotation of flagellar motors, producing tactic-like behaviours (Berg, 2003). In contrast to motor-dependent behaviours, receptor-dependent behaviours are characterized by transient changes in the swimming motility bias in response to effectors before a return to the pre-stimulus swimming bias: the phenomenon of adaptation (Miller & Koshland, 1980; Berg, 2003). Furthermore, a functional chemotaxis pathway is required for a response in receptor-dependent behaviours (Rowsell *et al.*, 1995; Miller & Koshland, 1980). By energy taxis, cells thus do not navigate toward the greatest concentration(s) of effectors but seek positions where metabolic rates are optimized.

Energy taxis encompasses taxis in gradients of diverse physico-chemical stimuli

Aerotaxis, taxis to alternative electron acceptors, phototaxis, redox taxis and, in some bacterial species, chemotaxis toward metabolizable substrates have been described as energy taxis (Taylor *et al.*, 1999). As long as the signal perceived originates within the energy-producing processes of the cells (changes in the electron flow in the ETS, in the redox status of the cell or in the PMF) and is not the stimulus per se (i.e. the effector does not bind directly to the receptor), then energy taxis can be inferred. For example, aerotaxis may be mediated by directly monitoring changes in the oxygen concentration or by monitoring changes in metabolism that result from the changes in oxygen concentration. Only the latter form of aerotaxis is energy taxis, because the signal for behaviour is metabolism-dependent. Aerobes such as *Bacillus subtilis* and *Halobacterium salinarum* seek a position in gradients where oxygen concentration is maximal, regardless of the growth substrate that they use. Both species use aerotaxis chemoreceptors that bind oxygen (Hou *et al.*, 2000). On the other hand, *Azospirillum brasilense* (Zhulin & Armitage, 1993; Zhulin *et al.*, 1996; Alexandre *et al.*, 2000) and *E. coli* (Rebbapragada *et al.*, 1997; Repik *et al.*, 2000; Watts *et al.*, 2004) monitor changes in redox that result from changes in oxygen concentration, and both species form aerotactic bands at low oxygen concentrations, with the growth conditions and substrates affecting the aerotactic response (Shioi *et al.*, 1988; Zhulin *et al.*, 1996; Alexandre *et al.*, 2000). Similarly, phototaxis is suggested to be an energy taxis behaviour in *Rhodobacter sphaeroides* (Gauden & Armitage, 1995) and *Rhodospirillum centenum* (Jiang *et al.*, 1997), since inhibitors that affect photosynthetic electron transport also prevent phototaxis. However, phototaxis is likely not mediated by energy taxis in cyanobacteria such as *Synechocystis*, since inhibitors of photosynthesis have no effect on phototaxis and cells respond to the direction of light but not to changes in the fluence rate (Bhaya, 2004; Hoff *et al.*, 2009). Accordingly, the TaxD1 and PixJ1 receptors mediate phototaxis in *Synechocystis* via chromophores that detect photons (Bhaya, 2004; Yoshihara & Ikeuchi, 2004; Hoff *et al.*, 2009).

The following lines of experimental evidence are generally suggestive of energy taxis: (i) a correlation between the strength of a chemostimulus as an attractant and its efficiency as a growth substrate (electron donors or acceptors); (ii) the lack of a behavioural response upon challenging the cells with non-metabolizable analogues of metabolizable attractants; and/or (iii) the observation that inhibiting the metabolism of the stimulus molecule (by mutation or by using chemical inhibitors) prevents the behavioural response (Alexandre *et al.*, 2000; Schweinitzer *et al.*, 2008; Baraquet *et al.*, 2009). Further evidence for the signal originating within the ETS may include the observation that the tactic response is prevented by subinhibitory concentrations of respiratory inhibitors, redox-active compounds or mutations that affect respiratory chain components. The assays employed to obtain such experimental evidence should preferably measure the locomotor behaviour directly, i.e. the probability of direction changes in free-swimming cells, because assays developed with model organisms often fail to yield

unequivocal evidence when applied to other bacterial species (Miller *et al.*, 2009; Li *et al.*, 2010).

