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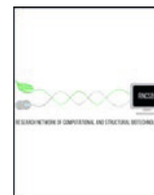

Review

The role of solute binding proteins in signal transduction

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The solute binding proteins (SBPs) of prokaryotes are present in the extracytosolic space. Although their primary function is providing substrates to transporters, SBPs also stimulate different signaling proteins, including chemoreceptors, sensor kinases, diguanylate cyclases/phosphodiesterases and Ser/Thr kinases, thereby causing a wide range of responses. While relatively few such systems have been identified, several pieces of evidence suggest that SBP-mediated receptor activation is a widespread mechanism. (1) These systems have been identified in Gram-positive and Gram-negative bacteria and archaea. (2) There is a structural diversity in the receptor domains that bind SBPs. (3) SBPs belonging to thirteen different families interact with receptor ligand binding domains (LBDs). (4) For the two most abundant receptor LBD families, dCache and four-helix-bundle, there are different modes of interaction with SBPs. (5) SBP-stimulated receptors carry out many different functions. The advantage of SBP-mediated receptor stimulation is attributed to a strict control of SBP levels, which allows a precise adjustment of the systems sensitivity. We have compiled information on the effect of ligands on the transcript/protein levels of their cognate SBPs. In 87 % of the cases analysed, ligands altered SBP expression levels. The nature of the regulatory effect depended on the ligand family. Whereas inorganic ligands typically downregulate SBP expression, an upregulation was observed in response to most sugars and organic acids. A major unknown is the role that SBPs play in signaling and in receptor stimulation. This review attempts to summarize what is known and to present new information to narrow this gap in knowledge.

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Abbreviations: AI-2, autoinducer-2; CCR, carbon catabolite repression; LBD, ligand binding domain; Pi, inorganic phosphate; SBP, solute binding protein; TCS, two-component system.

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1. Introduction

Bacteria need to take up compounds from the extracytosolic space in order to survive. To this end, bacteria have evolved a variety of transmembrane transporters that permit the specific transport of a variety of compounds. Several transporter families, like ATP-binding cassette (ABC), tripartite ATP-independent periplasmic (TRAP), and tripartite tricarboxylate transporters (TTTs) employ solute binding proteins (SBPs) to capture the transport substrate in the extracytosolic space and to present it to the transmembrane receptor permeases [1]. These proteins thus play a central role in defining the substrate specificity of the transporter.

SBPs are found in all kingdoms of life [1] and form a superfamily composed of many families, as defined by different domain profiles in the Pfam [2] and InterPro [3] databases. Whereas SBPs in Gram-negative bacteria are present as diffusible proteins in the periplasm, in Gram-positive bacteria and archaea they are tethered to the external face of the cytoplasmic membrane [4]. Although SBPs vary largely in size, from 20 to 65 kDa, they share the same overall topology that consists of two lobes linked by a hinge region [5]. The transport substrate binds to the interface of both lobes, a process that frequently induces significant structural rearrangements [6,7].

Other major constituents of prokaryotic membranes are signal transduction receptors [8]. The function of these proteins is to sense extracytoplasmic signals and to initiate a cellular response leading to a more optimal adaptation to a given environmental condition. The most abundant signal transduction receptors are sensor kinases, chemoreceptors, diguanylate cyclases and phosphodiesterases, adenylate cyclases, extracytosolic function sigma factors as well as Ser/Thr kinases and phosphatases [8]. Typically, these receptors are transmembrane proteins that contain an extracytoplasmic sensor or ligand binding domain (LBD) that is flanked by two transmembrane regions. Signal binding to the LBD creates a conformational change that is transmitted to the cytosolic part of the receptor to induce signaling cascades that lead to the final cellular response. Transmembrane signal transduction receptors mediate a variety of different responses. For example: (i) Sensor kinases form two component systems (TCSs) with response regulators that primarily regulate transcription [9]; (ii) Chemoreceptors form part of chemosensory pathways that primarily mediate chemotaxis but were also found to control second messenger levels or type IV pili-based motility [10]; (iii) Diguanylate cyclases/phosphodiesterases and adenylate cyclases, respectively, control the levels of c-di-GMP and cAMP, second messengers that in turn regulate a variety of different cellular processes [11,12].

Transmembrane receptors employ many different LBD types for signal sensing [13,14] as exemplified by the 80 different LBD types identified in chemoreceptors [13]. Frequently, a given LBD type is shared by different receptor families [14,15], which is consistent with the notion that LBDs are modules that can be recombined with different signaling proteins. Although the function of many transmembrane signal transduction receptors has been identified by phenotypic and transcriptomic analyses of the corresponding bacterial mutants, the signals recognized by many of these receptors remain unknown [16,17]. The scarcity of information about the signals recognized by these receptors represents a major research need in the field because this knowledge is indispensable to fully understand the corresponding regulatory circuit [18]. Over the last years, significant progress in this area has been made by high-throughput ligand screening using individual LBDs [18,19]. However, in a number of cases screening did not identify any ligand, which is consistent with the notion that some LBDs may not bind signals directly. A possible explanation is that some LBDs interact with signal-loaded SBPs. There are a number of examples, reviewed in this article, in which signal transduction receptors are stimulated by an interaction with an SBP. Some of these SBPs thus carry out a double function, as they may be involved in transport and signal transduction. Since cellular SBP levels are frequently subject to tight control, it has been proposed that this mechanism offers the possibility of coordinating different, but physiologically related, processes such as transport and chemotaxis [20]. The study of SBP-activated chemoreceptors has shown that the overall responses are highly sensitive to SBP levels, thus permitting a better control of the sensitivity to specific ligands in response to their nutrient environment and to coordinate chemotaxis with ligand transport [21]. However, the cost for this capacity is the much narrower dynamic response range of SBP-stimulated receptors as compared to those that recognize signal molecules directly [21].

Here, we review the data available on SBP-stimulated signal transduction receptors and compile information on the effect of signal molecules on the expression of their cognate SBPs. SBP-stimulated receptors showed a wide phylogenetic spread, and these systems reveal a significant diversity in the structure of receptor LBDs as well as SBPs, suggesting that indirect sensing is a rather widespread mechanism. We propose that the relatively low number of characterized SBP-stimulated systems is the consequence of the technical complexity of identifying such systems rather than their low abundance.

2. Universality and diversity of SBP interactions with bacterial sensor proteins

We have compiled the information on bacterial receptors that are stimulated by the binding of SBPs in Table 1. There was a significant phylogenetic spread of the corresponding organisms including α-, β-, γ- and ε-Proteobacteria, Actinobacteria, Firmicutes as well as Archaea (Table 1). The genes encoding SBPs are often found in the vicinity of genes encoding the cognate transporters or signal transduction receptors (Tables 1 and 2). Remarkably, genes encoding SBPs that interact with chemoreceptors are primarily found in the vicinity of genes encoding transporters, whereas those for SBPs that stimulate sensor kinases are associated with signaling genes (Table 1). Receptors belong to four families, namely chemoreceptors, sensor kinases, GGDEF-EAL domain-containing diguanylate cyclases/phosphodiesterases, and Ser/Thr kinases (Fig. 1).

For the former three families, the SBP binds to the LBD of the corresponding receptor protein. So far, there is only one characterized example of a SBP-stimulated Ser/Thr kinase, namely the tripartite GlnH/GlnX/PknG system [22]. GlnX is a transmembrane protein that has two 4HB LBDs at its periplasmic face. The binding of the GlnH SBP to GlnX generates a molecular stimulus that is transduced across the membrane to modulate the activity of the bound Ser/Thr kinase PknG [22]. The available data indicate that PknG phosphorylates primarily GarA, a regulatory protein that redirects metabolic fluxes towards the synthesis or degradation of glutamate by interacting with different enzymes involved in TCA cycle and glutamate metabolism [22–24]. More recent studies, however, have identified a significant number of physiological

Table 1
Direct or indirect evidence for the stimulation of different signal transduction receptors by SBPs.

Signal transduction receptor					Solute binding protein					
Name	UniProt	Species	Phylogenetic category	LBD family (Pfam/ InterPro)	Name/Gene associated with[a]	UniProt (size in kDa)[b]	Family Pfam/InterPro	Ligands (K_D in μM)	PDB	Ref.
Chemoreceptors										
Tar	P76301	*E. coli*	γ-Proteobacteria	TarH (PF02203)	MBP maltose binding protein/T[a]	P0AEX9 (43)	SBP_bac_8 (PF13416)	D-maltose (1.5)	2LIG	[26,40,126]
Tap	P76300	*E. coli*	γ-Proteobacteria	TarH (PF 02203)	DppA dipeptide binding protein/T[a]	P23847 (60)	SBP_bac_5 (PF00496)	Various dipeptides, (lower nM for Ala-Phe)	1DPE	[41,127]
Trg	P77448	*E. coli*	γ-Proteobacteria	TarH (PF 02203)	GBP galactose binding protein/T[a]	P0AEE5 (35)	Peripla_BP_4 (PF13407)	D-galactose (0.13)	2GBP	[37–39,42,128–130]
					RBP Ribose-binding protein/T[a]	P02925 (31)	Peripla_BP_4 (PF13407)	D-ribose (0.13)	2DRI	
					PotD spermidine binding protein/T[a]	P0AFK9 (39)	SBP_bac_8 (PF13416)	Spermidine (3.2)	1POY	[43,131]
Tsr	P02942	*E. coli*	γ-Proteobacteria	TarH (PF 02203)	LsrB/T[a]	P76142 (37)	Peripla_BP_4 (PF13407)	Autoinducer-2		[45,46]
TlpB	B5Z9N4	*Helicobacter pylori*	ε-Proteobacteria	sCache_2 (PF 17200)	AibA/T[a] AibB/T[a]	B5ZA64 (62) B5Z6J6 (28)	SBP_bac_5 (PF00496) ModA (IPR005950)	Autoinducer-2 Autoinducer-2		[56]
CtpL	G3XDA8	*Pseudomonas aeruginosa*	γ-Proteobacteria	HBM (PF 16591)	PstS/T[a]	G3XDA8 (34)	PBP_like_2 (PF12849)	Inorganic phosphate (0.009)	4OMB	[48]
PctA McpN	PA4309 PA2788	*P. aeruginosa*	γ-Proteobacteria	dCache (PF 02743) PilJ (PF13675)	GltB/T[a] & SP[a]	PA3190 (45)	SBP_bac_1 (PF01547)	Glucose (1.4)		[71]
BasT	B0R6I4	*Halobacterium salinarum*	Archaea	Not annotated (dCache-like)	BasB/SP[a]	B0R6I5 (41)	Periplа_BP_6 (PF13458)	Val, Ile, Met, Cys		[52,53]
CosT	B0R6A7	*H. salinarum*	Archaea	Not annotated (dCache-like)	CosB/SP[a]	B0R6A8 (36)	OpuAC (PF04069)	Glycine betaine, choline, carnitine		[53]
Sensor kinases										
LuxQ	P54302	*Vibrio harveyi*	γ-Proteobacteria	LuxQ-periplasm (PF09308) dCache-like	LuxP/SP[a]	P54300 (41)	Peripla_BP_4 (PF13407)	AI-2 (0.27)	2HJ9 1ZHH	[29,132,133]
LytS	A6LW08	*Clostridium beijerinckii*	Firmicutes	Not annotated (TarH-like)	XylFII/SP[a]	A6LW07 (36)	Peripla_BP_4 (PF13407)	D-xylose (0.37)	5XSJ	[27,134]
TorS	A0A0L8U5J8	*Vibrio parahaemolyticus*	γ-Proteobacteria	TorS sensor (IPR037952) HBM-like	TorT/SP[a]	Q87ID2 (37)	Peripla_BP_1 (PF0532)	Trimethylamine N-oxide (TMAO) (74)	3O1H 3O1I	[28]
TorS	P39453	*E. coli*	γ-Proteobacteria	TorS sensor (IPR037952) HBM-like	TorT/SP[a]	P38683 (38)	Peripla_BP_1 (PF0532)	TMAO (150)		[135]
HptS	Q2G1E0	*Staphylococcus aureus*	Firmicutes	Not annotated	HptA/SP[a]	X5DVD1 (37)	SBP_bac_11 (PF13531)	Glucose-6-phosphate (5), Galactose-6-phosphate (10)	6LKG 6LKH	[30,136,137]
VirA	P10799	*Agrobacterium tumefaciens*	α-Proteobacteria	Not annotated (dCache-like)	ChvE[c]/T[a]	P54082 (38)	Peripla_BP_4 (PF13407)	Arabinose (0.47), Galactose (0.13), Galacturonate (130), Glucuronate (3.1), D-xylose (17.3), D-fucose (2.2)	3URM	[105–107]
AioS	U6A267	*Agrobacterium tumefaciens*	α-Proteobacteria	Not annotated (sCache-like)	AioX/SP[a]	G8XNW6 (34)	Phosphonate-bd (PF12974)	As(III) (2.4)	6EU7	[118,119]
BctE	A0A3T0PKG6	*Bordetella pertussis*	β-Proteobacteria	2CSK_N (PF08521)	BctC/T[a] & SP[a]	A9HVV0 (35)	TctC (PF03401)	Citrate		[89,104]
ChiS	Q9KUA1	Vibrio cholerae	γ-Proteobacteria	Not annotated (dCache-like)	CBP/T[a] & SP[a]	Q9KUA3 (63)	SBP_bac_5 (PF00496)	$(GlcNAc)_2$ (1)	1ZTY	[58,59]
		Vibrio harveyi	γ-Proteobacteria	Not annotated (dCache-like)	CBP/T[a] & SP[a]	D0XC84 (63)	SBP_bac_5 (PF00496)	$(GlcNAc)_2$ (0.03) $(GlcNAc)_3$ (0.05) $(GlcNAc)_4$ (0.07)	5YQW	[138]
GtrS	PA3191	*Pseudomonas aeruginosa*	γ-Proteobacteria	Not annotated	GltB/ T[a] & SP[a]	PA3190 (45)	SBP_bac_1 (PF01547)	Glucose (1.4)		[71]

