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REVIEW

Methyl-accepting chemotaxis proteins: a core sensing element in prokaryotes and archaea

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Abstract Chemotaxis is the directed motility by means of which microbes sense chemical cues and relocate towards more favorable environments. Methyl-accepting chemotaxis proteins (MCPs) are the most common receptors in bacteria and archaea. They are arranged as trimers of dimers that, in turn, form hexagonal arrays in the cytoplasmic membrane or in the cytoplasm. Several different classes of MCPs have been identified according to their ligand binding region and membrane topology. MCPs have been further classified based on the length and sequence conservation of their cytoplasmic domains. Clusters of membrane-embedded MCPs often localize to the poles of the cell, whereas cytoplasmic MCPs can be targeted to the poles or distributed throughout the cell body. MCPs play an important role in cell survival, pathogenesis, and biodegradation. Bacterial adaptation to diverse environmental conditions promotes diversity among the MCPs. This review summarizes structure, classification, and structure–activity relationship of the known MCP receptors, with a brief overview of the signal transduction mechanisms in bacteria and archaea.

Keywords Chemoreceptor, ligand-binding domain · Signaling domain · Sensory domain · Structure–activity relationship · Protein structure

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Introduction

Chemotaxis is the directed motility that allows microbes to sense environmental cues and move towards factors that favor survival and away from toxic chemicals. Microbes have a diverse group of chemoreceptors that sense intracellular and environmental signals and relay them to the downstream signaling pathways in the cytoplasm [1, 2]. The methyl-accepting chemotaxis proteins (MCPs) are the predominant chemoreceptors in bacteria and archaea. They are involved in regulation of diverse aspects of cellular activities including biofilm formation [3], flagellum biosynthesis [1], degradation of xenobiotic compounds [4], encystment, fruiting body formation [1, 5–8], exopolysaccharide production [9], and production of toxins [10]. For example, an MCP is required for encystment of the photosynthetic bacterium, *Rhodospirillum centenum*, because this receptor senses harsh environmental conditions, where the cyst formation would allow survival [1]. *Pseudomonas aeruginosa* has membrane-bound MCP receptors which modulate biofilm formation by regulating the cellular cyclic dimeric guanosine monophosphate level [11]. MCPs play an important role in the pathogenicity of many bacteria including *P. aeruginosa* [12], *Campylobacter jejuni* [13], *Cronobacter sakazakii* [14], and *Vibrio cholerae* [15]. Some MCPs function as photoreceptors and direct bacterial movement in response to light (exemplified by the phototaxis of halophilic marine archaea *Halobacterium salinarum* [16, 17]).

Genes encoding MCPs were mainly found in genomes of motile microbes [18]. Currently, the InterPro database contains more than 102,346 MCP signaling domains (accession number IPR004089) [19]. Among them, 100,550 are from bacteria (76,295 in Proteobacteria, 20,335 in Terrabacteria, 2,459 in Spirochaetes, 250 in Thermotogae, 227 in PVC group, 203 in Nitrospirae, 195 in FCB group, 108

in Synergistetes, 72 in Deferribacteres, 52 in Aquificae, 43 in Thermodesulfobacteria, 28 in Chrysiogenetes, 24 in Acidobacteria and 259 in others, respectively), 1,596 from archaea, and 200 from eukaryotes (88 in Opisthokonta, 57 in Alveolata, 23 in Viridiplantae, 9 in Euglenozoa, 8 in Amoebozoa, 7 in Haptophyceae, 7 in Stramenopiles and 1 in Apusozoa, respectively). Bacteria living in a stable, nutrient-rich environment harbor a lower number of MCPs and response regulatory proteins than soil and aquatic bacteria [20, 21]. For example, many pathogenic bacteria (such as *Helicobacter pylori* [22, 23] and *C. jejuni* [24]) have fewer MCPs than bacteria that form a mutualistic/symbiotic relationship with other organisms [21]. Bacterial adaptation to diverse environmental conditions promotes diversity among their signaling proteins including MCPs [20, 21]. For example, *Myxococcus xanthus* is a soil bacterium that has a complex lifestyle which includes the development of biofilm and multicellular fruiting bodies. Its genome encodes 21 MCPs [6, 7]. *Magnetospirillum magnetotacticum* exhibits a unique feature—magnetotaxis—and is able to migrate along the geomagnetic field lines [25, 26]. It uses ferric iron as the terminal electron acceptor in the electron transport chain and harbors 65 putative MCP genes [27]. Symbionts commonly harbor 9–90 MCP genes in their chromosomes [21, 28, 29]. For example, *Sinorhizobium meliloti* that forms a symbiotic relationship with the alfalfa plant harbors 9 MCP genes in its chromosome [21, 27]. On the other end, the spectrum is *Azospirillum* sp. B510, an N_2-fixing soil bacterium that promotes the growth and disease resistance of its symbiotic partner *Oryza sativa* [30]. Its genome harbors 89 MCP genes [29]. MCPs are less common in archaea than in bacteria. Archaeal MCPs are believed to have originated via the horizontal gene transfer from bacteria [18].