Receptors that mediate energy taxis

Energy taxis differs from metabolism-independent taxis only by the presence of dedicated energy taxis receptors (Fig. 1). The Aer protein of *E. coli* mediates aerotaxis (Rebbapragada *et al.*, 1997) and is the energy taxis receptor for which the sensory mechanism has been studied in the greatest detail. Similar to the other four receptors encoded within the genome of *E. coli*, Aer is anchored to the membrane, but in contrast to prototypical chemoreceptors, it lacks a periplasmic sensory domain and contains sensory and signalling domains that are both located in the cytoplasm. The N-terminal sensory domain of Aer is a single PAS domain that binds an FAD cofactor (Bibikov *et al.*, 1997). The presence of FAD is essential to the sensory function of the receptor, since variant proteins impaired in FAD binding fail to mediate responses to changes in oxygen concentrations (Bibikov *et al.*, 2000; Repik *et al.*, 2000). Oxidation and reduction of the FAD cofactor within the PAS domain of Aer is postulated to produce the sensory input signal that is transmitted through the signalling domain (Bibikov *et al.*, 2000; Repik *et al.*, 2000; Watts *et al.*, 2004). Aer-like receptors which function in aerotaxis and/or other energy taxis behaviours are widespread and have been characterized in diverse bacteria (Taylor *et al.*, 1999; Alexandre *et al.*, 2004; Schweinitzer & Josenhans, 2010). Interestingly, a bipartite Aer-like receptor, encoded as two separate proteins, CetA (comprising the N-terminal PAS sensory domain) and CetB (comprising the membrane-anchored C-terminal signalling domain), has been shown to function as an energy taxis Aer-like transducer in *Campylobacter jejuni* (Hendrixson *et al.*, 2001; Elliott *et al.*, 2009).

Another PAS domain-containing energy sensor, named AerC, which binds FAD non-covalently, has been recently characterized in the alpha-proteobacterium *A. brasilense* (Xie *et al.*, 2010). In contrast to *E. coli* Aer, AerC is a soluble cytoplasmic receptor and contains two PAS domains at its N terminus. FAD cofactors are loosely bound to each of the two PAS domains of AerC via tryptophan residues that are conserved in the PAS domains of Aer and AerC (Xie *et al.*, 2010). Mutant alleles of *aerC* encoding proteins unable to bind FAD also fail to mediate energy taxis behaviours. AerC is thus proposed to function as an energy taxis receptor that monitors changes in the redox state of the cells via its associated FAD cofactors. Using multiple sequence alignments of PAS domain-containing receptor sequences, it has been suggested that AerC belongs to a novel family of soluble PAS domain-containing receptors that use FAD as cofactors, and which are widespread in bacteria and distinct from the well-studied *E. coli* Aer. Comparative genomics analysis has also identified three groups of PAS domain-containing recep-

