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Piston versus Scissors: Chemotaxis Receptors versus Sensor His-Kinase Receptors in Two-Component Signaling Pathways

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Abstract

In this issue of *Structure*, Molnar and colleagues present a pair of important advances: (1) a method to analyze multiple signaling states in on-off switch proteins and (2) evidence for a scissors-type mechanism of on-off switching in a full-length, membrane-bound receptor of the sensor histidine-kinase class.

Bacterial species typically possess dozens of two-component signaling pathways that sense key features of the extra-cellular or cytoplasmic environments and use this information to control a wide array of cell processes. Most of these pathways are regulated by one of two major classes of cell-surface transmembrane receptors.

Chemotaxis receptors (chemoreceptors) regulate the histidine kinase (HK) CheA and control cell movement in response to attractants and repellents, enabling cell migration toward an optimal living environment, including wound-seeking by pathogens (reviewed in Sourjik and Wingreen, 2012 and Hazelbauer et al., 2008). These chemoreceptors form an oligomer containing three receptor homodimers (a trimer of dimers), which assembles with CheA kinase and other components of the chemotaxis pathway to form a large, hexagonal array on the cell membrane containing thousands of receptor oligomers (Briegel et al., 2012; Liu et al., 2012). The binding of a chemoeffector ligand to a receptor triggers a piston, or swinging piston, displacement of the second transmembrane helix (TM2) that transmits conformational information across the lipid bilayer. The resulting piston-type displacement of the TM2 signaling helix that is normal to the bilayer has been shown by multiple, independent laboratories and methods to be directly linked to receptor on-off switching (reviewed in Sourjik and Wingreen, 2012 and Hazelbauer et al., 2008).

Unlike chemoreceptors that bind and regulate an independent His-kinase protein, sensor HK receptors typically contain a periplasmic sensor domain, a transmembrane signaling region and a cytoplasmic HK domain in the same polypeptide chain (Mascher et al., 2006). These receptors regulate most two-component pathways other than chemo-taxis, thereby controlling key aspects of cell metabolism, transport, growth, and virulence. Sensor HK receptors form homodimers and perhaps higher oligomers, but generally are not believed to

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form 2D arrays like chemotaxis receptors. Notably, relatively few mechanistic studies have been carried out on functional sensor HK receptors in their native membrane environment, making this receptor class especially ripe for study.

In this issue of *Structure*, Molnar et al. (2014) have employed a powerful new approach to detect two conformations in the representative membrane-bound sensor HK receptor, PhoQ, and plausibly argue these two conformations represent the receptor on- and off-signaling states. The study began with a standard disulfide crosslinking analysis (Bass et al., 2007) of the apo receptor conformation, but the resulting crosslinking data could not be adequately fit by a single conformational state. To address this conundrum, the authors developed a novel approach combining Bayesian statistical methods, crystallographic information, and molecular modeling to analyze the crosslinking data. The analysis revealed the coexistence of two distinct conformations in the receptor population differing by large diagonal displacements of helix pairs, suggesting that on-off switching occurs via a scissors-type mechanism (see Figures 3 and 7 in Molnar et al., 2014). Initial mutational studies, and the effects of ligand binding on disulfide crosslinking, yielded independent support for this scissors mechanism in PhoQ. More generally, analysis of the known structures of other sensor HK periplasmic domains for which multiple crystallographic conformers were available provided evidence that the scissors mechanism is widely conserved in this class of receptors.

Related mechanisms postulating helix swinging, torqueing, bending, or domain cracking have previously been presented for sensor HK receptors and may include scissor-like movements of adjacent or laterally displaced pairs of helices (Casino et al., 2009; Dago et al., 2012; Diensthuber et al., 2013; Wang et al., 2013). The present study represents a major advance, because it is first to detect scissoring and reciprocal diagonal helix displacements in a full-length membrane-bound receptor of the sensor HK class. As the authors point out, available evidence does not rule out smaller piston or rotational helix displacements that might also play a role in transmembrane signaling (Moore and Hendrickson, 2012).

Early studies of chemoreceptor periplasmic domains also proposed a scissors displacement of the two identical subunits (Milburn et al., 1991), but multiple, independent studies disproved the scissors hypothesis in this receptor class. Specifically, the subunit interface proposed to undergo scissoring was found to be static during receptor on-off switching, whereas the essential piston displacement of the signaling helix was discovered distal to the subunit interface and shown to be transmitted by a structural change within a single subunit of the homodimer (Falke and Hazelbauer, 2001; Chervitz and Falke, 1996; Hughson and Hazelbauer, 1996; Hazelbauer et al., 2008; see, for example, Figure 6C in Molnar et al., 2014).