Table 1 (*continued*)

Signal transduction receptor					Solute binding protein					
Name	UniProt	Species	Phylogenetic category	LBD family (Pfam/ InterPro)	Name/Gene associated with[a]	UniProt (size in kDa)[b]	Family Pfam/InterPro	Ligands (K_D in μM)	PDB	Ref.
Diguanylate cyclase/c-di-GMP phosphodiesterases (GGDEF/EAL)										
MbaA	Q9KU26	Vibrio cholerae	γ-Proteobacteria	Not annotated (dCache-like)	NspS/SP[a]	Q9KU25 (41)	SBP_bac_8 (PF13416)	Spermidine Norspermidine		[60,125]
ScrC	Q9AF11	Vibrio parahaemolyticus	γ-Proteobacteria	Not annotated (dCache-like)	ScrB/SP[a]	Q9AF12 (36)	SBP_bac_3 (PF00497)	S-signal		[139,140]
Serine/threonine kinase										
GlnX PknG[d]	P96258 P9WI73	Mycobacterium tuberculosis	Actinobacteria	4HB_MCP_1 (PF12729)	GlnH/SP[a]	P96257 (35)	SBP_bac_3 (PF00497)	Asp (5), Glu (15)	6H1U 6H20 6H2T	[22–24]

[a] Genes associated with: T: transporter genes; SP: Signaling protein genes.
[b] Size including signal peptide
[c] ChvE is also involved in chemotaxis; *chvE* mutants showed strongly reduced chemotaxis to D-galactose, D-glucose, L-arabinose, D-fucose, and D-xylose [141].
[d] The GlnH SBP binds to the transmembrane protein GlnX that interacts on the cytosolic side with the Ser/Thr kinase PknG.

alternative PknG phosphorylation targets that connect PknG with the regulation of protein translation and folding [25].

In general, bacterial receptors employ a large variety of different LBDs, but, from the structural point of view, most LBDs can be classified into four major classes: mono-modular (i.e. TarH, PilJ) and bi-modular (i.e. HBM, TorS sensor) 4HB domains as well as mono- (i.e., sCache, GAF or PAS) and bi-modular (i.e. dCache, LuxQ-periplasm) α/β folds [13,14]. Inspection of the LBDs of SBP-stimulated sensor proteins reveals that they include members of all four categories (Table 1, Fig. 2).

As shown in Fig. 2, the Tar chemoreceptor and the LytS sensor kinase possess mono-modular 4HB LBDs, whereas the chemoreceptor CtpL and the TorS sensor kinase possess bi-modular 4HB LBDs. The LuxQ and HptS sensor kinases employ dCache-like bimodular α/β-folds (Fig. 2D-F), whereas the TlpB chemoreceptor of *Helicobacter pylori* has the sCache_2 LBD monomodular α/β-fold (Table 1). In addition, homology modelling revealed that AioS has also a sCache-like LBD (Fig. 2G). SBP-stimulated receptors are thus found in phylogenetically different species, and a variety of different LBD types have evolved to recognize SBPs.

The diversity in the LBDs of receptor proteins is also reflected in the diversity of their SBP counterparts (Table 1). In total, SBPs of 13 different sequence-based protein families interact with receptors, the most abundant being members of the Peripla_BP_4 (PF13407), SBP_bac_5 (PF00496) and SBP_bac_8 (PF13416) families. Although SBPs share the same bi-modular lobe structure, they differ largely in size. The SBPs that bind to bacterial receptors span literally the entire size range that ranges from 31 kDa of AibB to the 63 kDa of the chitooligosaccharide-binding protein (CBP) (Table 1). There is no obvious correlation between the SBP family and the type of receptor protein or LBD. For example, the 6 SBPs that stimulate the 4 *E. coli* chemoreceptors, all possessing a TarH LBD, belong to three different families, namely SBP_bac_8, SBP_bac_5 and Peripla_BP_4 (Table 1).

The limited number of SBP-LBD co-crystal structures suggests that another layer of diversity resides in the mode by which SBPs interact with LBDs of similar structure. Based on extensive site-directed mutagenesis studies [33–35], the "mushroom" shaped model for the interaction of the maltose binding protein (MBP) with the Tar-LBD was established (Fig. 2A) [26]. Alternatively, the XylFII SBP binds sideways to the 4HB structure of LytS-LBD (Fig. 2B). Analogously, the LuxP SBP binds sideways to the LuxQ LBD of the "LuxQ-periplasm" family that belongs to the dCache domain superfamily (Fig. 2D) [14]. In contrast, the binding mode of HptA to the dCache-like LBD of HptS is different since the SBP bridges two HptS-LBD monomers (Fig. 2E-F).

3. Chemoreceptors

By far the most thoroughly investigated chemotaxis system is that of *Escherichia coli,* and most fundamental aspects of chemotaxis have been discovered using this species [36]. It has four transmembrane chemoreceptors with a TarH type LBD in the periplasmic space as well as an aerotaxis receptor. There is direct evidence that three of these chemoreceptors, Tar, Trg and Tap, are activated by the binding of SBPs loaded with different sugars or dipeptides, mediating chemoattraction to these compounds (Table 1) [26,37–42]. More recent data also indicate that Trg is activated by the spermidine SBP PotD [43]. Interestingly, the Tar chemoreceptor is stimulated by the direct binding of aspartate as well as of the maltose binding protein, and both stimuli were found to be additive and independent [44]. In addition, there is also indirect evidence that the fourth *E. coli* chemoreceptor, Tsr, is also activated by direct binding of serine and interaction with an SBP [45,46]. *E. coli* showed strong attraction to the autoinducer-2 (AI-2) quorum sensing signal. As this response depends on Tsr as well as on the AI-2 binding SBP LsrB, it is very likely

Table 2
Regulation of the expression of SBPs at the transcriptional and protein levels by different ligand families and environmental cues.

