Serine/threonine/tyrosine phosphorylation regulates DNA binding of bacterial transcriptional regulators

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Reversible phosphorylation of bacterial transcriptional regulators (TRs) belonging to the family of two-component systems (TCSs) is a well-established mechanism for regulating gene expression. Recent evidence points to the fact that reversible phosphorylation of bacterial TRs on other types of residue, i.e. serine, threonine, tyrosine and cysteine, is also quite common. The phosphorylation of the ester type (phospho-serine/threonine/tyrosine) is more stable than the aspartate phosphorylation of TCSs. The kinases which catalyse these phosphorylation events (Hanks-type serine/threonine protein kinases and bacterial protein tyrosine kinases) are also much more promiscuous than the TCS kinases, i.e. each of them can phosphorylate several substrate proteins. As a consequence, the dynamics and topology of the signal transduction networks depending on these kinases differ significantly from the TCSs. Here, we present an overview of different classes of bacterial TR phosphorylated and regulated by serine/threonine and tyrosine kinases. Particular attention is given to examples when serine/threonine and tyrosine kinases interact with TCSs, phosphorylating either the histidine kinases or the response regulators. We argue that these promiscuous kinases connect several signal transduction pathways and serve the role of signal integration.

Bacterial two-component systems (TCSs)

TCSs are signal transduction devices that were initially discovered in bacteria (Ninfa & Magasani, 1986; Nixon et al., 1986). They play an important role in signal sensing and response to various stimuli, enabling the organisms to adapt to environmental changes. A typical TCS consists of a histidine kinase (HK) and a corresponding response regulator (RR) (Stock et al., 2000; Gao & Stock, 2009). HK usually possesses a highly variable sensor domain and a conserved kinase core. Following environmental stimulus, a signal ligand binds to the sensor domain and results in the autophosphorylation of the kinase core at a conserved histidine residue, at the expense of ATP. Next, the phosphoryl group is transferred from HK to a conserved aspartate in the regulatory domain of the RR. RR usually contain two domains: a regulatory domain with the conserved phosphorylatable aspartate and a variable effector domain. Phosphorylation activates the effector domain of RR, triggering the physiological response. As phosphohistidine has a very short half-life in aqueous solutions at neutral pH, in the absence of the environmental signal the system switches itself off very rapidly.

Many effector domains of bacterial RR have DNA-binding capacity. This allows RR to function as transcriptional regulators (TRs) and consequently change gene transcription when they become phosphorylated. In Escherichia coli, osmoregulation of porin proteins OmpF and OmpC is under transcriptional control of the TCS EnvZ/OmpR. The phosphorylation of OmpR by EnvZ changes its affinity for the promoter region of ompF and ompC, resulting in different transcriptional levels of these genes (Forst et al., 1989; Rampersaud et al., 1994). The effector domains can also perform enzymic activities, bind RNA or engage in protein–protein interactions (Gao et al., 2007; Galperin, 2010). The TCS that consists of the HK CheA and two RR, CheY and CheB, is responsible for regulating the chemotaxis in E. coli. Phosphorylated CheY binds to flagellar motor switches to increase the tumble frequency, resulting in different swimming behaviour of the cell (Alon et al., 1998), whilst phosphorylated CheB has higher methylesterase activity, which diminishes the activity of chemotaxis receptors (Alon et al., 1999). Although the effector domains are diverse, the majority of them are DNA-binding domains. The classification of the effector domains
Bacterial TRs can be regulated by other types of phosphorylation

Examination of the available genome sequences reveals that TCSs are widely distributed in bacteria, and are present in archaea and some eukarya. As ~65% of all bacterial RR are TRs, TCSs typically account for ~5–25% of all TRs in a bacterial cell (this fraction varies considerably amongst different bacterial phyla). Whilst TCS TRs are regulated by reversible phosphorylation, it is widely presumed that other bacterial TRs are regulated by reversible ligand binding and not by phosphorylation. However, recent phosphoproteomics analyses have revealed that many bacterial TRs can be phosphorylated on serine, threonine and tyrosine residues (Macek et al., 2007; Prisic et al., 2010; Soufi et al., 2010; Derouiche et al., 2013). Moreover, some recent studies suggest that non-TCS bacterial TRs can also be phosphorylated on arginine (Schmidt et al., 2014), histidine (Hammerstrom et al., 2015) and cysteine residues (Sun et al., 2012).

