International Journal of Medical Microbiology 305 (2015) 243–251

Contents lists available at ScienceDirect

International Journal of Medical Microbiology

journal homepage: www.elsevier.com/locate/ijmm

Mini-Review

Intraprotein signal transduction by HAMP domains: A balancing act

Joachim E. Schultz[a,*], Kajal Kanchan[b], Miriam Ziegler[a]

[a] Pharmazeutische Biochemie, Pharmazeutisches Institut, Universität Tübingen, Auf der Morgenstelle 8, 72076 Tübingen, Germany
[b] Department of Biochemistry and Molecular Biology, Medical and Health Science Center, University of Debrecen, Debrecen H 4032, Hungary

ARTICLE INFO

Keywords:
Adenylate cyclase
HAMP domain
Signaling language
Membrane receptor

ABSTRACT

HAMP domains are small protein modules that predominantly operate as signal transducers in bacterial sensor proteins most of which are membrane delimited. The domain organization of such sensors has the HAMPs localized at the intersection between the membrane-anchored input sensor and the cytosolic output machinery. The data summarized here indicate that HAMP modules use a universal signaling language in balancing the communication between diverse membrane-bound input domains and cytosolic output domains that are completely foreign to each other.

© 2014 Elsevier GmbH. All rights reserved.

Introduction

Structures are deceptive as they tend to make us believe in still pictures where movement is permanent. To appreciate the simplicity and elegance of biochemical mechanisms at the molecular level we need more movies or animated transitions between active and inactive states (for an example see Suppl. material in Tews et al., 2005) and fewer snapshot structures of subdomains. In fact, a number of hypotheses concerning biochemical mechanisms debate rigid-looking structures which represent still pictures of peculiar domains of larger proteins and pay too little reference to structural equilibria which determine the function of a multidomain protein complex (for a striking example see Martinez et al., 2002, 2005; Pandit et al., 2009). Each protein is a balanced universe by itself. Folding of a protein into subdomains is no collapse into rigid and individually sized ice-cream scoops. Instead protein folding anticipates and mirrors the constant competitive balancing act between different domains. The small bacterial signal-transducing HAMP domain appears to be a lucid case in point where animated discussions based on the subdomain structure of larger proteins abound.

The HAMP module

HAMP domains are small, but many (about 55 amino acid residues; annotated >28,000 times in data bases). Usually, a HAMP is one module within a multi-domain protein. A HAMP represents about 10% of a protein. HAMPs are absent in mammals, but present in fungi (Meena et al., 2010). The acronym HAMP is derived from the proteins of first identification, i.e. in **H**istidine kinases, **A**denylate cyclases, **M**ethyl accepting proteins of chemotaxis and **P**hosphatases. A bioinformatic study has revealed the absence of any generally conserved amino acid position in HAMPs and has identified lines of domain coevolution. This has allowed classifying the majority of HAMP domains into a canonical and a divergent group (Dunin-Horkawicz and Lupas, 2010). The sequences have a uniform seven-residue repeat pattern labeled *a* to *g* in which the first (*a*) and the forth (*d*) position usually is occupied by hydrophobic residues. A canonical coiled coil structure is predicted (Crick, 1953; Gruber and Lupas, 2003). Most HAMP-containing proteins have a single module, yet arrays with 2 to 31 HAMPs exist. Usually a canonical HAMP alternates with a divergent one, e.g. in the light sensor system HtrII of the halophile *Natronomonas pharaonis*.

HAMPs have resisted all efforts of a structure elucidation for a long time. In 2006 the solution structure of an archeal HAMP dimer from the hyperthermophile *Archaeoglobus fulgidus* was elucidated by NMR (Fig. 1; Hulko et al., 2006). This membrane-anchored Af1503 HAMP lacks a distinct output domain. The structure was a surprise in that a complementary *x*-da conformation was observed in which hydrophobic side chains of the four-helix bundle alternatively point straight into the center at one level and sideways forming an interacting ring at another level (Fig. 1). The structure can rotate into a canonical knobs-into-holes coiled coil by a simple axial helical rotation of the four-helix bundle by 26° (Fig. 1).

Abbreviations: Tsr*E*, *coli* receptors for taxis toward serine; Tar*E*, *coli* receptors for taxis toward aspartate; HtrII, *Natronomonas* halobacterial transducer of rhodopsin II; HAMP-1first, HAMP domain of HtrII; HAMP-2second, HAMP domain of HtrII; TM, transmembrane helix.

* Corresponding author. Tel.: +49 7071 2972475; fax: +49 7071 202476.
E-mail address: joachim.schultz@uni-tuebingen.de (J.E. Schultz).

http://dx.doi.org/10.1016/j.ijmm.2014.12.007
1438-4221/© 2014 Elsevier GmbH. All rights reserved.