Characteristic structural features of MCPs

A typical MCP receptor consists of a ligand-binding domain (LBD), transmembrane (TM) helices, and a cytoplasmic signaling domain (SD) that interact with the downstream regulatory proteins including histidine kinase CheA, receptor coupling protein CheW, methyltransferase CheR, and methylesterase CheB [31, 32] (Fig. 1). The cytoplasmic domain harbors a histidine kinase, adenyl cyclase, methyl-accepting chemotaxis protein and phosphatase (HAMP) region, methylation helices (MH), flexible bundles (FB), and a signaling subdomain (SSD) [27, 33]. Some MCPs recognize their ligands directly [34, 35], while sensing by others may be mediated by the interaction with ligand-binding proteins (periplasmic binding proteins) [36, 37]. Upon interaction with signal molecules, MCPs transduce the signal to their cytoplasmic SDs that regulate

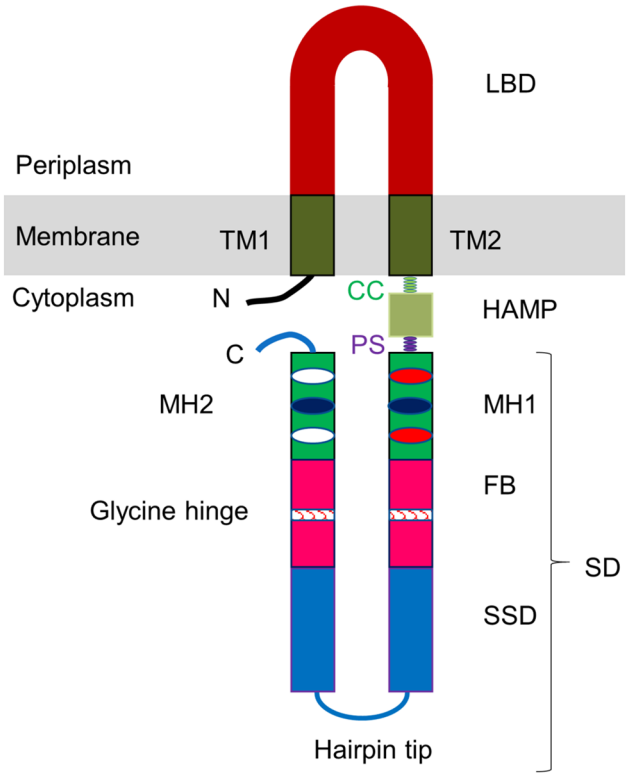

Fig. 1 Overall topology of typical methyl-accepting chemotaxis protein. *LBD* ligand binding domain, *TM* transmembrane helix, *CC* control cable, *HAMP* histidine kinase, adenyl cyclase, methyl-accepting chemotaxis protein and phosphatase region, *PS* phase stutter, *SD* signaling domain, *MH* methylation helix, *FB* flexible bundle, *SSD* signaling subdomain

the activity of CheA, the central kinase that phosphorylates its response regulator protein CheY [38]. The levels of phosphorylated CheY control the rotation of flagellar motors [31]. MCPs are arranged as trimers of dimers that form hexagonal arrays in the cytoplasmic membrane or the cytoplasm [38, 39]; molecules of CheA and CheW bound to the MCP's SSD stabilize this lattice. The assembly of the MCPs, CheA, and CheW into ordered arrays increases their local concentration and allows positive cooperativity, thus enhancing the sensitivity of the receptors and the speed of the response. Methylation/demethylation of glutamate residues within the MH subdomain by CheR and CheB, respectively, serves as the mechanism of sensory adaptation in many bacteria [31, 40].

Classification of MCPs based on LBD and membrane topology

The ligand binding domains (LBDs) are involved in recognition of a broad range of extracellular or intracellular chemical and physical cues, and accordingly, LBDs can

be located in the periplasm or the cytoplasm. Furthermore, MCPs can be membrane-embedded or cytoplasmic (soluble) [21, 41]. Bacterial receptors that sense extracellular signals commonly have a TM domain and a periplasmic LBD, whereas entirely cytoplasmic chemoreceptors often sense the energy state of the cell; the latter group of MCPs are more common in archaea than bacteria. Zhulin has classified MCPs into four major classes (I–IV) by analyzing their membrane topology [18]. Later, Wuichet and colleagues have subdivided class III into two (IIIm and IIIc) based on the presence of an LBD domain [42]. Subsequently, Lacal et al. [21] analyzed more than 3500 sequences of MCPs and elaborated the classification into seven different topologies (Ia, Ib, II, IIIm, IIIc, IVa, and IVb), where classes I and IV were subdivided based on the number of TM helices and the presence or absence of the LBD domain (Fig. 2). Based on the length of the primary sequence of the LBD, subclass Ia MCPs have been further grouped into two clusters (clusters I and II) [21].