Serine/threonine phosphorylation of bacterial TRs

In the past few years, it has been established that Hanks-type serine/threonine kinases (STKs) can phosphorylate TRs in many bacteria and regulate different functions, such as antibiotic resistance, virulence, capsule synthesis and sporulation (Wright & Ulijasz, 2014). The human pathogen Staphylococcus aureus possesses two Hanks-type STKs, Stk1 and Stk2, both implicated in regulating virulence and antibiotic resistance (Ohlsen & Donat, 2010; Tamber et al., 2010). Recently, it was established that the S. aureus Stk1 phosphorylates and regulates the activity of the global TR MgrA. MgrA belongs to the SarA/MgrA family of TRs that comprise a dimerization domain and a winged helix-turn-helix (HTH) motif (Cheung et al., 2008) (Fig. 1a). MgrA controls different virulence factors, such as the z-toxin, coagulase, protein A, autolysins and the synthesis of capsule polysaccharides. In addition, MgrA also controls the synthesis of several efflux pumps implicated in antimicrobial resistance in S. aureus (Truong-Bolduc et al., 2008). Stk1 phosphorylates purified MgrA at two adjacent serines, Ser110 and Ser113, located in the dimerization domain interface (Truong-Bolduc & Hooper, 2010) (Fig. 1a). It was suggested that this phosphorylation antagonizes MgrA dimerization and DNA binding, leading to de-repression of its target genes and therefore activation of the efflux pump under antibiotic-imposed stresses (Truong-Bolduc & Hooper, 2010). Another S. aureus global TR controlled by serine/threonine phosphorylation is SarA (Chien et al., 1999; Didier et al., 2010). SarA also controls virulence factors: the z-toxin, the immune evasion molecule Spa, and the haemolysins and proteolytic exotoxins (Cheung et al., 2008). In addition, SarA controls host colonization by regulation of the ica operon responsible for biofilm formation (Valle et al., 2003), as well as capsule synthesis and adherence (Cheung et al., 2008) (Fig. 1a). Didier et al. (2010) have shown that SarA is phosphorylated by both Stk1 and Stk2. Stk1 controls SarA by threonine phosphorylation, which enhances its binding to promoters of key target genes (Didier et al., 2010). In contrast, Stk2 phosphorylates SarA only on serine residue(s) and this provokes a decrease in DNA binding to known SarA-regulated promoters (Didier et al., 2010). Further work is needed on the SarA regulatory system to define the effects of phosphorylation with respect to infection and virulence. Another example of TRs regulated by STKs in S. aureus is CcpA (catabolite control protein A). CcpA belongs to a conserved family of LacI/GalR TRs and is a global gene regulator of the central carbon metabolism in many bacterial species. In Firmicutes, the HPr protein phosphorylated at a specific
serine residue interacts with CcpA and facilitates its binding to operator sites (Mijakovic et al., 2002; Fujita, 2009). CcpA is also involved in controlling virulence factors in *S. aureus* and many other bacterial pathogens (Seidl et al., 2006). Recently, it was shown that *S. aureus* CcpA is phosphorylated by Stk1, *in vivo* and *in vitro*, on two threonine residues (Thr18 and Thr33) (Fig. 1a). These residues are situated in the CcpA DNA-binding domain and are presumed to interact with the target DNA by forming hydrogen bonds. CcpA phosphorylation by Stk1 abrogates the protein–DNA interaction, and leads to activation of CcpA-repressed promoters implicated in sugar metabolism and biofilm formation (Leiba et al., 2012) (Fig. 1a). Interestingly, CcpA Thr18 and Thr33 are highly conserved in *Firmicutes* (Fig. 1b). Whilst it has been shown that CcpA orthologues from several other species could not be phosphorylated by their cognate STKs, cross-species phosphorylation was shown to be possible (Leiba et al., 2012).