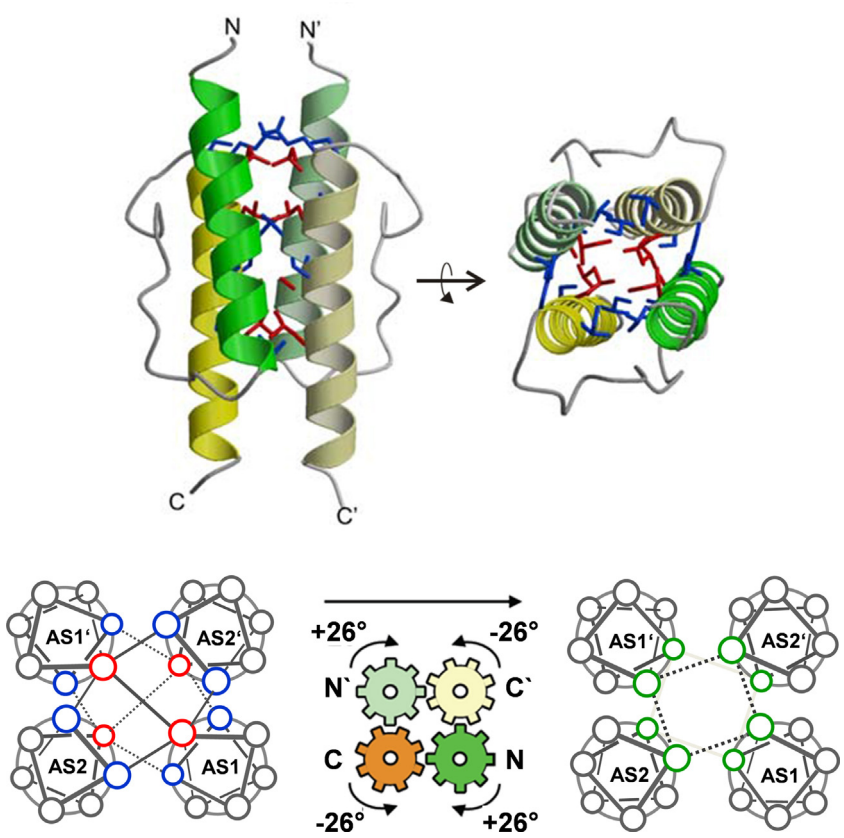

Fig. 1. *The gearbox model of HAMP mediated signal transduction.* Top: NMR structure of the Af1503 HAMP domain. The side chains of residues involved in packing interactions within the core of the module are in red (residues in *x*-layer geometry) and blue (da layer geometry; PDB 2ASW). View from top at right. Bottom: The gearbox model of the α-helices during signal transduction. Schematic representation of complementary *x*-da packing (left) versus canonical knobs-into-holes packing of the coiled coil (right). The two packing modes can be interconverted by rotating adjacent helices by 26° in opposite directions as illustrated by the cogwheel diagram (figure adapted from Hulko et al., 2006).

Supported by targeted biochemical experiments, it is proposed that HAMPs mediate signal transduction between signal input and output domains via reversible rotation between two almost isoenergetic states (Hulko et al., 2006). This has been supported by subsequent crystal structures which included additional protein subdomains (Airola et al., 2010; Ferris et al., 2011, 2012, 2014a,b). Superficially, the proposal clashes with a piston model in which a discrete ~1 Å vertical displacement of the second transmembrane helix of Tar toward the cytoplasm is proposed to signal to the chemotaxis machinery (Falke and Hazelbauer, 2001; Ottemann et al., 1999). Viewing this movement as a screw-like motion would reconcile both models. Based on genetic experiments, a "dynamic-bundle model" is proposed in which variant HAMP signaling states of not clearly defined structures are postulated to exist, i.e. "dynamic ensembles of different bundle conformations" (Ames et al., 2014; Parkinson, 2010; Zhou et al., 2011). Obviously, many structural details of intraprotein signaling mediated by HAMP domains remain to be uncovered.

Biochemical analyses of HAMP signaling are difficult because the module itself lacks an enzyme activity, i.e. each characterization is context-dependent. Most HAMPs are part of dimeric two-component signaling systems which serve as high-sensitivity detectors of the bacterial environment. Intracellularly, these systems are coupled via response regulators to swimming behavior and gene regulation. Accordingly, assays use the analysis of flagellar rotation and swimming behavior, of methylation of glutamate residues, of in vivo FRET-kinase in chemotaxis systems and of phosphorylation of cytoplasmic response regulators and gene expression in histidine kinases (Han and Parkinson, 2014; Hazelbauer et al., 2008; Jin and Inouye, 1994; Parkinson, 2010; Zhu and Inouye, 2003). So far, a signal transduction protein with a single HAMP module such as a bacterial adenylate cyclase is of little use for biochemical studies. Adenylate cyclase activity can be determined with great precision, yet no ligand is known for the membrane anchors/presumed receptors of HAMP-containing enzymes.

The ubiquity of HAMP domains in bacterial signaling proteins calls for a common mechanism of signal transduction. The poor sequence conservation is compatible with this claim as the sequence pattern of hydrophobic residue spacing defines a common structural feature. Actually, the basic design with relaxed sequence requirements allows HAMPs to be recruited as facilitators between different signal input and a functionally and molecularly more confined set of output domains (Schultz and Natarajan, 2013). In a protein which can shuffle between conformations of similar free energy subtle sequence differences are all what is needed to successfully conjoin variant input and output domains. Whether the evolution of the multitude of HAMPs was accompanied by structural/mechanistic adaptations under such conditions or a general HAMP signal transducing mechanism has been maintained remains an open question.

Formerly, chimeric sensor proteins mainly have used modules from different *E. coli* sensors (for examples see Appleman et al., 2003; Appleman and Stewart, 2003; Grebe and Stock, 1998; Jin and Inouye, 1994; Kishii et al., 2007). The studies demonstrate that a certain degree of interchangeability exists. We have generated sensor chimeras using signaling components from different bacterial species in which as a rule bacterial adenylate cyclases were

Download English Version:

https://daneshyari.com/en/article/8385313

Download Persian Version:

https://daneshyari.com/article/8385313

Daneshyari.com