SBP	Gene/ Gene associated with[a]	SBP family/Pfam	Species	SBP ligands	Experimental conditions	Fold change	Ref.
Amino acids and peptides							
AatJ	*PA1342*/T[a]	SBP_bac_3/PF00497	*Pseudomonas aeruginosa*	L-Glu	5 mM L-Glu *vs* 5 mM L-Arg	2.6[b]	[142]
					5 mM D-Glu *vs* 5 mM L-Arg	2.2[b]	
AliB	*spd_1357*/T[a]	SBP_bac_5/PF00496	*Streptococcus pneumoniae*	Oligopeptides	10 mM Arg *vs* 0.05 mM Arg	−2.9[b]	[143]
ApbA	*spd_0109*/T[a]	SBP_bac_3/PF00497	*S. pneumoniae*	Arg	10 mM Arg *vs* 0.05 mM Arg	−10.1[b]	[143]
ArtI	*artI*/T[a]	SBP_bac_3/PF00497	*Escherichia coli*	Arg, ornithine	0.6 mM Arg *vs* no Arg	−3.4[b]	[121]
					5.7 mM Arg *vs* no Arg	No change[c]	[144]
					5.0 mM ornithine *vs* no ornithine	No change[c]	
ArtJ	*artJ*/T[a]	SBP_bac_3/PF00497	*E. coli*	Arg	5.7 mM Arg *vs* no Arg	Reduced ArtJ levels in the presence of Arg[c]	[144]
					0.6 mM Arg *vs* no Arg	−11.4[b]/-14.3[d]	[121]
					LB medium *vs* human urine (low Arg)	−16.6[e]	[145]
						−4.7[b]	[146]
Atu2422	*atu2422*/T[a]	Peripla_BP_6/PF13458	*Agrobacterium fabrum*	GABA, L-Pro, L-Ala, L-Val	1 mM GABA *vs* no GABA	No change[b]	[147]
Atu4243	*atu4243*/T[a]	SBP_bac_8/PF13416	*A. fabrum*	GABA	1 mM GABA *vs* no GABA	No change[b]	[147]
DppA	*dppA*/T[a]	SBP_bac_5/PF00496	*E. coli*	Dipeptides	2% (w/v) casamino acids *vs* no casamino acids	Reduced DppA levels in the presence of casamino acids[c] Reduced *dppA* transcript levels in the presence of casamino acids[f]	[148]
					LB medium *vs* human urine	−4.1[b]	[146]
GltI	*gltI*/T[a]	SBP_bac_3/PF00497	*E. coli*	Glu, Asp	LB medium *vs* human urine (low Arg)	−3.4[b]	[146]
HisJ	*hisJ*/T[a]	SBP_bac_3/PF00497	*E. coli*	His, Arg	0.6 mM Arg *vs* no Arg	−2.5[b]	[121]
					0.6 mM Arg *vs* no Arg	-2.8[d]	[121]
					0.6 mM His *vs* no His	No change[e]	[91]
					LB medium *vs* human urine (low Arg)	−2.4[b]	[146]
LAO	*argT*/T[a]	SBP_bac_3/PF00497	*E. coli*	Lys, Arg, ornithine	0.6 mM Arg *vs* no Arg	No change[d]	[121]
					4 g/l glucose *vs* 10 mg/l glucose[q]	−2.5[g]	[108]
					1 g/l glucose *vs* 0.1 g/l glucose[q]	−8.3[b]	[109]
LivJ	*CJJ81176_1038*/T[a]	Peripla_BP_6/PF13458	*Campylobacter jejuni*	Leu, Ile, Val	CDM medium (0.7 mM L-Leu, 0.2 mM L-Ile, 0.9 mM L-Val) vs CDM-LIV medium (no L-Leu, L-Ile, L-Val)	No change[d]	[149]
LivJ	*livJ*/T[a]	Peripla_BP_6/PF13458	*E. coli*	Leu, Ile, Val	0.1 mg/ml Leu *vs* no Leu	−25[e]	[150]
					LB medium *vs* human urine	−2.4[b]	[146]
LivK	*livk*/T[a]	Peripla_BP_6/PF13458	*E. coli*	Leu	0.1 mg/ml Leu *vs* no Leu	−11.4[e]	[150]
MetQ	*metQ*/T[a]	Lipoprotein_9/ PF03180	*E. coli*	D- and L-Met	20 μg/ml L-Met *vs* no L-Met	−2.6[e]	[151]
					20 μg/ml D-Met *vs* no D-Met	−1.4[e]	
MppA	*mppA*/-	SBP_bac_5/PF00496	*E. coli*	Murein peptide L-alanyl-gamma-D-glutamyl-meso-diaminopimelate	4 g/l glucose *vs* <10 mg/l glucose, fed-batch conditions[q]	−3.0[g]	[108]
OppA	*oppA*/T[a]	SBP_bac_5/PF00496	*E. coli*	Two and five amino acids long peptides	4 g/l glucose *vs* <10 mg/l glucose, fed-batch conditions[q]	−2.2[g]	[108]
PEB1a	*Cj0921c*/T[a]	SBP_bac_3/PF00497	*C. jejuni*	Asp, Glu	7.5% (v/v) O_2 *vs* 1.9% (v/v) O_2[q]	5.6[h]/13.3[i]	[152]
Inorganic nutrients and metal ions (complexed and uncomplexed)							
AioX	*aioX*/SP[a]	Phosphonate-bd/ PF12974	*Agrobacterium tumefaciens*	As(III)	100 μM As(III) *vs* no As(III)	3.3[j]	[98]

Table 2 (*continued*)

SBP	Gene/ Gene associated with[a]	SBP family/Pfam	Species	SBP ligands	Experimental conditions	Fold change	Ref.
CeuE	*ceuE*/T[a]	Peripla_BP_2/PF01497	*C. jejuni*	Fe(III)-siderophore complexes	Iron replete (40 μM $FeSO_4$) *vs* iron-chelated	−3.0[b]	[153]
					Iron replete (40 μM $Fe_2(SO_4)_3$) vs iron-chelated	−16.6[b]	[154]
CeuE	*HP_1561*/T[a]	Peripla_BP_2/PF01497	*Helicobacter pylori*	Ni-(L-His)$_2$	0.5 mM Ni(II) *vs* no Ni(II)	−6.5[j]	[96]
					Non-chelated iron (high iron) *vs* iron-chelated (low iron)[q]	−3.5[b]	[155]
FatB	*VV2_0842*/-	Peripla_BP_2/PF01497	*Vibrio vulnificus*	Ferric vulnibactin	Non-chelated iron (high iron) *vs* iron-chelated (low iron)	−12.9[h]	[156]
FbpA	*NGO0217*/T[a]	SBP_bac_1/PF01547	*Neisseria gonorrhoeae*	Fe(III), Ga(III)	Iron replete (100 μM $Fe(NO_3)_3$) *vs* iron-chelated	−6.1[j]	[95]
FecB	*fecB*/T[a]	Peripla_BP_2/PF01497	*E. coli*	Fe(III)-citrate	High iron citrate (1 mM citrate, 100 μM Fe_2SO_4) *vs* low iron citrate (1 mM citrate, chelated iron)	−3.5[e]	[157]
					LB vs bovine milk (most iron is chelated or bound to proteins)	−10.6[d]	[158]
FepB	*fepB*/T[a]	Peripla_BP_2/PF01497	*E. coli*	Ferric-enterobactin complexes	High iron (20 μM $FeSO_4$) *vs* iron-chelated (low iron)	−8.3[e]	[159]
VcFhuD	*VC0395_A2582*/T[a]	Peripla_BP_2/PF01497	*Vibrio cholerae*	Hydroxamate and catecholate type xenosiderophores	LB (high iron) vs LB + iron chelator (iron-depleted)	−12[e]	[160]
HbpA	*hbpA*/-	SBP_bac_5/PF00496	*Haemophilus influenzae*	Reduced and oxidized glutathione, heme, hemin	10 μg/ml heme *vs* heme-deficient medium	6.2[d]	[161]
hHbp	*HD1816*/T[a]	ZnuA/PF01297	*Haemophilus ducreyi*	Heme	100 μg/ml heme *vs* 15 μg/ml heme	−3.9[h]	[162]
CpHmuT	*hmuT*/T[a]	Peripla_BP_2/PF01497	*Corynebacterium pseudotuberculosis*	Heme	Non-chelated (high iron) *vs* iron-chelated (low iron)	−1.9[j]	[163]
CgHmuT	*hmuT*/T[a]	Peripla_BP_2/PF01497	*Corynebacterium glutamicum*	Heme	36 μM $FeSO_4$ *vs* 1 μM $FeSO_4$	−8.8[b]	[164]
YpHmuT	*hmuT*/T[a]	Peripla_BP_2/PF01497	*Yersinia pestis*	Heme	40 μM $FeCl_3$ *vs* iron-chelated (low iron)	−6.8[b]	[165]
HtxB	*htxB*/T[a]	No data	*Pseudomonas stutzeri*	Hypophosphite, phosphite	2 mM Pi *vs* 0.1 mM Pi	−10.6[e]	[166]
					2 mM Pi *vs* 0.1 mM phosphite	−13.2[e]	
					2 mM Pi *vs* 0.1 mM hypophosphite	−17.5[e]	
IdiA	*Tery_3377*/-	No data	*Trichodesmium erythraeum*	Fe(III)	Non-chelated (high iron) *vs* iron-chelated (low iron)	−50[d]	[167]
MntC	*mntC*/T[a]	ZnuA/PF01297	*N. gonorrhoeae*	Mn(II), Zn(II)	Mn(II) excess *vs* Mn(II)-chelated	Increased MntC levels in the presence of ion chelator[c]	[90]
ModA	*modA*/T[a]	No data	*E. coli*	Molybdate, chromate, perrhenate	100 μM Mo(II) *vs* no Mo(II)	−36.7[e]	[168]
NikA	*nikA*/T[a]	SBP_bac_5/PF00496	*E. coli*	Ni(II)	250 μM Ni(II) *vs* no Ni(II)	−5.33[e]	[169]
					1 μM Ni(II) *vs* no Ni(II)	−4.5[e]	[170]
					10 mM nitrate *vs* no nitrate[q]	−3.6[e]	
NikZ	*cj1584c*/T[a]	SBP_bac_5/(PF00496	*C. jejuni*	Ni(II)	500 μM Ni(II) *vs* no Ni(II)	NikZ was not detected in the presence of nickel[k]	[171]
PhnD [87]	*phnD*/T[a]	No data	*E. coli*	Phosphonate, 2-	aminoethylphosphonate	2 mM Pi *vs* 0.2 mM Pi	−3466[e]
PstS	*pstS*/T[a]	PBP_like_2/PF12849	*P. aeruginosa*	Pi	1 mM Pi *vs* 0.2 mM Pi	−223[b]	[51]
PstS1	*Rv0934*/T[a]	PBP_like_2/PF12849	*Mycobacterium tuberculosis*	Pi	3.6 mM Pi *vs* Pi starvation	-2.2[d]	[172]
PstS3	*Rv0928*/T[a]	PBP_like_2/PF12849	*M. tuberculosis*	Pi	3.6 mM Pi *vs* Pi starvation	−6.5[d]	[172]
PtxB	*ptxB*/T[a]	No data	*P. stutzeri*	Pi, hypophosphite,	2 mM Pi *vs* 0.1 mM Pi	−15[e]	[166]

(*continued on next page*)

Table 2 (*continued*)