Class I MCP receptors

A typical class I MCP harbors a periplasmic LBD, a TM domain, and a cytosolic SD [21]. This is a predominant class of MCPs both in bacteria and in archaea [21]. Based on the number of TM helices, they are categorized into two subclasses: Ia (two TM helices) and Ib (one TM helix). The subclass Ia MCPs are more common than subclass Ib. As shown in Fig. 2, the subclass Ia proteins consist of an N-terminal TM helix followed by a periplasmic LBD, a second TM helix, and a C-terminal cytoplasmic SD (Fig. 2). The subclass Ib MCPs differ from subclass Ia in that they lack an N-terminal TM helix (Fig. 2).

The class I MCPs have been further subdivided into two clusters according to the size of their LBDs: (1) cluster I (the predominant one) with an LBD of approximately 120–215 amino acids (aa) and (2) cluster II with an LBD of approximately 215–299 aa [21]. About 80% of the cluster I LBDs are α-helical, with the remainder adopting an α/β fold. Cluster I LBDs are very diverse in their three-dimensional structures and can adopt a variety of folds including a four-helix bundle (4HB), Per-Arnt-Sim (PAS), cGMP-specific phosphodiesterases, adenylyl cyclases and FhlA (GAF), calcium channels and chemotaxis receptors (Cache), and cyclases/histidine kinases associated sensory extracellular (CHASE) fold. For example, the well-characterized *Escherichia coli* taxis to aspartate and repellents (Tar) and taxis to serine and repellents (Tsr) receptors are cluster I proteins with an LBD that possess a 4HB fold [43–45]. The acid-sensing chemoreceptor TlpB from *H. pylori* is a cluster I protein, the LBD of which adopts a PAS-like Cache fold [46]. *Geobacter sulfurreducens* has two cluster I MCPs that contain a periplasmic LBD with a PAS fold harboring a *c*-type heme-binding motif [47].

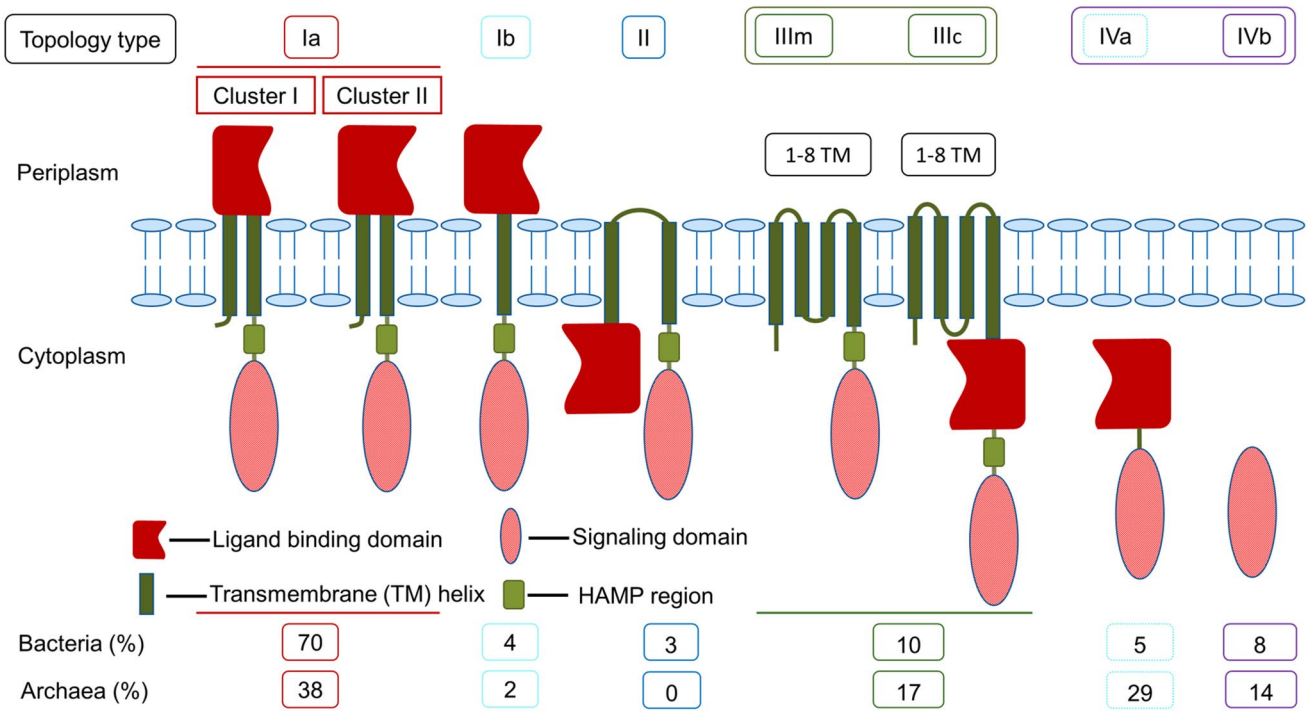

Fig. 2 Classification of methyl-accepting chemotaxis proteins based on membrane topology and LBD. The larger size of the LBD represents the longer amino acid sequence

Desulfovibrio vulgaris DcrA is also a *c*-type heme-binding protein with a 158-aa LBD that adopts a PAS fold [48]. DcrA is the cluster I MCP that serves as a redox and/or oxygen sensor [48].