The pathogenic bacterium *Mycobacterium tuberculosis* possesses a relatively large arsenal of STKs (11 kinases, named PknA to PknL). This bacterium is known for the emergence of antibiotic resistance phenomena, some of which can be related to regulation dependent on STKs (Molle & Kremer, 2010). Interestingly, many proteins regulated by *M. tuberculosis* STKs are TRs that play crucial roles in virulence. One of these TRs is EthR, a transcriptional repressor (belonging to the TetR family), which regulates the activation process of the antitubercular drug ethionamide (Baulard et al., 2000). Ethionamide is a pro-drug that

![Fig. 1. Staphylococcus aureus TRs controlled by STKs. (a) TRs are represented in tan and STKs in red. Phosphorylation reactions are shown as red arrows. Domain architecture and identified phospho-residues are shown for each TR. The dimerization domains (DD) and periplasmic binding domains (PDB) are shown in blue, and the DNA-binding HTH domains are shown in yellow (wHTH, winged HTH; lHTH, LacI family HTH). (b) Alignment of CcpA N termini from different bacteria: Bsele-nitireducens, *Bacillus selenitireducens* MLS10; Bbrevis, *Brevibacillus brevis*; Blicheniformis, *Bacillus licheniformis*; Bsubtilis, *Bacillus subtilis* 168; Lbrevis, *Lactobacillus brevis* ATCC 367; Lcasei, *Lactobacillus casei* BL23; Smutans, *Streptococcus mutans*; Spyogenes, *Streptococcus pyogenes* MGAS2096; Saureus, *Staphylococcus aureus* N315; Cbotulinum, *Clostridium botulinum* B; Csticklandii, *Clostridium sticklandii*. Residues phosphorylated by Stk1 in *Staphylococcus aureus* CcpA are indicated with red arrows.](image-url)
must undergo bioactivation by the mono-oxygenase EthA (DeBarber et al., 2000). Molle and colleagues have shown that EthR is a substrate of the M. tuberculosis STK PknF in vitro (Leiba et al., 2014). MS analysis has identified four phosphorylated residues in the unstructured N terminus of the EthR: Thr2, Thr3, Ser4 and Ser7. When these phospho-residues were mutated, in vitro binding of EthR to its target ethA promoter decreased (Leiba et al., 2014). Another M. tuberculosis TR phosphorylated by STKs is Rv2175c, which is considered to be implicated in cell wall synthesis (Cohen-Gonsaud et al., 2009). This was discovered in a proteomics-based study searching for novel kinase substrates (Canova et al., 2008). It was shown that PknL phosphorylates Rv2175c on a key threonine residue (Thr9), and phosphorylation disrupts the interaction of Rv2175c with the DNA (Cohen-Gonsaud et al., 2009).

In the Firmicutes model organism Bacillus subtilis, there is one global gene regulator, AbrB, known to be phosphorylated by STKs (Kobir et al., 2014). AbrB binds a number of DNA target sequences with the common feature of being structurally flexible and undergoing a conformational change upon TR binding (Bobay et al., 2004). AbrB acts as a global TR (Chumskul et al., 2011), regulating the expression of stationary-phase functions. Recently, AbrB was reported to be phosphorylated at residue Ser86 in a phosphoproteomics study (Soufi et al., 2010). AbrB phosphorylation depends on the presence of ATP and is stimulated by phosphorylation of SalA at Tyr327 by the BY kinase PtkA (Fig. 2a). This phosphorylation activates SalA ATP binding and hydrolysis, leading to repression of scoC and increased production of the exoprotease AprE (Derouiche et al., 2015).

Cysteine phosphorylation of bacterial TRs

The staphylococcal TRs of the SarA/MarR family were recently found to be phosphorylated on cysteine residues (Sun et al., 2012). This type of phosphorylation is considered to be a rare post-translational modification, usually with no known regulatory roles. In S. aureus, the STK Stk1 phosphorylates a number of TRs on cysteines: Cys9 of SarA, Cys13 of SarZ and Cys12 of MgrA, within their N-terminal dimerization domain (Fig. 2a) (Sun et al., 2012). In vivo and in vitro evidence, as well as the structural analysis, demonstrate that Stk1-dependent cysteine phosphorylation regulates several virulence traits and vancomycin resistance (Sun et al., 2012).