SBP	Gene/ Gene associated with[a]	SBP family/Pfam	Species	SBP ligands	Experimental conditions	Fold change	Ref.
				phosphite, methylphosphonate			
					2 mM Pi *vs* 0.1 mM phosphite	−20[e]	
					2 mM Pi *vs* 0.1 mM hypophosphite	−17[e]	
Sbp	*XAC1017*/T[a]	No data	*Xanthomonas citri*	Sulfate	2 mM sulfate *vs* 1 mM sulfate	−1.9[k]	[173]
VatD	*VV2_1012*/T[a]	Peripla_BP_2/PF01497	*V. vulnificus*	Ferric aerobactin, ferric vulnibactin	Non-chelated iron (high iron) *vs* iron-chelated (low iron)	−9.0[h]	[156]
ViuP	*viuP*/T[a]	Peripla_BP_2/PF01497	*V. cholerae*	Ferric vibriobactin	40 μM $FeSO_4$ *vs* no iron	−6.1[b]	[174]
ZnuA	*znuA*/T[a]	ZnuA/PF01297	*E. coli*	Zn(II), Co(II), Cu(II), Cu (I), Cd(II)	5 μM $ZnSO_4$ *vs* $ZnSO_4$-depleted	−20[e]	[175]
					0.2 mM $ZnSO_4$ *vs* no $ZnSO_4$	No change[b]	[176]
Organic acids							
AdpC	*adpC (RPA4515)*/SP[a]	TctC/PF03401	*Rhodopseudomonas palustris*	Adipate, 2-oxoadipate, *trans-trans*-muconate, pimelate, suberate, azelate	1 μM adipate *vs* no adipate	5.8[d]	[103]
					10 mM adipate *vs* no adipate	−2.6[d]	
					10 mM pimelate *vs* no pimelate	−2.8[d]	
					10 mM suberate *vs* no suberate	−10.0[d]	
					10 mM azelate *vs* no azelate	−10.0[d]	
BctC	*bp3867*/T[a] & SP[a]	TctC/PF03401	*Bordetella pertussis*	Citrate	10 mM citrate *vs* no citrate	16.9[e]	[89]
CouP	*RPA1789*/T[a]	Peripla_BP_6/PF13458	*R. palustris*	*p*-coumarate, ferulate, caffeate, cinnamate	3 mM *p*-coumarate *vs* 3 mM benzoate	5.7[b]/4.3[g]	[177]
MatC	*RPA3494*/T[a]	TctC/PF03401	*R. palustris*	L- and D-malate, succinate, fumarate, L- and D-Met	10 mM succinate *vs* 3 mM *p*-coumarate	No change[b]	[177]
					10 mM succinate *vs* 3 mM benzoate	No change[b]	
SiaP	*siaP*/T[a]	DctP/PF03480	*H. influenzae*	Sialic acid, *N*-acetylneuraminic acid, *N*-glycolylneuraminic acid	0.1 mM sialic acid *vs* no sialic acid	3.3[d,l]	[178]
TarP	*RPA1782*/T[a]	DctP/PF03480	*R. palustris*	*p*-coumarate, ferulate, caffeate, cinnamate	3 mM *p*-coumarate *vs* 10 mM succinate	2.3[b]/3.2[g]	[177]
TauA	*tauA*/T[a]	OpuAC/PF04069	*E. coli*	Taurine, N-(2-acetamido)-2-aminoethanesulfonic acid, 2-(N-morpholino) ethanesulfonate	250 μM taurine *vs* 250 μM sulfate	143[e]	[88]
Polyamines and quaternary ammonium compounds							
BetS	*betS*	BCCT/PF02028	*Sinorhizobium (Ensifer) meliloti*	Glycine betaine, proline betaine	1 mM glycine betaine *vs* no glycine betaine	No change[e]	[179]
					0.3 M NaCl *vs* no NaCl[q]	No change[e]	
ChoX	*choX*/T[a]	OpuAC/PF04069	*S. meliloti*	Choline, acetylcholine	7 mM choline *vs* no choline	Increased ChoX levels in the presence of choline[c]	[180]
NspS	*VC0704*/SP[a]	SBP_bac_8/Pf13416	*V. cholerae*	Spermidine, norspermidine, spermine	Increased *vs* low c-di-GMP levels[q]	2.9[b]	[181]
OpuAC	*opuAC*/T[a]	OpuAC/PF04069	*Bacillus subtilis*	Glycine betaine, proline betaine, arsenobetaine, dimethylglycine	1 mM glycine betaine *vs* no glycine betaine	−2.2[b]	[124]
					1.2 M NaCl *vs* no NaCl[q]	2.1[b]	

Table 2 (*continued*)

SBP	Gene/ Gene associated with[a]	SBP family/Pfam	Species	SBP ligands	Experimental conditions	Fold change	Ref.
					0.5 M NaCl *vs* no NaCl[q]	Increased transcription under osmotic stress[m]	[182]
PotD	*potD*/T[a]	SBP_bac_8/Pf13416	*E. coli*	Spermidine, putrescine	0.1 mg/ml putrescine *vs* no putrescine	−2[m]	[183]
ProX	*proX*/T[a]	OpuAC/PF04069	*E. coli*	Glycine betaine, proline betaine	0.7 M sorbitol *vs* no sorbitol[q]	10.0[h]	[184]
					0.4 M NaCl *vs* no NaCl[q]	9.3[h]	
					1 mM glycine betaine *vs* no glycine betaine	−5.7[e]	[123]
SpuD	*spuD*/T[a]	SBP_bac_8/PF13416	*P. aeruginosa*	Putrescine	20 mM putrescine *vs* no putrescine	8.4[e]	[185]
SpuE	*spuE*/T[a]	SBP_bac_8/PF13416	*P. aeruginosa*	Spermidine	20 mM spermidine *vs* no spermidine	14[e]	[185]
Mono-, oligo- and polysaccharides							
AguE	*TM_0432*/T[a]	SBP_bac_1/PF01547	*Thermotoga maritima*	α-1,4-digalacturonate	10 mM pectin *vs* 10 mM D-ribose	24[b]	[186]
AlgQ2	*algQ2*/T[a]	SBP_bac_1/PF01547	*Sphingomonas* sp. A1	Alginate oligosaccharides	0.5% (w/v) alginate *vs* 0.5% (w/v) glucose	AlgQ2 was only detected in cells growing in alginate[c]	[187]
AraF	*araF*/T[a]	Peripla_BP_1/PF00532	*E. coli*	L-Arabinose, D-arabinose, D-fucose	0.2% (w/v) arabinose *vs* no arabinose	27.8[b]	[94]
BglE	*TM_0031*/T[a]	SBP_bac_5/PF00496	*T. maritima*	Cellobiose and laminaribiose	10 mM cellobiose *vs* 10 mM D-ribose	5[b]	[186]
CBP	*VC_0620*/T[a] & SP[a]	SBP_bac_5/Pf00496	*V. cholerae*	Chitin oligosacharides ($(GlcNAc)_x$)	0.6 mM GlcNAc *vs* no GlcNAc	No change[b,d]	[102]
					0.6 mM $(GlcNAc)_2$ *vs* no $(GlcNAc)_2$	67.9[b]/129[d]	
					0.6 mM $(GlcNAc)_3$ *vs* no $(GlcNAc)_3$	48.8[b]	
					0.6 mM $(GlcNAc)_4$ *vs* no $(GlcNAc)_4$	108.2[b]	
					0.6 mM $(GlcNAc)_5$ *vs* no $(GlcNAc)_5$	51.0[b]	
					0.6 mM $(GlcNAc)_6$ *vs* no $(GlcNAc)_6$	54.1[b]	
					0.6 mM $GlcN_2$ *vs* no $GlcN_2$	No change[b,d]	
ChvE	*chvE*/T[a]	Peripla_BP_4/PF13407	*A. tumefaciens*	Galactose, glucuronic acid, galacturonic acid, arabinose and glucose	L-arabinose (3[g] or 5[c] mM) *vs* no L-arabinose	8[e]/increased ChvE levels[c]	[188,189]
					D-fucose (3[g] or 5[c] mM) *vs* no D-fucose	6[e]/increased ChvE levels[c]	
					D-galactose (3[g] or 5[c] mM) *vs* no D-galactose	5[e]/increased ChvE levels[c]	
					D-glucose (3[g] or 5[c] mM) *vs* no D-glucose	No changes[e]/increased ChvE levels[c]	
					5 mM glucoronic acid *vs* no glucuronic acid	No changes[e]	
GltB	*PA3190*/T[a] & SP[a]	SBP_bac_1/PF01547	*P. aeruginosa*	Glucose	10 mM glucose *vs* no glucose	64.5[e]	[71]
MalE	*malE*/T[a]	SBP_bac_1/PF01547	*E. coli*	Maltose, maltotriose, maltetrose, maltotetraose	1 g/l glucose *vs* 0.1 g/l glucose[q]	−67.4[b]	[109]
					58 mM maltose *vs* no maltose	~12.0/24.0[e,n]	[190]
					0.2% (w/v) arabinose *vs* no arabinose	−12.1[b]	[94]
MalE	*lmo2125*/T[a]	SBP_bac_8/PF13416	*Listeria monocytogenes*	Maltose	25 mM maltose *vs* no maltose	25[d]	[191]
					12.5 mM maltotriose *vs* no	57[d]	

(*continued on next page*)

Table 2 (*continued*)

SBP	Gene/ Gene associated with[a]	SBP family/Pfam	Species	SBP ligands	Experimental conditions	Fold change	Ref.
					maltotriose		
MalE1	*TM_1204*/T[a]	SBP_bac_8/PF13416	*T. maritima*	Maltose, maltotriose, β-(1-4)-mannotetraose	5 g/l trehalose *vs* 5 g/l glucose[q]	Increased expression in trehalose[f]	[192]
					5 g/l lactose *vs* 5 g/l glucose[q]	Increased expression in lactose[f]	
MalE2	*TM_1839*/T[a]	SBP_bac_8/PF13416	*T. maritima*	Maltose, maltotriose, trehalose	5 g/l trehalose *vs* 5 g/l glucose	Increased expression in trehalose[f,h]	[192]
					5 g/l maltose *vs* 5 g/l glucose	Increased expression in maltose[h]	
					5 g/l maltose *vs* 5 g/l glucose	3.3[b]/26.1[d]	[193]
MglB (or GBP)	*mglB*/T[a]	Peripla_BP_4/PF13407	*E. coli*	D-Galactose, D-glucose	0.01-10 mM galactose *vs* no galactose	Strong induction of *mglB* transcription[o]	[92]
					4 g/l glucose *vs* <10 mg/l glucose	−3.5[g]	[108]
					1 g/l glucose *vs* 0.1 g/l glucose	−28.0[b]	[109]
MglB (or GBP)	*mglB*/T[a]	Peripla_BP_4/PF13407	*Salmonella typhimurium*	D-Galactose, D-glucose	2 g/l glucose *vs* no glucose	−5.8[e]	[194]
MnBP3	*TM_1223*/T[a]	SBP_bac_5/PF00496	*T. maritima*	Mannose, mannobiose, cellobiose, laminaribiose, xylobiose, mannopentaose, cellopentaose, xylopentaose, laminaripentaose, mannohexaose	0.25% (w/v) mannose *vs* 0.25% (w/v) arabinose	Up-regulated[b]	[195]
MnBP6	*TM_1226*/T[a]	SBP_bac_5/PF00496	*T. maritima*	Mannose, Mannobiose, cellobiose, laminaribiose, xylobiose, mannopentaose, cellopentaose, xylopentaose, laminaripentaose, mannohexaose	0.25% (w/v) mannose *vs* 0.25% (w/v) arabinose	Up-regulated[b]	[195]
RBP	*TM_0958*/T[a]	Peripla_BP_4/PF13407	*T. maritima*	D-ribose	10 mM D-ribose *vs* 10 mM L-arabinose	22[b]	[186]
					10 mM D-ribose *vs* 10 mM L-trehalose	42[b]	
RbsB	*rbsB*/T[a]	Peripla_BP_4/PF13407	*E. coli*	D-ribose	10 mM D-ribose *vs* no D-ribose	43.8[p]	[93]
					4 g/l glucose *vs* <10 mg/l glucose	−4.4[g]	[108]
ThuE	*thuE*/T[a]	SBP_bac_1/PF01547	*S. meliloti*	Trehalose, maltose	0.4% (w/v) trehalose *vs* 0.4% (w/v) sucrose	6.5[e]	[196]
					0.4% (w/v) maltose *vs* 0.4% (w/v) sucrose	No change[e]	
XloE	*TM_0071*/T[a]	SBP_bac_5/PF00496	*T. maritima*	Xylobiose, xylotriose	10 mM D-xylose *vs* 10 mM D-ribose	26[b]	[186]
YtfQ	*ytfQ*/T[a]	Peripla_BP_4/PF13407	*E. coli*	Galactofuranose, arabinose, galactose, talose, allose, ribose	1 g/l glucose excess *vs* 0.1 g/l glucose[q]	−11.4[b]	[109]
					4 g/l glucose *vs* <10 mg/l glucose[q]	−7.8[g]	[108]
Cofactors and terminal electron acceptors							
BtuF	*synpcc7002_a0635*/T[a]	Peripla_BP_2/PF01497	*Synechococcus* sp. PCC 7002	Cyano-cobalamin (vitamin B12)	4 μg/L cobalamin *vs* no cobalamin	-18.1[j]	[197]
TorT	*torT*/SP[a]	Peripla_BP_1/PF00532	*E. coli*	Trimethylamine N-oxide (TMAO)	Anaerobic *vs* aerobic growth[q]	2.5[e]	[97]
Opines and quorum sensing molecules							