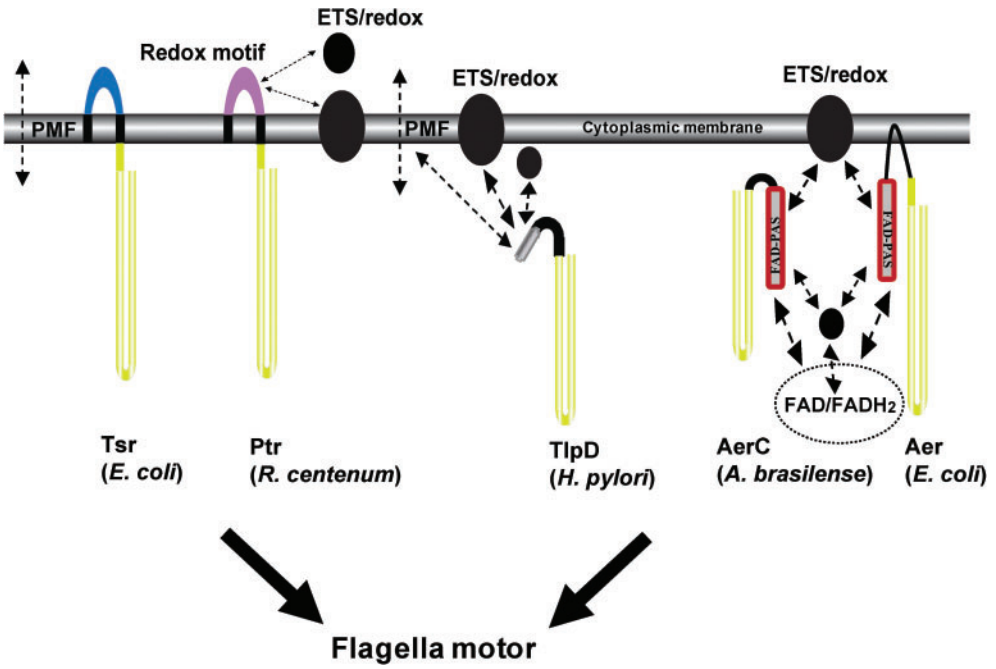

Fig. 1. Diversity of proposed energy-sensing mechanisms of energy taxis receptors. The filled circles represent electron transport components. 'FAD/$FADH_2$' represents the FAD/$FADH_2$ pool. The dashed arrows represent putative interactions or sensing mechanisms. The pink and blue arcs represent sensory domains. Examples of representative receptors are indicated in each case.

tors (Fig. 2). Interestingly, PAS domain sequences from class I and class II also correlate with topologies. Class I PAS domain-containing receptors are represented by Aer and are all predicted to be membrane-anchored receptors. Class II PAS domain-containing receptors are typified by both of the PAS domains of AerC, and the great majority of these (>98 % of the sequences) are predicted to be soluble cytoplasmic receptors. A third group comprises apparently divergent and unrelated PAS domain-containing receptors. The greatest sequence conservation is observed between class I and class II PAS domain-containing receptors, which all possess a strictly conserved tryptophan residue within the PAS domain, suggesting that these receptors represent a broad group of FAD-binding PAS domain-containing bacterial receptors (Xie *et al.*, 2010). The widespread occurrence of AerC (class II) receptor homologues in sequenced bacterial genomes suggests that energy taxis behaviours are mediated by similar energy sensors in diverse bacteria.

Possible molecular mechanisms of FAD–PAS sensing by energy taxis receptors

Changes in the redox state of the FAD–PAS in Aer could be modulated by oxidation/reduction of the bound FAD cofactor by components of the respiratory chain, by interaction with cytosolic electron donors (e.g. NADH) or by a diffusible redox component which itself is reduced by the ETS (e.g. FAD) (Fig. 1). FAD is a major coenzyme for redox reactions, and the FAD : $FADH_2$ ratio depends on the growth substrates and electron donors used by the central metabolic pathways and the activity of the ETS. Aer and AerC mediate aerotaxis and other energy taxis behaviours (chemotaxis to oxidizable substrates and taxis to alternative electron acceptors) under diverse environmental conditions that do not strictly correlate with the expression of any specific respiratory complex. In *E. coli*, strong redox signals perceived by Aer originate in part at the NADH dehydrogenase I complex, but NADH dehydrogenase I is not required for Aer-mediated aerotaxis (Edwards *et al.*, 2006). In *A. brasilense*, AerC-mediated aerotaxis responses correlate with the expression level of the receptor and the total FAD content of the cells (Xie *et al.*, 2010). Overexpressing Aer or AerC results in an increase in the cellular FAD content of *E. coli* (Bibikov *et al.*, 1997) or *A. brasilense* (Xie *et al.*, 2010), respectively, suggesting co-regulation between FAD biosynthesis and Aer or AerC expression and a potential functional link. Taken together, it is possible that the FAD–PAS of Aer and/or of AerC monitors changes in redox by directly sensing the FAD/$FADH_2$ pool (Taylor, 2007).