The cluster II LBDs are found mainly in archaea. 90% of the archaeal cluster II LBDs are α-helical and 10% are α/β protein [21]. In contrast, most of the bacterial cluster II LBDs have an α/β fold (78%), with only 22% adopting an α-helical structure [21]. The structurally characterized LBDs of the cluster II receptors include the helical bimodular (HBM) and double Cache [previously named tandem-PAS or double PDC (PhoQ, DucS, CitA)] domains [34, 36, 49–52]. For example, *P. putida* McpS is a cluster II receptor with a 258-aa LBD that adopts an HBM fold. This receptor mediates chemotaxis towards tricarboxylic acid cycle intermediates and butyrate [51]. *C. jejuni* Tlp3 is a different cluster II receptor that contains a double Cache LBD (250 aa) and is responsible for directly sensing the branched-chain amino acid isoleucine [34].

Structural studies of cluster-I and cluster-II LBDs suggested that the former have one ligand-binding pocket [43, 46, 53, 54], whereas the latter are composed of two subdomains, each containing a putative ligand-binding site [34, 51]. There appears to be no correlation between the ligand specificity and whether the LBD belongs to cluster I or cluster II. For example, the cluster I LBD of CtpL and cluster II LBD of CtpH from *P. aeruginosa* are both involved in sensing inorganic phosphate, despite sharing no significant sequence homology [55].

Class II MCP receptors

Class II receptors harbor an N-terminal cytoplasmic LBD followed by two TM helices, a cytoplasmic HAMP region and a cytoplasmic SD (Fig. 2). The class II receptors are present solely in bacteria and are much less common (3%) in comparison with other classes of receptors [21]. They are known to be involved in aerotaxis or sensing of the cellular redox status. Examples of class II MCPs are *E. coli* aerotaxis receptor (Aer) [56] and *Azotobacter vinelandii* redox sensor NifL [57], both harboring an N-terminal cytoplasmic sensing PAS domain [57, 58]. In archaea, aerotaxis is mediated by receptors with a different topology [59].

Class III MCP receptors

Class III MCPs have a variable number of TM helices (1–8), with the sensor element located either within the membrane part (subclass IIIm), or in the cytoplasm, after the last TM helix (subclass IIIc), and followed by the cytoplasmic HAMP region and SD (Fig. 2) [21, 42]. They are more common in archaea than in bacteria [21]. For example, HtrVIII (halobacterial transducer of rhodopsin) from the archaeon *H. salinarum* is a subclass IIIm MCP that has six TM helices harboring a heme-binding site that serves as an oxygen sensor [59]. The *H. salinarum* sensory rhodopsin-I is a phototaxis receptor that has seven TM helices at the N-terminus, with a covalently bound light-sensitive retinal chromophore and a cytoplasmic SD [60]. Examples of bacterial class III MCPs include *Bacillus subtilis* KinB, a subclass IIIm receptor with six TM helices which is involved in spore formation, and *B. subtilis* KinD, a subclass IIIc receptor that plays a major role in bacterial survival in harsh environmental conditions [61, 62].

Class IV MCP receptors

Class IV MCPs are cytoplasmic (soluble) proteins with or without an identifiable LBD (subclasses IVa or IVb, respectively) [21]. They are more common in archaea than in bacteria [21]. Well-studied examples of archaeal and bacterial subclass IVa MCPs are aerotaxis receptor HemAT (haem-based aerotaxis transducer) from *H. salinarum* [17] and *B. subtilis* [63], respectively, that contain a globin motif in their LBD. The mechanism of ligand recognition by subclass IVb MCPs remains to be established. An example of an archaeal receptor from subclass IVb is Tm14 from *Thermotoga maritima* (278 aa) [64, 65]. The class IV chemoreceptors are also found in bacteria including *Rhodobacter sphaeroides* [66] and *V. cholerae* [41].