Table 2 (*continued*)

SBP	Gene/ Gene associated with[a]	SBP family/Pfam	Species	SBP ligands	Experimental conditions	Fold change	Ref.
AccA	*accA*/T[a]	SBP_bac_5/PF00496	*A. fabrum*	Agrocinopine D, agrocinopine-3'-O-benzoate, agrocin 84, agrocinopine A, D-glucose-2-phosphate, L-arabinose-2-isopropylphosphate, L-arabinose-2-phosphate	20 μM agrocinopines *vs* no agrocinopines (under phosphate limiting conditions; 0.1 mM Pi)	4.5[e]	[198]
					20 μM agrocinopines *vs* no agrocinopines (under phosphate rich conditions; 25 mM Pi)	No change[e]	
LuxP	*luxP*/SP[a]	Peripla_BP_4/PF13407	*Vibrio harveyi*	AI-2	1 μM AI-2 *vs* no AI-2	No change[e]	[199]
LsrB	*lsrB*/T[a]	Peripla_BP_4/PF13407	*E. coli*	AI-2	100 μM AI-2 *vs* no AI-2	10.5[b]	[200]
LsrB	*SM_b21016*/T[a]	Peripla_BP_4/PF13407	*S. meliloti*	AI-2	80 μM AI-2 *vs* no AI-2	13.0[d]	[201]
NocT	*atu6027*/T[a]	SBP_bac_3/PF00497	*A. tumefaciens*	Nopaline, pyronopaline, octopine	Nopaline/pyronopaline mix (1 mM) *vs* no nopaline/ pyronopaline	54.5[b]/68.1[d]	[202]

[a] Genes associated with: T: transporter genes; SP: Signaling protein genes.
[b] Microarray data.
[c] Western blot.
[d] Quantitative real-time PCR.
[e] Reporter gene expression.
[f] Northern hybridizations.
[g] Mass spectrometry proteome analysis.
[h] Protein expression profiling (2D protein gels followed by mass spectrometry/peptide mass fingerprinting).
[i] Exponentially modified protein abundance index [emPAI].
[j] RNA-sequencing.
[k] SDS-PAGE gel analysis.
[l] Induction was only observed in a *nanAsiaB* double mutant that can neither catabolize nor activate sialic acid.
[m] Primer extension analyses.
[n] Lowest and highest fold-change values measured at the different pH values ranging from 4.75 to 5.75.
[o] *In vitro* transcription assays.
[p] Genomic SELEX screenings.
[q] Regulation mediated by non-cognate ligands or by environmental cues associated with SBP function.

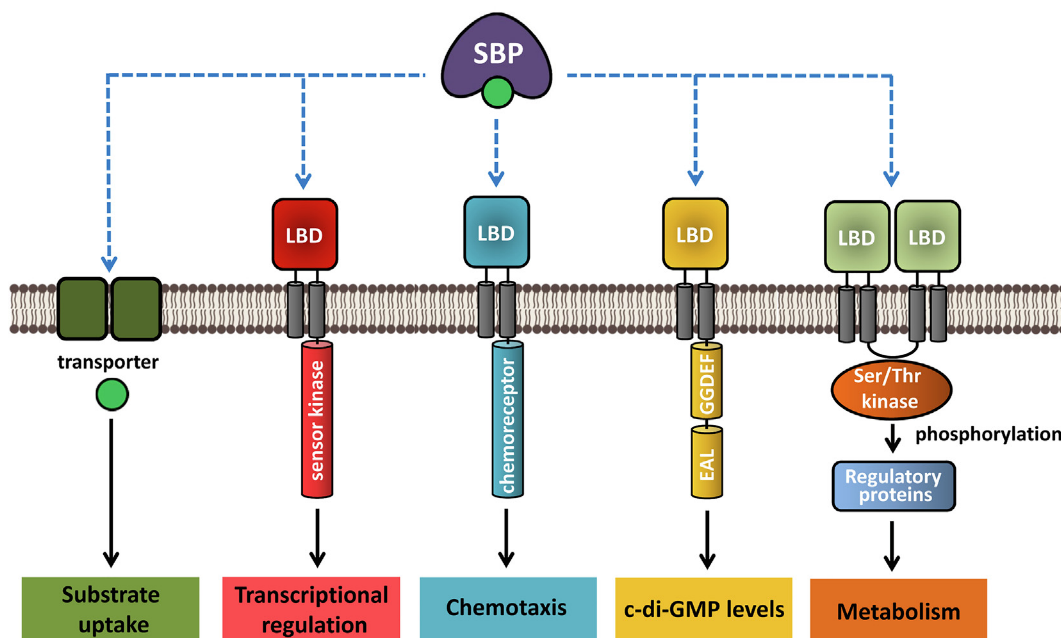

Fig. 1. Schematic of the different membrane proteins that bind solute binding proteins (SBPs) and their corresponding primary functions. LBD: Ligand binding domain, GGDEF: diguanylate cyclase; EAL: phosphodiesterase. In some cases binding of ligand-free SBP to receptor protein has been observed.

that these two proteins interact in the periplasm [45,46]. The notion that all four chemoreceptors of the model organism most-studied for chemotaxis are activated by SBP binding gives further support to the notion that this type of sensing is widespread.

Apart from the *E. coli*, there are relatively few characterized chemoreceptor – SBP interactions. A well-characterized example is *Pseudomonas aeruginosa* chemotaxis to inorganic phosphate (Pi) [47,48], which is a central signal molecule that controls bacterial virulence [49]. Pi chemotaxis is due to the action of two chemoreceptors, CtpH and CtpL, that respond to high and low Pi concentrations, respectively [47,48]. The concerted action of both receptors thus provides an expansion of the response range. The two receptors employ different sensing mechanisms: whereas CtpH recognizes Pi directly via its TarH type LBD, CtpL contains an HBM type LBD and is activated by the binding of the Pi-loaded PstS SBP [48]. PstS is part of the Pst uptake system for phosphate [50] and binds Pi ultra-tightly (K_D= 9 nM) [48]. The transcript levels of *pstS* are very tightly regulated by Pi; a reduction from 1 to 0.2 mM Pi in the medium increased *pstS* transcript levels 223-fold (Table 2) [51].

The genes encoding SBPs that interact with *E. coli* and *P. aeruginosa* chemoreceptors are associated with transporter but not with chemoreceptor genes (Table 1). Interestingly, in the archaeum *Halobacterium salinarum* the SBP genes *basB* and *cosB* were identified just upstream the genes encoding the BasT and CosT chemoreceptors, respectively [52,53]. BasB and CosB are homologous to SBPs that bind short chain aliphatic amino acids and quaternary amines, respectively. Notably, deletion of either *basT* and *cosT* gene abolished chemotaxis to these compounds, suggesting that these proteins cooperate to mediate these responses. In addition, the chemotaxis phenotype of *basB* and *basT* mutants was similar [52,53].

The data that are currently available indicate that direct binding of a signal molecule to a chemoreceptor LBD causes chemoattraction [54], whereas repellent chemotaxis appears to be caused by alternative mechanisms [55]. The evidence that repellent taxis can occur through activation of a chemoreceptor by an SBP is thus far indirect [43,56]. *H. pylori* is repelled by AI-2, a response that depends on the TlpB chemoreceptor [57]. However, deletion of the genes encoding the AibA and AibB SBPs prevented this chemorepellent response. Both SBPs were shown to bind AI-2 *in vitro* and the authors suggested that both SBPs interact with the TlpB chemoreceptor [56]. In another study, it was demonstrated that *E. coli* shows strong repellent responses to spermidine. In contrast to the wild type strain, the *potD* mutant showed chemoattraction to spermidine, indicating that: (1) the SBP PotD is responsible for the observed repellent chemotaxis response; and (2) that there is another mechanism responsible for chemoattraction to spermidine [43].

4. Sensor kinases, diguanylate cyclases/phosphodiesterases and Ser/Thr kinases

The functions and regulons of sensor kinases, diguanylate cyclases/phosphodiesterases and Ser/Thr kinases that are stimulated by SBP binding are listed in Table 3. The SBP-stimulated systems carry out a number of different functions, including transport, respiration, compound catabolism or virulence, suggesting that there is no apparent restriction to the function of SBP-stimulated systems. These data also support the idea that these regulons are associated with specific and well-defined functions. As indicated above, the only characterized SBP-stimulated Ser/Thr kinase is PknG, which phosphorylates several target proteins that are involved in very different cellular processes [25]. Several studies of SBP-activated sensor kinases have provided insight into the sensing and transmembrane signaling mechanism that is summarized below.

4.1. The sensing mechanism

SBP-stimulated systems are composed of three molecules that mutually interact. The thermodynamics of this interaction have been established for the TorS-LBD/TorT/TMAO system [28] that is illustrated in Fig. 3.