Energy taxis receptors that may monitor the redox state via conserved motifs in the periplasmic domains

Ptr is a membrane-anchored receptor required for phototaxis in the photosynthetic alpha-proteobacterium *Rhodospirillum centenum* (Jiang & Bauer, 2001). Positive and negative phototaxis in anoxygenic photosynthetic purple bacteria requires a functional photosynthetic ETS, including the reaction centre and cytochrome bc_1 complex, and Ptr may thus mediate phototaxis by energy taxis (Grishanin & Armitage, 1997; Jiang & Bauer, 2001). Ptr is predicted to possess a periplasmic domain with a *b*-type haem-binding motif. This motif could provide a redox-

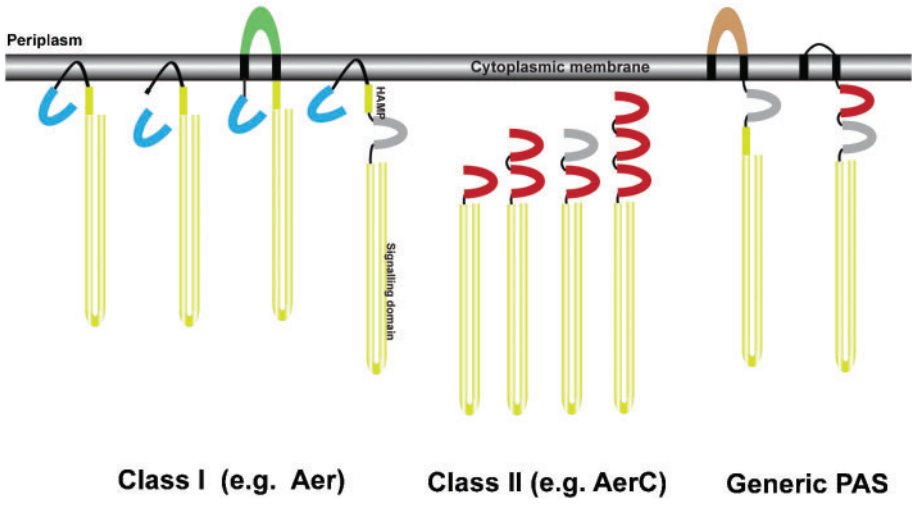

Fig. 2. PAS domain-containing receptors can be classified into three major groups based on sequence conservation (Xie *et al.*, 2010). Class I (red arcs) and class II (blue arcs) receptors bind FAD non-covalently and are exemplified by *E. coli* Aer and *A. brasilense* AerC, respectively. The third group (grey arcs) comprises unrelated PAS domain-containing receptors, which may not bind FAD. PAS domains from any of the three groups can be found in combination within receptors. The brown and green arcs represent sensory domains.

sensing mechanism by which Ptr would monitor the redox state of the photosynthetic ETS (Jiang & Bauer, 2001). Interestingly, homologues of the Ptr receptors are also found encoded in the genomes of non-photosynthetic bacterial species, including *Rhizobium leguminosarum* (McpB) (Yost *et al.*, 1998), which may suggest more general redox- and energy-sensing functions for these receptors (Fig. 1).

DcrA from *Desulfovibrio vulgaris* may also sense the redox state of the ETS, since this receptor contains a *c*-type haem-binding motif in its periplasmic domain (Fu *et al.*, 1994). However, the *c*-type haem may also bind oxygen directly, in which case it would detect the presence/absence of oxygen and not changes in energy resulting from metabolism, and would therefore not be an energy taxis receptor per se.