Phosphorylation of TCS HKs and RRs by STKs

Over recent years an increasing number of studies have described unconventional TCS RRs. In this section we summarize several examples of TCS in which the RRs lack a cognate HK (orphan RRs) and require phosphorylation by a STK. In some cases, STK-dependent phosphorylation also occurs on RRs which have a designated HK. This double phosphorylation, catalysed by HKs and STKs, respectively, diversifies the inputs modulating RR activity. There are also reported cases of cross-phosphorylation between HKs and STKs in bacteria.

The B. subtilis TCS DegS/DegU is part of a complex regulatory network involving the control of competence, exoprotease production, motility and complex colony and biofilm formation (Msadek et al., 1990; Ogura et al., 2001; Verhamme et al., 2007; Kobayashi, 2007; Mader et al., 2002). DegS is a cytosolic HK, which seems to integrate various signals pertaining to the metabolic condition of the cell. Interestingly, DegS was found to be phosphorylated on
Residue Ser76, situated in its signal-sensing domain (Macek et al., 2007). Jers et al. (2011) demonstrated that DegS Ser76 can be phosphorylated by two B. subtilis STKs: PrkD (YbdM) and YabT (Fig. 3a). Phosphorylation of DegS Ser76 stimulates its HK kinase activity and the transfer of phosphate to the RR DegU. As a consequence, the non-phosphorylated degS mutant S76A behaves like a strain with low levels of DegU-P in vivo. These results suggest that STK-dependent phosphorylation of the HK DegS can act as an additional input for activating this TCS.

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**Fig. 2.** *Bacillus subtilis* TRs controlled by serine/threonine/tyrosine phosphorylation. (a) TRs are represented in tan and kinases in red. Phosphorylation reactions are shown as red arrows. Domain architecture and identified phospho-residues are shown for each TR. The dimerization domains are shown in blue, and the DNA-binding HTH domains are shown in yellow (the AbrB DNA-binding domain is also referred to as the loop-hinge helix fold). (b) Alignment of AbrB C-termini from different bacteria: Parvae, *Paenibacillus larvae*; Ppolymyxa, *Paenibacillus polymyxa* E681; Hemedesticaldum, *Heliopectinella modesticaldum* Ice1; Bsubtilis, *Bacillus subtilis* 168; Bamyloiqeufaciens, *Bacillus amyloliquefaciens* DSM7; Batrophaeus, *Bacillus atrophaeus* 1942; Blicheniformis, *Bacillus licheniformis* DSM13; Bcereus, *Bacillus cereus* G9842; Apasteurianus, *Acetobacter pasteurianus*. The residue phosphorylated by STKs in *B. subtilis* AbrB is indicated with a red arrow. (c) Alignment of N-termini of *Bacillus subtilis* FatR orthologues from different bacteria: Bthuringiensis, *Bacillus thuringiensis* BMB171; Bcereus, *Bacillus cereus*; Bmegaterium, *Bacillus megaterium*; Bsubtilis, *Bacillus subtilis* 168; Lcasei, *Lactobacillus casei* BL23; Abaumannii, *Acinetobacter baumannii*; Pseudomonas, *Pseudomonas mendocina*; Smitis, *Streptococcus mitis* SK597; Kpneumoniae, Klebsiella pneumoniae subsp. pneumoniae; Senterica, *Salmonella enterica*. The residue phosphorylated by the *Bacillus subtilis* BY kinase PtkA is indicated with a red arrow.
In *Streptococcus pneumoniae*, RitR (repressor of iron transport regulator) is a TCS-like TR that is required for lung pathogenicity. It controls iron uptake and remediation of iron-catalysed reactive oxygen species (Throup *et al.*, 2000; Ulijasz *et al.*, 2004; Ong *et al.*, 2013). RitR is annotated as a TCS RR, but because it does not possess a cognate HK it is called an orphan RR (Ulijasz *et al.*, 2004). Instead of a conserved aspartate residue in its regulatory domain, RitR has an asparagine residue at the expected phosphate acceptor site. *Streptococcus pneumoniae* phospho-serine/threonine protein phosphatase PhpC, and its cognate STK StkP, were identified as interaction partners of RitR (Ulijasz *et al.*, 2009) (Fig. 3b). StkP was further shown to phosphorylate the RitR C-terminal DNA-binding domain in vitro. Further *in vitro* studies have suggested that PhpP and StkP compete for interaction with RitR. Both StkP and PhpP seem to affect the expression of RitR target genes *in vivo*, i.e. the Piu haem transporter. These observations suggest that the orphan RR RitR is in fact regulated by STK-dependent phosphorylation.