The convincing, new evidence for a scissors displacement in full-length, membrane-bound PhoQ, as well as in the isolated periplasmic domains of related receptors, would therefore represent a new type of signaling mechanism unique to the sensor His-kinase receptors (Molnar et al., 2014). To test the hypothesis that scissoring is central to on-off switching in this receptor class, the methods successfully employed in chemoreceptors may prove useful (Falke and Hazelbauer, 2001; Hazelbauer et al., 2008). For example, engineered disulfide

bonds that covalently trap the two scissors conformations would be predicted to lock a receptor in its native on- and off-states and could facilitate high resolution structural studies of those states.

The subtle low-amplitude piston mechanism of chemoreceptor transmembrane signaling is well suited to the extensive structural constraints imposed by the chemosensory array on its receptors. Cryo-EM studies show that the array architecture is largely static during receptor on-off switching, consistent with a low amplitude transmembrane signal (Briegel et al., 2011). The piston mechanism provides a simple explanation for the ability of a low-energy ligand binding event (for example, the binding of a serine or aspartate molecule) to send a long-range signal well over 100 Å through the periplasmic and transmembrane regions of the receptor to the cytoplasmic domain (Falke and Hazelbauer, 2001; Hazelbauer et al., 2008). Attractant occupancy sterically locks the ligand binding site in its open state, thereby displacing the signaling helix 1.5–2.0 Å toward the cytoplasm. The relative incompressibility of the α helix, together with the virtually isoenergetic nature of helix sliding displacements under 2.5 Å , ensure this small helix displacement can be carried the entire helix length without damping. By contrast, many types of nonpiston small amplitude displacements could be susceptible to isoenergetic helix bending and thus more easily damped over long distances.

The larger amplitude scissors displacements proposed for sensor HK receptors are compatible with the conformational freedom afforded by their existence as free oligomers lacking the steric constraints imposed by chemoreceptor arrays. Like chemoreceptors, however, many sensor HK receptors are regulated by the binding of small molecules with correspondingly small binding free energies. Thus, it will be interesting to understand how sensor HK receptors harness these small binding energies to faithfully regulate on-off switching in transmembrane signals that may span hundreds of angstroms.

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REFERENCES

Bass RB, Butler SL, Chervitz SA, Gloor SL, Falke JJ. Methods Enzymol. 2007; 423:25–51. [PubMed: 17609126]

Briegel A, Beeby M, Thanbichler M, Jensen GJ. Mol. Microbiol. 2011; 82:748–757. [PubMed: 21992450]

Briegel A, Li X, Bilwes AM, Hughes KT, Jensen GJ, Crane BR. Proc. Natl. Acad. Sci. USA. 2012; 109:3766–3771. [PubMed: 22355139]

Casino P, Rubio V, Marina A. Cell. 2009; 139:325–336. [PubMed: 19800110]

Chervitz SA, Falke JJ. Proc. Natl. Acad. Sci. USA. 1996; 93:2545–2550. [PubMed: 8637911]

Dago AE, Schug A, Procaccini A, Hoch JA, Weigt M, Szurmant H. Proc. Natl. Acad. Sci. USA. 2012; 109:E1733–E1742. [PubMed: 22670053]

Diensthuber RP, Bommer M, Gleichmann T, Möglich A. Structure. 2013; 21:1127–1136. [PubMed: 23746806]

Falke JJ, Hazelbauer GL. Trends Biochem. Sci. 2001; 26:257–265. [PubMed: 11295559]

Hazelbauer GL, Falke JJ, Parkinson JS. Trends Biochem. Sci. 2008; 33:9–19. [PubMed: 18165013]

Hughson AG, Hazelbauer GL. Proc. Natl. Acad. Sci. USA. 1996; 93:11546–11551. [PubMed: 8876172]

Liu J, Hu B, Morado DR, Jani S, Manson MD, Margolin W. Proc. Natl. Acad. Sci. USA. 2012; 109:E1481–E1488. [PubMed: 22556268]

Mascher T, Helmann JD, Unden G. Microbiol. Mol. Biol. Rev. 2006; 70:910–938. [PubMed: 17158704]

Milburn MV, Privé GG, Milligan DL, Scott WG, Yeh J, Jancarik J, Koshland DE Jr, Kim SH. Science. 1991; 254:1342–1347. [PubMed: 1660187]

Molnar KS, Bonomi M, Pellarin R, Clinthorne GD, Gonzalez G, Goldberg SD, Goulian M, Sali A, DeGrado WF. Structure. 2014; 22:1239–1251. this issue. [PubMed: 25087511]

Moore JO, Hendrickson WA. Structure. 2012; 20:729–741. [PubMed: 22483119]

Sourjik V, Wingreen NS. Curr. Opin. Cell Biol. 2012; 24:262–268. [PubMed: 22169400]

Wang C, Sang J, Wang J, Su M, Downey JS, Wu Q, Wang S, Cai Y, Xu X, Wu J, et al. PLoS Biol. 2013; 11:e1001493. [PubMed: 23468592]