Energy taxis mediated by receptors that may sense the PMF

Other energy taxis receptors lacking any redox cofactor or conserved energy-sensing motif in the sensory domain have been suggested to monitor changes in the PMF. Evidence supporting this hypothesis is strongest for the *E. coli* Tsr receptor. Tsr is a prototypical membrane-anchored chemoreceptor with a large periplasmic domain that can bind serine, but Tsr is also implicated in energy taxis responses, including aerotaxis (Rebbapragada *et al.*, 1997). Mutant strains of *E. coli* lacking Aer are impaired but not null for aerotaxis, which is abolished only when *tsr* is also deleted (Rebbapragada *et al.*, 1997). In addition to mediating aerotaxis and taxis to serine, Tsr also senses pH (Umemura *et al.*, 2002) and mediates energy taxis in gradients of electron donors that support maximal growth and biomass production (e.g. sugars; Greer-Phillips *et al.*, 2003). The lack of any conspicuous redox-sensing motif in Tsr, combined with its ability to sense pH, led to the suggestion that Tsr-mediated energy sensing is due to the ability of this receptor to detect changes in the PMF, since ΔpH is a component of the PMF generated by the ETS (Levit & Stock, 1999; Rebbapragada *et al.*, 1997). In direct support of this hypothesis, Edwards *et al.* (2006) demonstrated that the energy taxis responses mediated by Tsr in gradients of chemicals that serve as growth substrates correlate with the increase in the membrane potential resulting from the metabolism of these effectors. Positively charged residues on the cytoplasmic side of the transmembrane helices of Tsr could provide a sensory input transmitted to the signalling domain upon changes in the PMF (Fig. 1).

In *Shewanella oneidensis*, taxis to the alternative electron acceptors DMSO, trimethylamine *N*-oxide (TMAO) and nitrate has recently been shown to depend on the ΔpH component but not the membrane potential component of the PMF, and thus may be energy taxis (Baraquet *et al.*, 2009). Interestingly, four membrane-anchored receptors, which possess large periplasmic domains of unknown function, have been shown to contribute to these behavioural responses. None of the four PAS domain-containing receptors encoded within the genome of this organism contributes to the energy taxis responses detected. Given the dependence of the responses observed on the ΔpH component of the PMF, the lack of a redox-sensing motif in the periplasmic domain of the receptors and analogy with Tsr, PMF sensing has been suggested to underlie energy taxis in this organism (Baraquet *et al.*, 2009).

Other receptors mediating energy taxis

Several other receptors that have topologies similar to that of *E. coli* Tsr, in that they possess a periplasmic domain lacking any redox-responsive prosthetic group, have been implicated in energy taxis in other bacterial species. These receptors have been suggested (rather than directly shown) to sense changes in the PMF by a mechanism yet to be determined but which may be similar to that of Tsr.

Tlp1 has been shown to function in energy taxis in *A. brasilense* (Greer-Philips *et al.*, 2004). A mutant lacking Tlp1 is impaired, but not null, for all energy taxis responses, including aerotaxis, taxis to alternative electron acceptors, chemotaxis to oxidizable substrates, and taxis in a gradient of oxidized quinones (Greer-Philips *et al.*, 2004).

The TlpB receptor of *Helicobacter pylori* has been shown to mediate taxis away from acidic environments of pH lower than 3, which corresponds to conditions that abolish motility and inhibit growth (Stingl *et al.*, 2002; Croxen *et al.*, 2006). The TlpD receptor has recently been implicated in mediating energy taxis responses in *H. pylori* (Schweinitzer *et al.*, 2008). TlpD is one of four receptors encoded within the genome of *H. pylori* and is also the only cytoplasmic receptor. TlpD possesses a short N-terminal sensory domain with no similarity to any known or conserved domain, and its energy-sensing mechanism(s) remains to be determined (Fig. 1).