Cross-talk between Stk1/Spot1 and GraS/GraR signalling pathways was shown in *S. aureus* (Fridman *et al.*, 2013). Stk1/Spot1 is a Hanks-type STK/phosphatase pair and GraS/GraR is a TCS which controls the resistance to cationic antimicrobial peptides. A study by Fridman *et al.* (2013) reported that Stk1 specifically phosphorylates the RR protein of the GraS/GraR TCS, GraR, at the DNA-binding domain, which increases its DNA-binding activity. Thr128, Thr130 and Thr149, located in the N terminus of its DNA-binding domain, were suggested as phosphorylation sites. This phosphorylation was found to be dependent on the intact tertiary structure of GraR, as denatured GraR did not undergo phosphorylation by Stk1. The specificity of the phosphotransfer between Stk1 and GraR was further investigated in BceR, a homologue of Stk1 in *B. subtilis*, which did not exhibit Stk1-dependent phosphorylation. GraR is involved in regulation of the *dltABCD* operon, which provides the addition of D-alanine to the wall teichoic acid. Wall teichoic acid isolated from *S. aureus* RN6390 *AgraR* strain showed reduced D-alanine content.

**Fig. 3.** Overview of the cross-talk between bacterial TCSs and STKs. Two-component HKs and RRs are represented in tan, STKs are in red and phosphatases are in green. Domain architecture is indicated for phosphorylated RRs, DNA-binding domains are in yellow, regulatory domains (RD) are in blue and dimerization domains (DD) in light grey. Identified phosphorylated residues are indicated. The depicted TCSs are (a) *Bacillus subtilis* DegS/DegU, (b) *Streptococcus pneumoniae* orphan RR RitR, (c) *Staphylococcus aureus* VraS/VraR, (d) *M. tuberculosis* DosS/DosT/DosR, (e) streptococcal CovS/CovR and (f) *Staphylococcus aureus* GraS/GraR. ROS, reactive oxygen species.
This result suggests that Stk1 an modulate the modification of wall teichoic acid. Depending on the environmental signals, expression of the dltABCD operon is controlled by two distinct phosphorylations of GraR, catalysed by either Stk1 or GraS.

In *S. aureus*, the TCS RR VraR is phosphorylated by a cognate HK, VraS (Belcheva & Golemi-Kotra, 2008). In addition, it is also phosphorylated by a cognate STK, Stk1 (Canova *et al.*, 2014) (Fig. 3c). VraR belongs to the *S. aureus* vancomycin resistance-associated sensor and RR system (VraTSR). VraTSR responds to several antibiotics targeting the cell wall. VraR, the RR, modulates the expression of the cell wall stress regulon in response to antibiotics. VraR is regulated by phosphorylation catalysed by VraS and Stk1 (Canova *et al.*, 2014). Stk1-dependent phosphorylation sites on VraR were determined in vitro, and confirmed by site-directed mutagenesis. These comprise four threonines: Thr106, Thr119, Thr175 and Thr178. Stk1-mediated phosphorylation sites are of crucial importance for VraR activity. Residues Thr175 and Thr178 are located in the HTH domain of VraR, while the other two sites are in the VraR regulator domain. The structural context of the phosphorylation sites suggests that VraR phosphorylation should inhibit its DNA binding, and this was confirmed experimentally (Canova *et al.*, 2014). VraR regulation is a prominent example of a bacterial TR that is regulated simultaneously by two types of phosphorylation: aspartate and threonine, catalysed by a HK VraS and a STK Stk1, respectively.