Subcellular location of MCPs

Subcellular localization of MCPs is determined by the type of signals they sense. Membrane-embedded MCPs with periplasmic LBD are involved in sensing environmental cues, while cytosolic MCPs and membrane-embedded MCPs with cytoplasmic LBD sense intracellular signals. Both bacterial and archaeal membrane-embedded MCPs exist as trimers of dimers that are arranged in highly ordered one-layer hexagonal arrays [39, 67, 68]. These arrays are stabilized by the interactions between the cytoplasmic tips of the receptors and the CheW and CheA proteins [41]. Cytoplasmic MPCs are arranged in hexagonal arrays in a fashion similar to that of transmembrane MCPs. However, in contrast to transmembrane MCPs, the cytoplasmic MCP arrays in bacteria [41] and archaea [68] form a two-layer structure, sandwiched between two CheA-CheW plates. LBDs in the cytoplasmic MCP arrays are thought to be positioned in the middle of the sandwich [41]. This hexagonal packaging of MCPs facilitates cooperative interactions between the receptors and thereby plays an important role in signal transduction [69].

The location of the hexagonal arrays of transmembrane and soluble MCPs within the cell varies between species, and also between different MCPs within one organism.

In bacteria, most transmembrane MCPs are localized to the pole(s) of the cell [67], although membrane-embedded MCP with lateral localization has also been found [70]. Polar localization of transmembrane receptor arrays (reported as polar organelle) has also been found in the archaeon *H. salinarum* [71]. Bacterial soluble MCPs can be targeted to the poles or distributed throughout the cell body [41], while the archaeal cytosolic MCPs are often located near the mid-section of the cell [68]. For example, all four MCPs from *E. coli* are membrane proteins that are clustered at the cell poles [72]. Both membrane-embedded and cytosolic MCPs of *V. cholerae* [73] localize to polar regions. Membrane-embedded MCPs of *R. sphaeroides* are mainly localized at cell pole, while its soluble MCPs form clusters in the cytoplasm, grouped around the mid-section or ¼ and ¾ positions, depending on the cell-cycle stage [74]. The WspA protein in *P. aeruginosa* is a membrane-embedded MCP that forms clusters both at the poles and lateral locations [70]. The methane-producing archaeon *Methanoregula formicica* has six cytosolic MCPs which are arranged as bilayer hexagonal arrays near the mid-cell [68].

In many well-characterized species, there appears to be no direct link between the position of the chemoreceptor arrays and the cellular localization of flagella. For example, the polar location of *E. coli* MCPs does not correlate with the random distribution of its flagella around the cell. Similarly, in *R. sphaeroides*, the predominantly polar location of its membrane receptor clusters is distinct from the location of its single flagellum that is randomly positioned on the side of the cell body. It is believed that the subcellular location and distribution of the chemoreceptor arrays, which often changes in different stages of the bacterial cell cycle, ensures receptor inheritance on division, so that both progeny cells possess the complete chemosensory apparatus [75].

HAMP region

The HAMP region is composed of one or more ~50 aa long signal relay modules that play a crucial role in the propagation of the signal from the sensing domain to the cytoplasmic SD [76, 77]. In most MCPs, one end of the HAMP region is connected to a TM helix by a five-residue control cable, while the other end is linked to the methylation helix (sensory-adaptation subdomain) of SD via a four-residue phase stutter [78]. The single HAMP module has a parallel four-helix bundle fold and is a dimer of two pairs of parallel amphipathic α-helices (AS1 and AS2) joined by a 14-amino-acid long flexible connector [79, 80]. The amino acid sequence of aliphatic α-helices AS1 and AS2 contains a typical seven-residue heptad repeat (*a–b–c–d–e–f–g*), where one heptad repeat corresponds exactly to two α-helical turns. The hydrophobic side chains of the residues at positions a and d form "knobs" that are directed inwards and are buried in the core of the molecule [80, 81]. In most characterized HAMP modules, the flexible connector between AS1 and AS2 harbors a conserved motif with a consensus sequence G-x-HR1-x-x-x-HR2, where HR1 and HR2 are conserved hydrophobic residues [76, 80]. Removal of the HAMP domain results in inactivation of the receptor [33, 76]. Although the sequence identity among HAMP domains of different proteins is very low [82], they can be swapped between different MCPs without altering their cellular functions which suggest a common mechanism of the signal relay by this domain [76]. In addition, the number of HAMP modules varies among different receptor proteins [83]. For example, *P. aeruginosa* cytosolic aerotaxis receptor harbors five HAMP domains [81], while the *E. coli* Aer receptor contains only one domain [84]. Hulko and colleagues [80] reported the first 3D structure of a HAMP domain from *Archaeoglobus fulgidus* Af1503 which was solved by nuclear magnetic resonance. Later, the structure of a polyHAMP domain of *P. aeruginosa* Aer2 receptor has been reported [81, 84].

The role of an HAMP domain is to transmit signal received at the LBD to the SD. A canonical HAMP domain serves as a universal signal converter which tunes a broad range of input signals into conformational changes in the downstream SD via concerted axial rotation of all helices [80, 83]. Zhou and colleagues [85] proposed a three-state dynamic bundle model for the signal transmission by the *E. coli* HAMP domain. In the presence of an attractant, HAMP helices form a stable bundle, which results in a loose packing of the downstream four-helix methylation bundle and a kinase-off state of the receptor. In contrast, interaction with a repellent result in destabilization of the HAMP bundle and a more stable packing of the methylation bundle, which induces the kinase-on conformation of the SD. The detailed signal transduction mechanism by the HAMP modules has been described elsewhere [77, 81, 85].