Distinctive features of energy taxis receptors: sensory sensitivity and adaptation

Sensory cues that trigger energy taxis often overlap with other sensory abilities, and it is commonly observed that mutants lacking an energy taxis receptor have an impaired but not a null phenotype (Rebbapragada *et al.*, 1997; Alexandre *et al.*, 2000; Greer-Phillips *et al.*, 2003; Alvarez-Ortega & Harwood, 2007; Sarand *et al.*, 2008; Schweinitzer *et al.*, 2008). This is not unexpected, since in energy taxis, cells monitor energy-related parameters that change as a result of metabolism and not a chemical per se, which could itself be detected by a dedicated chemoreceptor. Chemoreceptors detect ligands at low concentration, which is in contrast to energy taxis receptors, which mediate responses to relatively high concentrations of metabolizable chemoeffectors (Zhulin *et al.*, 1997; Alexandre *et al.*, 2000).

For example, maltose, ribose and galactose are detected by ligand-binding to Tar (maltose) or Trg (ribose and galactose) in *E. coli*. When Aer or Tsr is expressed as the sole receptor in an *E. coli* strain lacking all other receptors, the cells navigate in gradients of maltose, ribose or galactose by energy taxis. However, the Tsr- and Aer-mediated responses occur only at high concentrations (at least 100-fold higher than in ligand-mediated chemotaxis) of these chemicals (Greer-Phillips *et al.*, 2003). The relatively low sensitivity of energy sensors to chemical substrates may be related to the requirement for high concentrations in order to trigger sufficient changes in the energy-related parameters that are detected by energy taxis receptors.

Methylation-dependent sensory adaptation is a hallmark of bacterial chemotaxis. Differential methylation of chemoreceptors has been shown to modulate chemotaxis sensitivity and signal detection over a broad range of background chemoeffector concentrations (Szurmant & Ordal, 2004; Hazelbauer *et al.*, 2008). However, methylation-independent behaviours, including aerotaxis and chemotaxis to phosphoenolpyruvate-dependent phosphotransferase system sugars, have been demonstrated in *E. coli* (Niwano & Taylor, 1982; Bibikov *et al.*, 2004) as well as for aerotaxis and chemotaxis to succinate in *A. brasilense* (Stephens *et al.*, 2006). The exact mechanism of methylation-independent sensory adaptation is currently not known for any bacterial species. However, *E. coli* Aer has been shown to mediate aerotaxis and energy taxis behaviours by a methylation-independent mechanism (Bibikov *et al.*, 2004). Aerotaxis is not abolished in strains lacking CheR or CheB, or by site-specific mutations at potentially methylatable sites in the signalling domain of Aer (Bibikov *et al.*, 2004). This latter finding is also consistent with the observation that the signalling domain of Aer lacks conserved methylation sites present in other receptors for which methylation-dependent adaptation has been demonstrated (Zhulin, 2001; Szurmant & Ordal, 2004; Bibikov *et al.*, 2004). Furthermore, when the N-terminal FAD–PAS sensory and transducing HAMP domains of Aer are fused with the signalling domain of Tar, which is a methylation-dependent receptor, aerotaxis is maintained in strains lacking both CheR and CheB. These observations not only convincingly establish that Aer is a methylation-independent receptor but also suggest that signalling and sensory methylation-independent adaptation in Aer is a function of the PAS-HAMP region (Bibikov *et al.*, 2004). One possibility is that a transient change in the redox status of the FAD cofactor non-covalently bound to the PAS-HAMP domain of Aer is the mechanism for methylation-independent adaptation. Given that (1) aerotaxis is methylation-independent in *A. brasilense* (Stephens *et al.*, 2006); (2) AerC lacks any conserved methylatable motif at its C terminus; and (3) AerC, which also binds FAD non-covalently within its PAS domains (but lacks a HAMP domain) (Xie *et al.*, 2010), mediates aerotaxis, it is conceivable that similar signalling and/or methylation-dependent adaptations are conserved in Aer and AerC-like energy sensors.