Two apoTorT molecules were found to bind to the TorS-LBD dimer with high affinity (K_d=1.79 μM). ApoTorT bound its signal molecule TMAO (trimethylamine N-oxide) with a relatively modest affinity of 74 μM. However, TMAO recognition by the TorS-LBD/TorT complex occurred with negative cooperativity, with the two respective K_d values being 1.36 and 121 μM. This result indicates that TMAO binds preferentially to the SBP when it is associated to the sensor

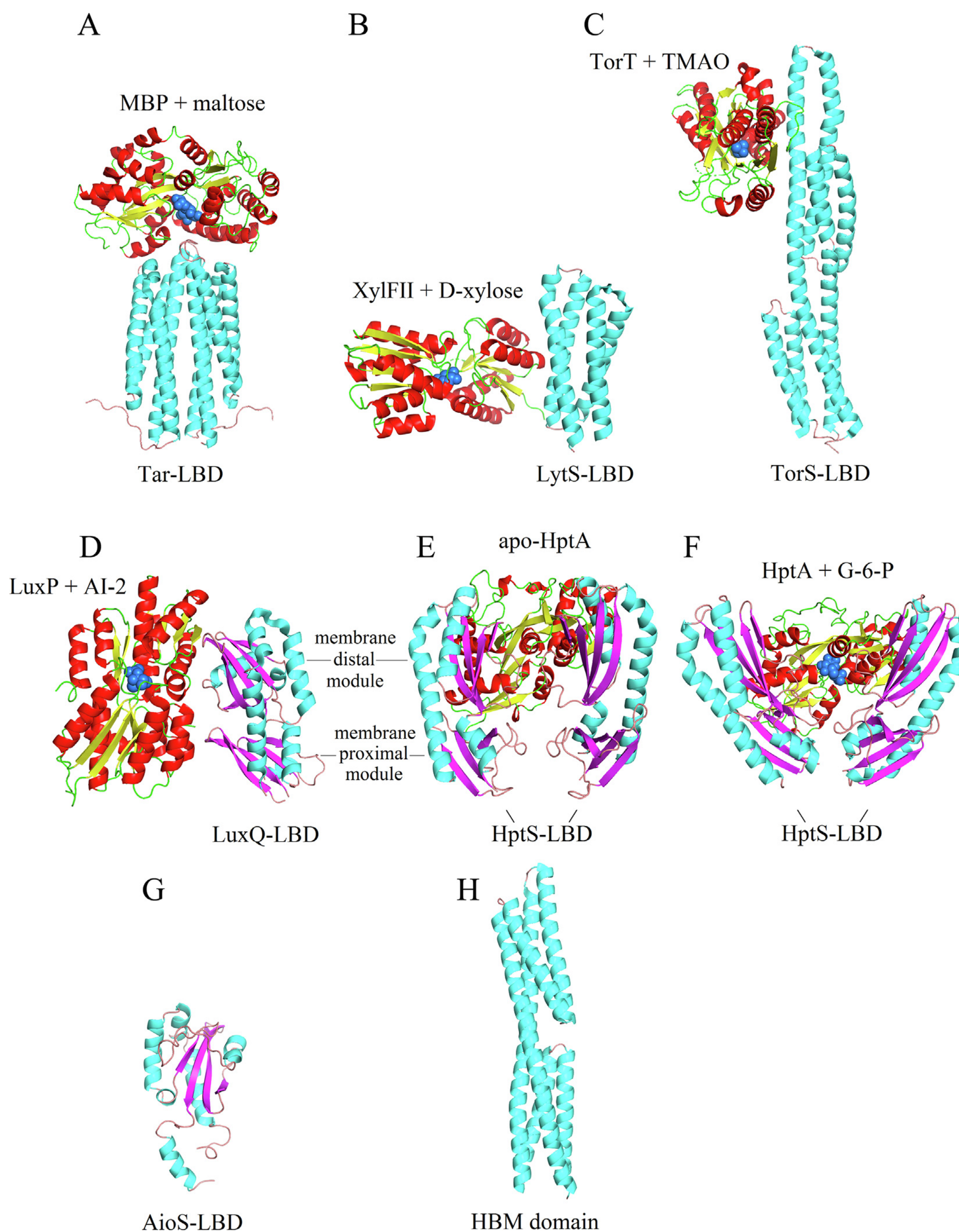

Fig. 2. Structural information available on the interaction of SBPs with the ligand binding domains (LBDs) of signal transduction receptors. A) Proposed model for the interaction of the LBD of the Tar chemoreceptor with the maltose binding protein (MBP). Model reconstructed according to [26]. B) Sensor kinase LytS with XylFII [27] (Protein Data Bank [PDB] 5XSJ). C) Sensor kinase TorS with TorT [28] (PDB 3O1H). D) Sensor kinase LuxQ with LuxP [29] (PDB 2HJ9). E,F) Sensor kinase HptS in complex with apo and ligand-loaded HptA [30] (PDB 6LKG, 6LKH). For clarity, only a single monomer of the sensor kinase LBD is shown. G) Homology model of the AioS sensor kinase generated by Phyre2 [31]. This domain has a sCache domain-like fold. H) Structure of an HBM domain [32] (PDB 2YFA), the domain type predicted for the CtpL chemoreceptor. Structures are coloured according to secondary structure and protein type: cyan: LBD α-helix; pink: LBD β-strand; red: SBP α-helix; yellow: SBP β-strand. Ligands bound to SBPs are shown as blue spheres.

kinase as compared to the free form. Analytical ultracentrifugation studies also showed that TMAO binding to apoTorT increases its affinity for TorS-LBD, a finding that was also reflected in decreased atomic mobility at the TorS-LBD/TorT interface. In a similar way, the CBP SBP interacts with the non-canonical DNA binding sensor kinase ChiS to repress its activity, and the binding of chitin oligosaccharides by the CBP/ChiS complex activates ChiS without triggering the dissociation of the complex [58]. Of note is that these findings do not agree with a previous publication that suggested a ligand-induced dissociation of CBP from ChiS [59]. However, the sensing mechanisms established for these systems may not be generally applicable to all SBPs. For example, the working model of the MbaA-NspS system proposes that the binding of spermidine to the SBP NspS induces its dissociation from the MbaA sensor domain [60].

4.2. The mechanism of signal transduction: multiple events leading to a lateral displacement of transmembrane helices

The currently available data suggest that there may be multiple mechanisms by which signal-loaded SBPs control sensor autokinase

Table 3
The functions of SBP-stimulated signal transduction receptors.

Receptor	SBP	Function of system	Regulon/Comment	Ref.
Chemoreceptors				
Tar	MBP	Chemoattraction to maltose		[26
Tap	DppA	Chemoattraction to dipeptides		[41]
Trg	GBP	Chemoattraction to galactose		[384243]
	RBP	Chemoattraction to ribose		
	PotD	Chemorepellence from spermidine		
Tsr	LsrB/T[a]	Chemoattraction to AI-2		[45,46]
TlpB	AibA AibB	Chemorepellence from AI-2		[56]
CtpL	PstS	Chemoattraction to low Pi concentrations		[48]
BasT	BasB	Chemoattraction to amino acids		[53]
CosT	CosB	Chemoattraction to quaternary amines		[53]
Sensor kinases				
LuxQ	LuxP	Quorum sensing	Five small regulatory RNAs (*Qrr*1-5) that target the master quorum sensing regulator LuxR	[203]
LytS	XylFII	D-xylose transport	*xylFGH* operon encoding an D-xylose ABC transporter	[134]
TorS	TorT	Respiration on TMAO	*torCAD* operon encoding the trimethylamine oxide (TMAO) reductase system	[204]
HptS	HptA	Glucose-6-phosphate transport	*uhpT* encoding the hexose phosphate transporter	[137]
VirA	ChvE	Virulence	*vir* genes and the *repABC* operon whose expression leads to the insertion of *A. tumefaciens* T-DNA from Ti plasmid into host cells, causing tumor formation	[205]
AioS	AioX	Control of As(III) oxidation	*aioBA* genes encoding an As(III) oxidase	[206]
BctE	BctC	Citrate transport	*bctCBA* operon encoding a tripartite tricarboxylate transporter	[89]
ChiS	CBP	Degradation of chitin	50 genes, most of which encode proteins involved in chitin catabolism	[59]
GtrS	GltB	Glucose transport	*gltBFGK-oprB* operon encoding glucose transporter	[71]
Diguanylate cyclase/c-di-GMP phosphodiesterases (GGDEF/EAL)				
MbaA	NspS	Control of biofilm formation	Changes in c-di-GMP levels that alter expression of *vps* genes (among others), encoding proteins for biofilm polysaccharide synthesis	[207]
ScrC	ScrB	Motility and capsular polysaccharide production	Changes in c-di-GMP levels that alter expression of *laf* (lateral flagellum) and *cps* (capsular polysaccharide) genes, resulting in altered swarming motility and colony morphology	[208]
Serine/threonine kinase				
GlnX/PknG[a]	GlnH	Control of glutamate levels by regulating the activities of enzymes involved in TCA cycle and glutamate metabolism; evidence for additional PknG phosphorylation targets	PknG phosphorylates the regulatory protein GarA. Recent mass spectrometry approaches identified novel candidate PknG substrates that have roles in metabolism, cell wall synthesis and protein processing, translation and folding	[22,24,25,209]

[a] The transmembrane protein GlnX interacts with the periplasmic SBP GlnH and with the Ser/Thr kinase PknG in the cytosol.

activity. Such mechanisms involve signal-induced changes in the symmetry of the LBD dimer, structural rearrangements and/or induction of the formation of larger hetero-complexes [61]. However, it appears that all of these alterations ultimately result in a lateral displacement of the transmembrane regions of the sensor kinase that may be the molecular stimulus that alters autokinase activity.

In the absence of the AI-2 signal, LuxP and LuxQ-LBD form hetero-dimers [29]. Upon signal binding, two LuxP/LuxQ-LBD pairs interact to form an asymmetric hetero-tetramer. In this asymmetric tetramer, both LuxQ-LuxP pairs are related by a rotation of 140 degrees, which represents a significant asymmetry. As a consequence of this asymmetry, the transmembrane helices are displaced laterally, which may be the molecular stimulus triggering changes in autokinase activity [29]. The mechanism of the LuxQ-LuxP system thus involves the signal-induced introduction of protein asymmetry and the formation of the hetero-tetramer complex. Analogously, the XylFII SBP forms hetero-dimers with the LBD of the LytS sensor kinase [27]. In the presence of the D-xylose signal, two dimers interact to form the hetero-tetramer. In the working model of the XylFII-LytS system, the authors propose that the formation of this signal-induced complex formation also causes a lateral displacement of the sensor kinase transmembrane regions [27].

In the crystallographic study of the TorS-TorT system [28], the authors used a covalently linked TorS-LBD dimer that makes it impossible to observe individual SBP-LBD complexes as observed in the two systems just discussed. The authors reported the structures of the apoTorT/TorS-LBD complex as well as of complex structures that contained the TMAO signal or isopropanol (present in the crystallization buffer) in the TorT ligand-binding site [28]. The structures of the two complexes were almost identical, indicating that isopropanol binding had the same effect as TMAO binding. In these structures, the TorS-LBD dimer formed a complex with two TorT monomers. In the signal-free structure, this hetero-complex was asymmetric and characterized by two distinct TMAO-binding sites. The thermodynamic studies mentioned above show that TMAO binds both sites with negative cooperativity (Fig. 3). The symmetry of the hetero-complex is achieved when TMAO binds to both sites, and the authors suggest that asymmetry must be reinforced by TMAO binding to the first, high-affinity site. Therefore, signal binding in this system causes an asymmetry-to-symmetry transition that is the opposite of the symmetry-to asymmetry transition observed in the LuxQ-LuxP system [28].