Cytoplasmic signaling domain

The cytoplasmic signaling domain (SD) is the most conserved element of MCP receptors, consisting of adaptation (methylation) subdomain, connected to the signaling subdomain (SSD) via a flexible bundle (Fig. 1). Alexander and Zhulin [27] have categorized MCPs into seven major (44, 40, 38, 36, 34, 28, and 24 H) and five minor (48, 42, 52, 58, and 64 H) classes based on the analysis of sequence conservation and on the number of heptads in the SD (Fig. 3). The seven major classes contained ~90% of the ~2000 analyzed MCPs. The amino-acid sequence of the SSD is highly conserved; the adaptation subdomain shows a moderate degree

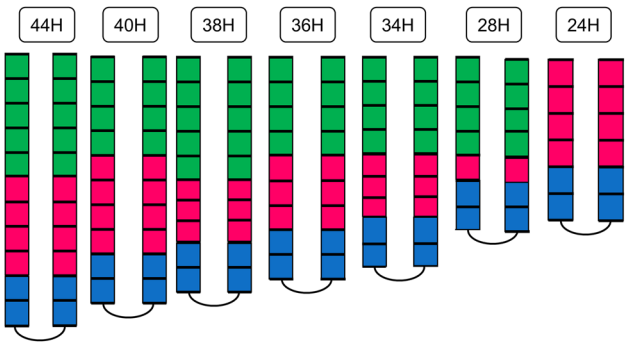

Fig. 3 Seven major classes of cytoplasmic signaling domains of methyl-accepting chemotaxis proteins. The methylation bundle, flexible bundle, and signaling subdomain are colored *green, purple*, and *blue*, respectively. Each *box* represents two heptads. The names of MCP classes were assigned according to the number of heptads (24–44 H) [27]

of conservation, while the flexible bundle is the least conserved part of the SD (Figs. 1, 3) [27].

Methylation subdomain

The methylation subdomain [often referred to as methylation helices (MH)] harbors several crucial residues that, in most characterized receptors, undergo signal-dependent reversible methylation; changes to the extent of the methylation lead to sensory adaptation. In many bacteria, the MH subdomains of different MCPs contain the consensus sequence-[A/S/T/G]-[A/S/T/G]-X-X-[E/Q]-[**E/Q**]-X-X-[A/S/T/G]-[A/S/T/G]-, where one of the two consecutive Glx (E/Q) residues is the methylation site [27, 86]. The methylation is catalyzed by CheR, while CheB and CheD are responsible for demethylation and deamidation of the site, respectively [87–89]. The small conserved residues flanking the EQ pairs are believed to be important for proper docking of the helical turn in the active site of the methylation modification enzymes [90]. An example of a bacterium that deviates from the above-mentioned MH consensus sequence is *T. maritima*, the six transmembrane chemoreceptors of which have the methylation sites -[A/S]-[A/S/T/G]-X-[**E/Q**]-[E/Q]-X-[A/S/T/G]-[A/S]- [91]. The number and location of the methylation sites vary among different classes of MCP receptors.

Flexible bundle subdomain

The flexible bundle (FB) subdomain connects the methylation/adaptation subdomain MH with the signaling subdomain (SSD) [27]. The only conserved amino acid sequence features are the glycine hinge at midpoint that plays an important role in the formation of a trimer of dimers in signaling complexes [78] and the hydrophobic knob residues a and d of the heptads (*a–b–c–d–e–f–g*) that form interactions that define the conformation of the four-helical bundle. The precise mechanism of how the FB subdomain transmits signal is yet to be established.

Signaling subdomain

The signaling subdomain (SSD) located at the tip of the cytoplasmic SD directly interacts with CheA and CheW for the modulation of bacterial flagellum rotation [78]. The kinase-activating hairpin tip of the SSD, showing the highest amino acid sequence conservation among MCPs (Alexander and Zhulin [27]), fluctuates between two stable conformations in a signal-dependent manner [92]. The interactions between the hairpin tip, CheA and CheW stabilize the clusters of trimers of dimers, and thereby, modulate the formation and activity of the receptor signaling complexes [78, 93]. The tip contains two conserved residues (F396 and E391 in *E. coli* Tsr) that play a crucial role in switching between the two output states of the MCP receptor [78, 92, 93]. Substitutions of the surface-exposed E391 residue with an apolar residue resulted in fast switching between the kinase-on and off states which suggested that this tip dynamics is likely to be involved in regulation of the kinase activity [93]. The two buried side chain of F396 on the two halves of the receptor stack against each other which stabilizes the dimer interface; flipping of the stacking arrangement due to rotameric freedom of the two rings results in an alternative tip conformation and hence, alternative signaling state [92]. Crosslinking studies confirmed the proximity between E391 of MCP and CheW [94] and identified the MCP tip residues that interact with CheA [95].