A similar case of two phosphorylation systems converging on the same RR was observed in *M. tuberculosis*. Dormancy in *M. tuberculosis* is mediated by the RR DosR (Park *et al.*, 2003). The DosR regulon is transcriptionally activated in response to hypoxia, carbon monoxide and nitric oxide. The activation of the DosR-regulated genes is triggered by two cognate HKs: DosS and DosT (Roberts *et al.*, 2004; Kumar *et al.*, 2007). In addition to DosR- and DosT-dependent phosphorylation, DosR can also be phosphorylated by a STK PknH (Fig. 3d). This phosphorylation occurs on DosR residues Thr198 and Thr205, situated in the key regulatory helix z10 (Chao *et al.*, 2010). DosR aspartate and threonine phosphorylations act synergistically; both were shown to enhance DosR DNA binding in vitro. Consequently, both types of phosphorylation correlate with transcriptional activation of the DosR regulon in vivo. As the effect is synergistic, both types of phosphorylation are required to achieve full transcriptional response.

In the case of DosR, aspartate and threonine phosphorylation elicit a synergistic effect. By contrast, the two phosphorylation systems converging on the streptococcal RR CovR have antagonistic effects. The CovS/CovR TCS regulates the expression of genes involved in the production of capsule, major virulence factors, penetration of blood–tissue barriers and avoidance of the immune system by group A/B streptococci (Federle *et al.*, 1999; Jiang *et al.*, 2005; Whidbey *et al.*, 2013). Rajagopal *et al.* (2006) showed that deletion of the STK Stk1 leads to inability to produce the key virulence factor β-haemolysin/cytolysin. This effect is based on Stk1-dependent phosphorylation of the residue Thr65 in CovR (Fig. 3e). CovR Thr65 phosphorylation by Stk1 antagonizes CovR phosphorylation at Asp53 by CovS. This inhibitory effect also extend in the opposite direction; CovR phosphorylation at Asp53 decreases Stk1-dependent phosphorylation at Thr65. As a consequence, phosphorylation of CovR at Thr65 (by Stk1) antagonizes the activating effect of CovS-dependent phosphorylation and ultimately decreases CovR affinity for DNA targets.

**Concluding remarks**

Phosphorylation of bacterial TRs by STKs and BY kinases at first glance serves the same purpose as phosphorylation of TCS RRs by their HKs. Phosphorylation affects the affinity of TRs for DNA and serves as an activity switch. However, aspartate phosphorylation of RRs is inherently short-lived, and the signal is rapidly transmitted and quickly extinguished. Conversely, serine/threonine and tyrosine phosphorylation is chemically much more stable in the bacterial cytosol, and dedicated phosphatases are required to remove it from phosphorylated TRs. Another important difference between HKs, on the one hand, and STKs and BY kinases, on the other, is substrate selectivity. HKs discriminate very strictly amongst cognate RRs and typically phosphorylate only one or two targets. STKs and BY kinases are much less specific, and their actions are more pleiotropic (Shi *et al.*, 2014a; Wright & Ulijasz, 2014). Each STK and BY kinase can phosphorylate a number of different cellular substrates (Mijakovic & Deutscher, 2015), and this relaxed substrate specificity can be traced to a lack of co-evolution between the kinase and its substrates (Shi *et al.*, 2014b). These kinases are often capable of extensive cross-talk with other kinases (Shi *et al.*, 2014a). STKs and BY kinases in some cases functionally interact with the TCSs, phosphorylating either HKs or RRs. In this context, we would argue that STKs and BY kinases may act more like signal-integrating than simple signal-transmitting devices. The impact of TCSs on regulation of gene transcription has often been described as a rapid and reversible ‘on/off’ response. With STKs and BY kinases, the dynamics of the response are likely to be different. These kinases are known to phosphorylate substrates less efficiently and are therefore likely to elicit fine-tuning than a classical ‘on/off’ response. Therefore, it would be interesting to see some time-resolved *in vivo* studies measuring the phosphorylation stoichiometry of TRs phosphorylated on serine/threonine/tyrosine residues, and even more interesting to correlate these to the effects on target gene transcription. The thermodynamic stability of phospho-serine/threonine/tyrosine residues probably means that the regulatory effects of phosphorylation may last longer. In several cases described above, serine/threonine/tyrosine phosphorylation of TRs acts as a secondary regulatory mechanism, in addition to some previously known
ligand or stimulus. This strengthens the notion of fine-tuning or, in some cases, desensitizing the TR to the primary ligand/signal. Evaluating the impact of this transcriptional fine-tuning on the systems level will soon be possible by combining time-resolved transcriptomics and phosphoproteomics studies.

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