A crystallographic study of the HptA/HptS-LBD complex has been reported recently [30]. The HptS-LBD belongs to the family of dCache domains that are composed of two α/β modules, generally referred to as membrane distal and membrane proximal mod-

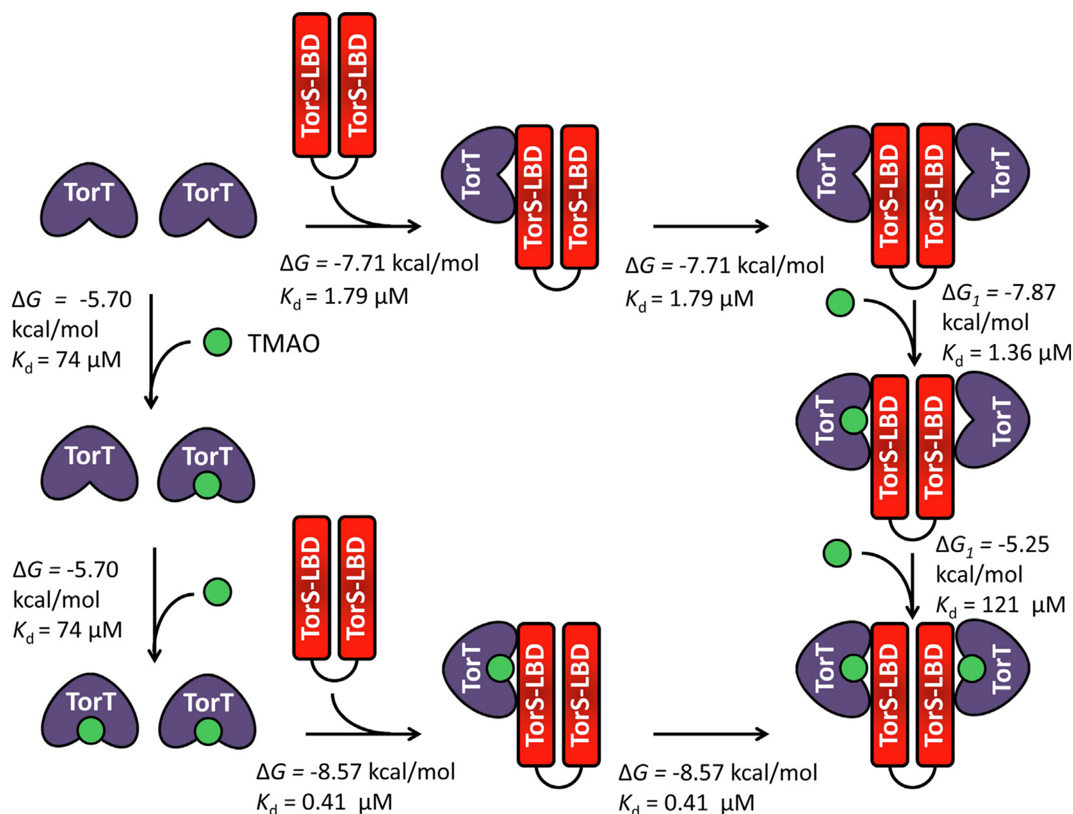

Fig. 3. The mechanism of TorT and TMAO recognition by the ligand-binding domain of TorS. Because sensor kinases form stable dimers in the membrane, experiments were conducted using a dimeric TorS-LBD in which both monomers are covalently linked by a 25 amino acid flexible linker. The thermodynamic parameters derived from analytical ultracentrifugation and isothermal titration calorimetry experiments are indicated. Data were taken from [28].

ule. In the apo form, a hetero-tetramer was observed in which apo HptA SBP interacted with the membrane distal modules of both HptS-LBD monomers (Fig. 2E). However, binding of the signal molecule glucose-6-phosphate (G-6-P) caused large structural rearrangements. The result of these rearrangements was that HptA linked the membrane-distal module of one HptS-LBD monomer with the membrane-proximal module of the other (Fig. 2F). These large structural rearrangements caused a tilting of HptS-LBD, leading to a lateral displacement of both transmembrane regions in a manner reminiscent of the other systems studied [30].

Cache domains are the most abundant extracytosolic bacterial sensor domains [13,14,62] and the majority of Cache domains are present in their dCache configuration. A large number of dCache domains have been studied, and, in almost all cases, ligands bind to the membrane-distal module [63–66]. That circumstance raised the question as to the function of the membrane-proximal module. The X-ray study of HptS-LBD in a complex with HptA described above may provide an answer to this question. It was shown that signal-bound HptA links two HptS-LBDs by establishing contacts with the membrane-distal and membrane-proximal modules [30]. Other than the finding that lactate binds to the membrane-proximal module of the TlpC chemoreceptor of *H. pylori* [67], this is the first demonstration of a role for the membrane-proximal module of dCache domains in the signaling process. Future studies will show to what degree other dCache domains operate by the same mechanism.

The signal transduction mechanism for systems that sense signals directly is still subject to debate [61]. Ligand binding at LBDs has been shown to induce a number of different reorientations, such as helical rotation, piston shifts or helix scissoring movements. Frequently, these changes occur concomitantly, and several reorientations of the receptor LBD, like scissoring movements, are compatible with lateral displacements of the transmembrane regions [68–70]. Further research will be required to determine to what degree lateral displacements of transmembrane regions cause the activation, whether direct or indirect, of ligand-triggered signal-transduction receptors.

5. GltB: A SBP that interacts with a sensor kinase and chemoreceptors

Another layer of complexity of SBP-mediated regulation is added by the observation that the glucose-sensing SBP GltB interacts with the periplasmic domain of the GtrS sensor kinase as well as with the LBD of the PctA and McpN chemoreceptors [71]. The GtrS-LBD had been previously shown to bind two glucose derivatives, 2-ketogluconate and 6-phosphogluconate, and to regulate the expression of genes involved in glucose metabolism [72]. Xu *et al.* show that the binding of glucose-loaded GltB is essential for the GtrS-mediated control of genes involved in glucose transport [71]. Chemoreceptors PctA and McpN were previously found to bind amino acids and nitrate, respectively, and to mediate chemoattraction to these compounds [73–75]. Although the authors of this study demonstrate the binding of GltB to the LBDs of PctA and McpN, they did not explore whether this resulted in chemotaxis. GtrS, PctA and McpN each possesses a different type of LBD. The LBD of GtrS is not recognized by any domain profile, whereas PctA and McpN possess a dCache and PilJ type LBD, respectively [64,75]. The PctA chemoreceptor is a prime example of the complexity of bacterial signal transduction. Apart from binding amino acids [64] and GltB [71], PctA also mediates chemotaxis to AI-2 [76] and histamine [63]. It has been shown that the PctA-LBD binds AI-2 directly with high affinity [76], whereas it has been

proposed that PctA mediates histamine chemotaxis through binding an unidentified SBP [63].

6. Additional studies suggesting SBP-mediated stimulation of signal transduction receptors

There are a number of other studies that provide indirect evidence for activation of signaling receptors by SBP binding. One example is the mechanism for chemotaxis of *Sphingomonas* sp. strain A1 to the polysaccharide pectin. The SBP SPH1118 binds pectin, and a knockout mutation in the corresponding gene abrogates pectin chemotaxis [77], suggesting an indirect activation mechanism. However, the molecular mechanism by which a polysaccharide interacts with an SBP remains to be established. Furthermore, the Tlp1 chemoreceptor of *Campylobacter jejuni* mediates chemotaxis to aspartate [78]. However, the 3D structure of the LBD revealed that the binding pocket is too small to accommodate this ligand and the individual Tlp1-LBD failed to bind aspartate. The authors thus suggest that Tlp1 is activated by SBP binding [78]. Another example is that of the McpC chemoreceptor of *Bacillus subtilis,* which supports chemotaxis to 17 amino acids. However, binding studies revealed that only 11 of them bound directly to the purified McpC-LBD [79]. To investigate a potential involvement of SBPs, the authors conducted pull-down experiments with immobilized McpC-LBD. This study detected interactions of MpcC with the amino acid-sensing SBPs ArtP, MetQ and YckB. The authors thus conclude that McpC employs two different mechanisms based on direct and indirect sensing [79]. Furthermore, chemotaxis of *P. aeruginosa* towards histamine is based on the concerted action of three chemoreceptors: TlpQ, PctA and PctC [63]. Whereas TlpQ-LBD bound histamine with nanomolar affinity, no direct binding was detected for the PctA and PctC chemoreceptors, which are known to bind different amino acids directly [64]. These data suggest that the histamine signal mediated by PctA and PctC signaling depends on their interaction with one or more histamine-binding SBPs. The Tlp1, McpC, PctA and PctC chemoreceptors all possess dCache-type LBDs. This observation, in combination with the available structural and functional data (Fig. 2, Table 1), suggests that SBP-mediated receptor stimulation may be a property of many dCache domains.

In *Bacillus subtilis*, the SBP-encoding gene *ydbE* is located next to genes encoding the sensor kinase-response regulator pair YdbFG. YdbE shows homology to SBPs that sense C4-dicarboxylates, and the YdbFG TCS regulates the utilization of fumarate and succinate [80]. Inactivation of either *ydbFG* or *ydbE* abolished this regulatory activity, and it was suggested that YdbE plays a sensory role by stimulating the YdbFG TCS [80]. Furthermore, the genes encoding homologs of the AI-2 SBP LsrB are typically found next to the AI-2 transporter. Interestingly, in *Treponema primitia* and *Treponema azotonutricium lsrB* genes are located next to genes encoding sensor kinase/response regulator pairs, suggesting a participation in TCS signaling rather than transport [81].

7. Regulation of SBP levels

What are the advantages of SBP-mediated receptor stimulation as compared to systems that recognize signals directly? The overall responses of SBP-activated chemoreceptors have been shown to be highly sensitive to the SBP levels, permitting more-precise control of the sensitivity to specific ligands in response to their nutrient environment [21]. Although regulation of the expression of SBPs has been reviewed several times [82–86], the role of ligands on the expression of their cognate SBPs has not been analysed on a global scale. To assess the effect of different ligand families on SBPs levels, we have surveyed the results of studies on 88 SBPs from 27 different phylogenetically diverse bacterial species with different lifestyles, including plant, animal and human pathogens, beneficial plant-associated bacteria, as well as non-pathogenic marine and soil bacteria. These SBPs bind a wide range of compounds, including amino acids, peptides, organic acids, sugars, polyamines, quaternary amines, cofactors, opines, quorum-sensing molecules or inorganic nutrients. The effects of these ligands on the expression of their cognate SBPs are compiled in Table 2, and the resulting patterns are illustrated in Fig. 4.

A major conclusion of this study is that 87 % of the ligands modulated the expression of their cognate SBPs (Table 2). The magnitude of regulation stretches from a 3466-fold downregulation of *phnD* expression in the presence of 2 mM as compared to 0.2 mM Pi [87] to a 143-fold upregulation in the expression of *tauA* in the presence of taurine[88]. Although the regulatory proteins that control the expression of several of the SBPs have been identified [89–98], the corresponding molecular mechanisms of the regulation are not the focus of this review.