Ligand sensing and signal transduction mechanisms

MCP receptors allow the cell to navigate in gradients of various chemical (e.g. pH, osmolarity, concentration) and physical (e.g., light, temperature, magnetic field) cues. Ligand sensing mechanism has been extensively studied in *E. coli* MCPs Tar and Tsr, where ligand-binding to the LBD was shown to induce a small (~2 Å) piston-like sliding of one of the TM helices (TM2) in the MCP dimer, in the direction normal to the plane of the membrane [96]. This inward movement of the TM2 helix is believed to modulate the control cable helicity (by creating a kink or break in a α-helix) that enhances the HAMP bundle packing stability [97]. The phase stutter that connects the HAMP region with the MH bundle propagates the signal in a counter-phase manner: tight packing of the HAMP bundle causes loose packing of the MH subdomain and vice versa [98, 99]. The modulation of the packing geometry or axial motions of the MHs controls the output state of the

SSD. Bending at the glycine hinge of the flexible bundle subdomain that links the MH subdomain with the SSD is thought to play an important role during the assembly of trimers of dimers or during the switching of SSD between 'kinase ON' and 'kinase OFF' states [67, 100]. The SSD's interaction with kinase CheA is mediated by the receptor coupling protein CheW; the three proteins function as the MCP/CheA/CheW signaling complex [31]. The 'kinase ON' and 'kinase OFF' states of SSD control the activity of CheA, thus influencing the level of phosphorylation of its cognate response regulator CheY (Fig. 4). The CheY-P shuttles between the receptor-signaling complexes and the flagellar motors [31, 78]; interaction of CheY-P with the motors controls the rotation of the flagella. In *E. coli*, the direction of flagella rotation (counter-clockwise or clockwise) depends on the ratio of CheY:CheY-P. Removal of a phosphate group from CheY-P by a phosphatase CheZ terminates the signal.

Response to a temporal variation of ligand (attractants or repellents) concentration is controlled by a system consisting of methylesterase CheB and methyltransferase CheR. The CheR is a constitutively active; it methylates the conserved glutamate or deamidated glutamine residues in the MH subdomain of the chemoreceptors using S-adenosylmethionine as a cofactor. Elevated methylation results in inhibition of MCP signaling [31, 78], which is the core adaptation mechanism. The activity of methylesterase CheB is controlled by the levels of activated CheA: the CheA phosphorylates and thus activates CheB. The activated CheB removes methyl groups from MCPs and thereby restores their signaling capacity (Fig. 4). CheB and CheR act in coordination to allow the cell to modulate its stimulation level. This adaptation system enables a cell to navigate in gradients of signals (attractants or repellents) over a broad range of concentrations, from nanomolar to millimolar [40]. Interestingly, a different signaling paradigm has been found in *B. subtilis*. While increasing concentration of attractants decreases the kinase activity in *E. coli*, the opposite effect is found in *B. subtilis* [101]. Examples of archaea have been reported, where the chemotaxis systems use an additional protein, CheF, to relay the signal from CheY-P to the motors [16].