Energy taxis receptors and contribution to niche adaptation

Energy taxis-dependent motility behaviours

Bacterial motility and chemotaxis have been suggested, and experimentally demonstrated, to contribute to the ability of bacteria to colonize a variety of niches (Alexandre *et al.*, 2004; Miller *et al.*, 2009; Schweinitzer & Josenhans, 2010). Since the receptor repertoire specifies the sensory ability of the organism, characterizing the contribution of specific sensory abilities afforded by a receptor to the ability of a micro-organism to colonize a particular niche provides a powerful insight into the environmental cues that may affect the physiology and survival of a micro-organism. In agreement with this assumption, the *C. jejuni* Cca chemoreceptor (also known as Tlp1) has been found to specifically bind aspartate, and Cca-mediated chemotaxis to aspartate has been shown to contribute to intestinal tract colonization, which identifies aspartate as a key environmental cue modulating the establishment of *C. jejuni* in its preferred niche (Vegge *et al.*, 2009; Hartley-Tassell *et al.*, 2010). One of the predicted advantages of energy taxis is that changes in the tactic behaviour are not dependent on the concentration of a specific effector, and the sensory signal that triggers the tactic response instead results from an integration of environmental conditions and the current metabolic activity of the cell. Characterizing the environmental conditions in which energy taxis receptors modulate the motility pattern of cells is thus expected to provide significant information regarding the conditions that are more directly affecting cellular metabolism.

Insights into how *H. pylori* may be maintained in a narrow zone within the stomach mucus were obtained by identifying TlpD as an energy taxis receptor that allows cells to integrate sensory information about all nutrient and pH gradients into a single response in order to navigate toward niches that support optimal energy generation (Schreiber *et al.*, 2004; Schweinitzer *et al.*, 2008). Similarly, Tlp1 functions as an energy sensor that promotes competitive colonization of wheat roots by *A. brasilense*, suggesting a strategy by which an apparent metabolism-dependent association with plants contributes to host specificity in this ubiquitous soil micro-organism (Greer-Philips *et al.*, 2004). Aer-like receptors that function as energy taxis transducers in *Ralstonia solanacearum* are also essential for successful colonization of the tomato host (Yao & Allen, 2007). In addition to providing a tantalizing hypothesis for metabolism-dependent host specificity in various model systems, evidence for the contribution of energy taxis receptors to optimizing the metabolism of various organisms begins to emerge. *Pseudomonas* species are metabolically versatile, a feature that may contribute to their environmental success. Energy taxis, mediated by Aer-like proteins, has been proposed to

contribute to their ability to grow on and catabolize a range of substrates, including methylphenols (Sarand *et al.*, 2008) and over 60 other chemoattractants (Ferrandez *et al.*, 2002; Hong *et al.*, 2004). Energy taxis is a dominant behaviour in *A. brasilense* in that signals for most tactic responses originate within the ETS (Alexandre *et al.*, 2000). In *A. brasilense*, the strongest behavioural response is aerotaxis. Aerotaxis guides the bacteria to a preferred low oxygen concentration (4 μM), which appears to be the optimal oxygen concentration for energy generation and nitrogen fixation (Zhulin *et al.*, 1996). AerC mediates aerotaxis under nitrogen fixation conditions by monitoring the redox status of the ETS via FAD cofactors. AerC-mediated aerotaxis plays a major role in navigating cells to optimum niches for metabolism and the energy-demanding process of nitrogen fixation, illustrating the role of energy taxis in the diazotrophic lifestyle of this microaerophilic organism (Xie *et al.*, 2010). Interestingly, expression of AerC parallels changes in the cytosolic FAD content of cells, suggesting a strategy by which an energy sensor functions to fine-tune sensory behaviour with metabolism (Xie *et al.*, 2010).