7.1. Sugars and organic acids generally upregulate the expression of cognate SBPs

Sugars and organic acids are often preferred carbon sources for bacteria [99–101], and SBPs have been identified for mono-, oligo- and polysaccharides, tricarboxylic acid cycle intermediates, sugar acids and aromatic acids (Table 2). The analysis of the expression of 27 sugar and organic acid SBPs from 11 different bacterial genera revealed a preferential upregulation in the presence of their cognate ligands (Table 2). Notable examples were the genes encoding CBP and TauA. whose expression was upregulated more than 100-fold in the presence of chitin oligosaccharides [102] and taurine [88], respectively. In some cases, different regulatory effects were observed at different ligand concentrations. For example, the transcript levels of *adpC* encoding an aliphatic dicarboxylate SBP were increased in the presence of micromolar concentrations of its dicarboxylate ligands but reduced in the presence of millimolar concentrations of these dicarboxylates [103]. As shown in Table 1, the SBPs BctC, ChvE and CBP stimulate the sensor kinases BctE [89,104], VirA [105–107] and ChiS [59,102], respectively, and their cognate ligands upregulate the expression of BctC, ChvE and CBP at the levels of both transcription and protein synthesis (Table 2).

In contrast to the general tendency that sugars enhance SBP expression, the presence of an excess of glucose reduced the expression of the sugar-binding, amino acid-binding and peptide-binding SBPs LAO/ArgT, MalE, MppA, MglB, OppA, RbsB and YtfQ either at the transcript or protein level (Table 2). This effect was mainly due to a global regulatory mechanism, termed carbon catabolite repression (CCR), that modulates up to 10% of all genes in a given bacterium [99–101]. The mechanism implies that in the presence of preferred carbon sources, such as glucose in *Escherichia coli* and *Bacillus subtilis*, the expression of genes involved in the catabolism and transport of non-preferred carbon sources is repressed. As shown in Table 2, CCR plays an important role in the regulation of multiple SBPs in *E. coli* and *Salmonella typhimurium.* A mechanistic reason for the CCR-mediated SBP repression may be related to the fact that *E. coli* preferentially uses the phosphoenolpyruvate–carbohydrate phosphotransferase system for glucose transport (independent of SBPs) when growing on millimolar concentrations of sugars and switches to high affinity transport systems dependent on SBPs under glucose-limiting conditions [82,108,109]. Thus, the synthesis of a number of ABC transporter SBPs is upregulated at low glucose concentrations (Table 2).

7.2. Downregulation of SBPs by inorganic ligands

Phosphorous and metal ions like iron, nickel, manganese and zinc are essential elements for many biological processes They also

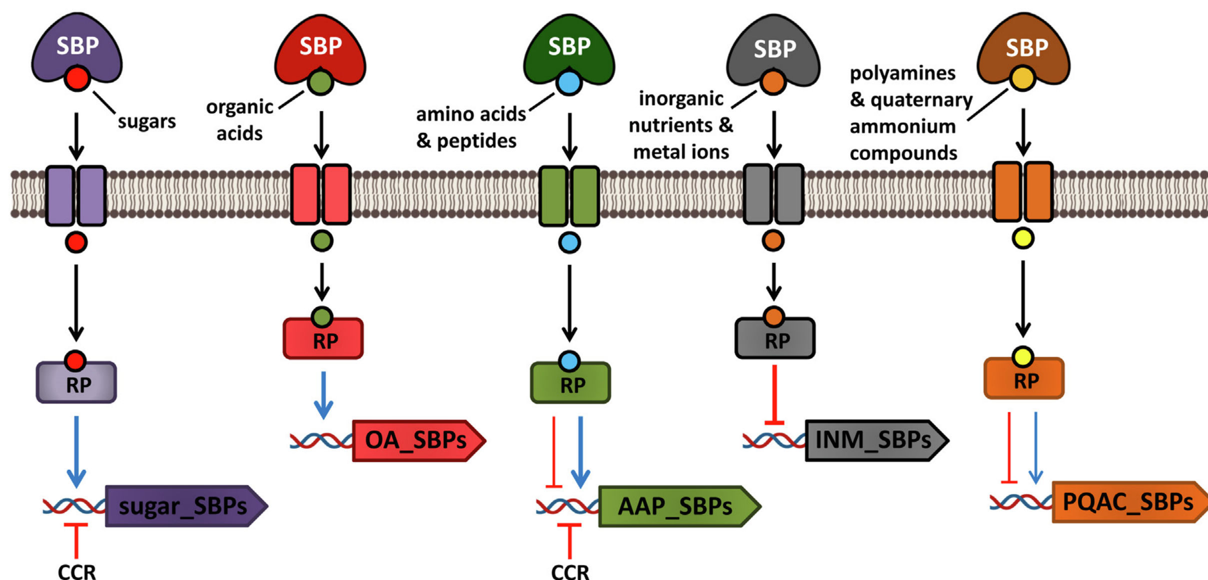

Fig. 4. Overview of the effect of different ligand families on the expression of solute binding proteins. Activation and repression are represented by triangular and flat arrowheads, respectively. The thickness of the lines represents a stronger upregulation or downregulation of the expression of target SBPs. SBP, solute-binding protein; RP, regulatory protein; CCR, carbon catabolite repression; OA, organic acids; INM, inorganic nutrients and metal ions; AAP, amino acids and peptides; PQAC, polyamines and quaternary ammonium compounds.

play important roles in bacterial signaling by modulating gene expression [110–114] and chemotactic processes [48,115,116]. The analysis of the expression of 28 phosphorous and metal ion SBPs from 16 different bacterial species revealed that these elements strongly repress the expression of their cognate SBPs (Table 2). Phosphorous and metal ions have a limited bioavailability due to their low abundance or insolubility. SBPs for these compounds are generally characterized by a very high affinity for their cognate ligands, permitting responses at very low concentrations. Representative examples are the binding of molybdate and Pi to their cognate SBPs ModA and PstS, respectively, that occurs with a much higher affinity (K_D~10 nM) than in other compound families [48,117]. In addition, the intracellular concentration of these elements needs to be finely balanced to avoid cellular toxicity. The repression of SBPs in response to elevated concentrations of metal ions and inorganic nutrients is a mechanism to maintain homeostatic intracellular levels [85,86,111,113,114]. As shown in Table 1, the SBP AioX binds arsenite and subsequently stimulates the TCS AioSR [118,119]. In contrast to the effect of most inorganic compounds on SBP expression, arsenite induced *aioX* expression (Table 2), which may be due to the fact that AioSR induces the expression of the genes involved in arsenite oxidation (Table 3), a process that reduces the toxicity of the ligand.

7.3. Dissimilar effects of amino acids, polyamines and quaternary ammonium compounds on cognate SBPs expression

Contrary to what was observed for sugars and organic acid SBPs, the expression of SBPs specific for amino acids and peptides in *E. coli* was generally downregulated at both the gene expression and protein levels in the presence of their cognate ligands (Table 2). An interesting case is that of the four *E. coli* SBPs ArtI, ArtJ, HisJ and LAO/ArgT that bind arginine (Table 2) [120]. These SBPs are encoded in two different clusters, *argT-hisJQMP* and *artPIQM-artJ*, which also encode the ABC-type transporters HisQMP and ArtPQM, respectively [9]. The expression of the genes encoding ArtJ, ArtI and HisJ, but not ArgT, was downregulated in the presence of arginine in a regulatory process mediated by the transcriptional repressor ArgR [91,121]. Whereas a strong downregulation was observed for *artJ*, only a weak repression was noted for *hisJ* and *artI* (Table 2). Current data suggest that this differential regulation is associated with the different physiological functions of ArtJ, ArtI, HisJ and LAO/ArgT. Thus, the arginine-specific ArtJ as well as the arginine-binding and ornithine-binding SBP ArtI were suggested to be mainly involved in the uptake of amino acids for biosynthetic processes [91,120]. In contrast, the expression of *argT* is activated by the nitrogen regulatory protein NtrC in response to nitrogen limitation [122], and ArgT may be primary implicated in the transport of arginine under conditions of nitrogen starvation. HisJ binds histidine with a 10-fold higher affinity than arginine [91] and its weak repression by arginine (Table 2) may ensure efficient histidine uptake when arginine is abundant. The primary role of amino acid-binding and peptide-binding SBPs is the uptake of nutrients for growth, but the dipeptide-binding SBP DppA of *E. coli* is involved in both chemotaxis and transport (Tables 1 and 3) and its expression was downregulated at both the transcriptional and protein synthesis levels in the presence of casamino acids (Table 2).

The expression profiles of polyamine-binding and quaternary ammonium compound-binding SBPs in the presence of their cognate ligands was dissimilar, with these SBPs showing either upregulation, downregulation or unaltered expression (Table 2). Several of these SBPs bind the osmoprotectants glycine betaine and proline betaine, and their expression was induced in *E. coli* and *B. subtilis* under conditions of osmotic stress to permit a rapid adjustment of the intracellular osmotic strength (Table 2) [123,124]. In accordance with the regulation of the expression of SBPs by environmental cues that are associated with the SBP function, the expression of *torT* encoding a SBP that binds the terminal electron acceptor TMAO was upregulated under anaerobic conditions [97]. In addition, second messengers were also found to modulate the expression of SBPs. As indicated above, the SBP NspS of *V. cholerae* forms a signaling system with the transmembrane GGDEF-EAL protein MbaA to control biofilm formation in response to polyamines [125]. Increased c-di-GMP intracellular levels were shown to upregulate the expression of *nspS* (Table 2).

8. Conclusions and research needs

The studies reviewed here strongly suggest that SBP-mediated activation of transmembrane receptors is a general and widespread

phenomenon. Researchers working in the field are thus encouraged to design experimental strategies, using either genetic or protein biochemistry approaches, to identify further systems. The overall final objective of these research efforts, which will lead to a larger number of characterized systems, is to get a more comprehensive understanding of which signaling systems are stimulated by direct binding and which by SBP-based mechanisms. Accumulating information will also enable us to see more clearly the physiological constraints that have led to the evolution of receptor activation by direct and indirect binding. Central questions still to be answered are:

(1) SBPs and receptor LBDs form superfamilies composed of many individual families. Do members of all or only some families participate in indirect receptor activation? Is it possible to identify sequence features specific for SBP-LBD interactions?
(2) Whereas signal-loaded SBPs stimulate receptors, much less information is available on the role of the SBP apo forms. What are the affinities of apo- and holo-SBPs for their respective targets? What is the effect of apo-SBP binding on receptor activity?
(3) Several receptors bind signals directly as well as in complexes with SBPs. How frequent are such systems and what is the flexibility in the response afforded by these dual input mechanisms for receptor activation?
(4) What is the concentration of SBPs in the periplasmic space?
(5) What factors determine whether the expression of an SBP is regulated by its cognate ligand?
(6) What is the evolutionary history of the receptor proteins that are activated by both direct and indirect ligand binding?

The answers to these questions will not only increase our fundamental knowledge about signal transduction mechanisms but also may offer alternative strategies to fight pathogenic bacteria by interfering with their ability to sense, respond and adapt to their environment.

CRediT authorship contribution statement

Miguel A. Matilla: Conceptualization, Data curation, Funding acquisition, Writing - original draft, Writing - review & editing. **Álvaro Ortega:** Conceptualization, Data curation, Writing - review & editing. **Tino Krell:** Conceptualization, Data curation, Funding acquisition, Writing - original draft, Writing - review & editing.

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