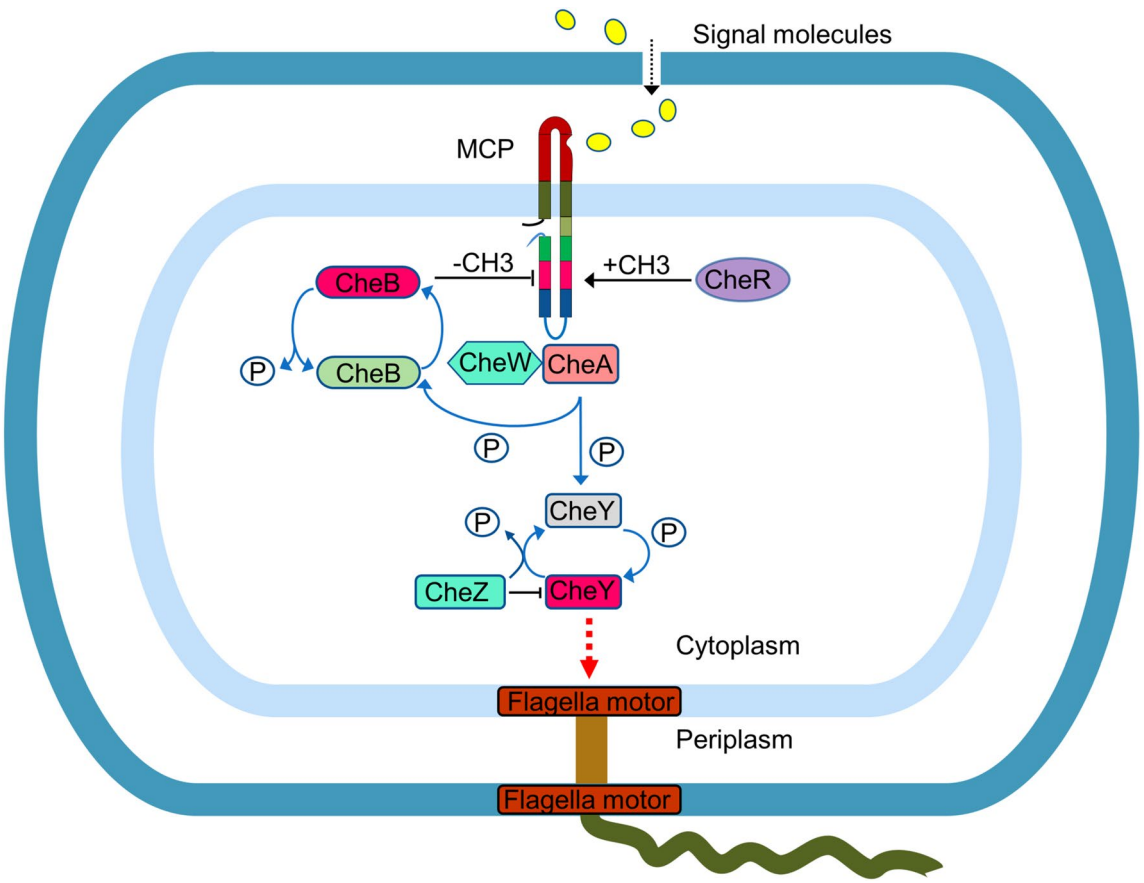

Fig. 4 Signal recognition and transduction mechanism by a typical MCP receptor in bacteria

Conclusions and future directions

Chemotaxis plays an important role in the ecology of bacterial populations [32, 102]. Signal recognition by MCPs and a cell response in the form of modulation of its motile behavior underpin the ability of bacteria and archaea to colonize nutrient-rich microenvironmental niches—the process central to symbiosis and pathogenesis. Chemotaxis is essential for the host colonization and virulence of many pathogenic bacteria that cause diseases in humans, animals, and plants [103, 104]. For example, chemotaxis towards chemicals released by corals and their symbionts plays an important role in the infection of corals by pathogenic bacteria associated with coral disease [104]. Sustainable and renewable production of nitrogen for agriculture via a symbiotic association between Rhizobium bacteria and legumes is dependent on the ability of bacteria to sense and move to legume roots [105]. Furthermore, bacterial chemotaxis plays a key role in large-scale biogeochemical fluxes, including carbon, nitrogen, and sulfur cycling [106]. Owing to its ubiquitous nature, detailed understanding of how bacteria and archaea sense attractants and repellents is important.

The cognate signal molecules are known for few chemoreceptors, and ligand identification represents a major research need in this area. Many other challenges lie ahead including answering the question of how the same chemoreceptor can sense, and differentiate between, attractants and repellents [43, 107]. The current understanding of ligand sensing mechanism mainly comes from the studies on the *E. coli* chemoreceptors. However, the signal transduction mechanisms in microorganisms that lead a more complex lifestyle utilize additional proteins and chemoreceptors with a distinctly different signaling domain. It remains to be established how chemoreceptors with the sensing domain that differs from the four-helix bundle (such as HBM, Cache, and so on) transmit signals across the membrane. The mechanisms of signal amplification in many bacteria and archaea that deviate from the *E. coli* CheA/CheW/CheY paradigm are not yet fully defined.

Currently, only low-resolution cryo-electron microscopy structures of a full-length chemoreceptor are available. No crystal structure of a receptor/repellent complex has been elucidated so far. In addition, the complete three-dimensional structure of the signaling complex is yet to determined. It remains to be established if the patterns of receptor arrangement are conserved across different bacteria and archaea. Furthermore, how the clusters of chemoreceptors are targeted to their subcellular localization is not yet understood.

Knowledge derived through the extensive structural and biochemical analysis of chemoreceptors would have many biotechnological applications, including the design of biofertilizers that are based on the chemoattractants for the symbiotic Rhizobia, and bioengineering of chemoreceptors to enhance the bacterial ability for bioremediation of xenobiotic compounds [108]. As chemotaxis was shown to be required for the long-term persistence of many pathogenic bacteria in the host, inhibiting chemoreceptors with small molecules offers an alternative strategy for treatment of bacterial infections. MCPs represent a convenient target for drug design as they are absent in humans. Inhibition of MCPs would have a detrimental effect on the survival and virulence of bacteria, helping the host to clear the infection, while not creating conditions that are likely to give rise to resistance. Thus, detailed structural studies of the mechanisms of sensing and signaling by chemoreceptors may pave the way to the structure-guided design of novel therapeutics.

Compliance with ethical standards

Conflict of interest The authors have no conflict interest.

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