Other cellular behaviours may be mediated by energy taxis receptors

In addition to modulating the swimming motility pattern, experimental evidence suggests that chemotaxis-like signal-transduction pathways regulate cellular behaviours other than motility, including cell differentiation, adhesion, cell-to-cell aggregation and cell length (Hickman *et al.*, 2005; Bible *et al.*, 2008; Kirby, 2009). The sensory input perceived by energy taxis receptors may thus ultimately modulate diverse cellular behaviours. This assumption is supported by the recent finding that the lack of a functional AerC affects clumping in *A. brasilense*, in addition to affecting locomotor behaviour (Xie *et al.*, 2010). Clumping is a cell-to-cell aggregation phenotype recently shown to be regulated by the Che1 chemotaxis-like pathway in this species (Bible *et al.*, 2008). AerC localization at the cell poles depends on the presence of molecular components of the Che1 pathway, suggesting that redox sensing by AerC is transduced in a Che1-dependent manner, which could also explain the clumping behaviour (Xie *et al.*, 2010). Non-aerotactic mutant strains of *Ralstonia solanacearum* lacking Aer-like proteins have an increased propensity for biofilm formation on abiotic surfaces (Yao & Allen, 2007), suggesting that other cellular responses are regulated by energy taxis receptors in this species. A similar hypothesis may be suggested for the function of the soluble AerC-like BdlA receptor of *Pseudomonas aeruginosa* (Morgan *et al.*, 2006). BdlA promotes nitric oxide-induced biofilm dispersion via a mechanism that has not been elucidated, but depends on changes in intracellular c-di-GMP levels (Barraud *et al.*, 2009). The sequence similarity between BdlA and AerC suggests that BdlA mediates NO-dependent biofilm dispersal by acting as an energy sensor, a hypothesis consistent with the observation that biofilm dispersal is a metabolism-dependent process (Sauer *et al.*, 2004; Barraud *et al.*, 2009).

Conclusions and perspectives

One predicted outcome of the energy-sensing strategy is that a dynamic interplay between sensing/signalling and metabolism can be maintained under diverse environmental conditions, and the metabolic rate ultimately provides the cue perceived by energy taxis receptors. Experimental evidence (examples of which are reviewed in this article) and recent mathematical modelling of metabolism-based chemotaxis/energy taxis (Goldstein & Soyer, 2008; M. Egbert, personal communication) provide support for these assumptions. Evidence for the operation of energy taxis in various motile micro-organisms is now clearly established, but the sensory mechanisms involved are only beginning to emerge. While a redox-sensing mechanism is clearly demonstrated for the *E. coli* Aer energy sensor, the mechanism underlying Tsr energy-sensing abilities remains elusive. The hypothesis that Tsr mediates energy taxis by monitoring changes in the PMF, perhaps the ΔpH, is intriguing. Given that several functional features of receptor arrays, such as cooperativity as well as chemosensory sensitivity and adaptation, are modulated by relative receptor abundance, and that Tsr is a high-abundance receptor (Salman & Libchaber, 2007; Besschetnova *et al.*, 2008; Hazelbauer *et al.*, 2008), it may be that the energy-sensing abilities of Tsr are related to its expression level, the physical environment in which receptor clusters are assembled, such as local properties of the plasma membrane, or a combination of these features. The suggestion that Tsr senses the ΔpH via charged residues close to the membrane, and the fact that environmental conditions that affect membrane lipid composition (temperature and pH) also affect receptor functions (Slonczewski *et al.*, 1982; Levit & Stock, 1999; Salman & Libchaber, 2007), may provide some credible support to this hypothesis. The finding that receptors from other bacteria with topologies similar to that of Tsr but unrelated sensing and signalling domains are implicated in energy taxis (e.g. Tlp1 of *A. brasilense*) suggests either that (1) the energy-sensing mechanisms by which these receptors function are dissimilar or that (2) a universal energy-sensing mechanism that may be related to a more fundamental feature of all receptors (perhaps the organization of receptors in clusters) is involved and common to all of these seemingly unrelated energy taxis receptors. Future investigations into the energy-sensing mechanisms of diverse energy taxis receptors will undoubtedly be productive.

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