Mini-Review

Novel $\sigma^B$ regulation modules of Gram-positive bacteria involve the use of complex hybrid histidine kinases

Mark de Been,1,2,3,4 Christof Francke,1,3 Roland J. Siezen1,3,5 and Tjakko Abee2,3

Correspondence
Mark de Been
mdebeen@cmbi.ru.nl

1Centre for Molecular and Biomolecular Informatics (CMBI), NCMLS, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands
2Laboratory of Food Microbiology, Wageningen University and Research Centre, Wageningen, The Netherlands
3TI Food and Nutrition (TIFN), Wageningen, The Netherlands
4Faculty of Veterinary Medicine, Department of Veterinary Biosciences, Veterinary Microbiology and Epidemiology, University of Helsinki, Helsinki, Finland
5NIZO food research BV, Ede, The Netherlands

A common bacterial strategy to cope with stressful conditions is the activation of alternative sigma factors that control specific regulons enabling targeted responses. In the human pathogen Bacillus cereus, activation of the major stress-responsive sigma factor $\sigma^B$ is controlled by a signalling route that involves the multi-sensor hybrid histidine kinase RsbK. RsbK-type kinases are not restricted to the B. cereus group, but occur in a wide variety of other bacterial species, including members of the low-GC Gram-positive genera Geobacillus and Paenibacillus as well as the high-GC actinobacteria. Genome context and protein sequence analyses of 118 RsbK homologues revealed extreme variability in N-terminal sensory as well as C-terminal regulatory domains and suggested that RsbK-type kinases are subject to complex fine-tuning systems, including sensitization and desensitization via methylation and demethylation within the helical domain preceding the H-box. The RsbK-mediated stress-responsive sigma factor activation mechanism that has evolved in B. cereus and the other species differs markedly from the extensively studied and highly conserved RsbRST-mediated $\sigma^B$ activation route found in Bacillus subtilis and other low-GC Gram-positive bacteria. Implications for future research on sigma factor control mechanisms are presented and current knowledge gaps are briefly discussed.

Introduction

Bacteria use dedicated sets of sensory modules to tightly coordinate gene expression in response to environmental fluctuations. A commonly used sensory module is the two-component signal transduction system (TCS), which includes a transmembrane sensor histidine kinase (HK) and its cognate response regulator (RR). The mode of signal transduction by TCSs involves a phospho-transfer reaction between a conserved histidine and aspartate residue located in the HK phosphotransferase and RR receiver (REC) domain, respectively. RRs generally function as transcription factors that, upon phosphorylation, bind to specific sites on the DNA to alter the expression of the genes involved in adaptive responses (Hoch, 2000). Another bacterial strategy for tight control of gene expression is the use of alternative sigma factors. In exponentially growing cells, most of the transcription is mediated by a ‘housekeeping’ sigma factor that is equivalent to $\sigma^{70}$ in Escherichia coli and $\sigma^A$ in Bacillus subtilis. However, under specific conditions, such as severe environmental stress, the housekeeping sigma factor gets replaced from the RNA polymerase by alternative sigma factors that recognize specific promoters and control specialized regulons (Gruber & Gross, 2003). One of the best-studied alternative sigma factors is the key stress-responsive sigma factor $\sigma^B$ of low-GC Gram-positive bacteria of the genera Bacillus, Listeria and Staphylococcus (Hecker et al., 2007; Price, 2002). Besides mediating the

Abbreviations: HK, histidine kinase; MCP, methyl-accepting chemotaxis protein; RR, response regulator; REC, RR receiver; TCS, two-component signal transduction system.

Six supplementary figures are available with the online version of this paper.
Fig. 1. Established and predicted signalling routes for the control of $\sigma^B$ activity in different Gram-positive bacteria. Locations of potential stimulus perception are indicated by 'explosion' symbols. (a) The extensively studied ‘*B. subtilis* module’ for the control of $\sigma^B$. The *B. subtilis* stressosome is an ~1.8 MDa supramolecular complex that consists of multiple copies of RsbR and RsbS (Chen et al., 2003; Delumeau et al., 2006; Dufour et al., 1996; Marles-Wright et al., 2008). Different environmental stresses and signals are thought to stimulate RsbT kinase activity towards its stressosome substrates (Akbar et al., 2001; Ávila-Pérez et al., 2006; Gaidenko et al., 2006; Kim et al., 2004; Voelker et al., 1995). This leads to dissociation of RsbT from the stressosome to activate RsbU and subsequently $\sigma^B$ (Delumeau et al., 2004). Return of the stressosome to the unphosphorylated state is achieved by RsbX (Chen et al., 2004). A second *B. subtilis* $\sigma^B$ activation pathway involves the hydrolase or acyltransferase RsbQ and the PP2C-type phosphatase RsbP, which are required for triggering $\sigma^B$ activity in red light and conditions of energy stress (Ávila-Pérez et al., 2010; Brody et al., 2001, 2009; Vijay et al., 2000). Note that RsbRST-dependent $\sigma^B$ activation is conserved across several other low-GC Gram-positive bacteria, but that RsbQP-dependent $\sigma^B$ activation has so far only been found in *B. subtilis*. (b) Model for the control of $\sigma^B$ in *B. cereus*. Upon different stresses, RsbK most likely ‘auto’-phosphorylates a conserved histidine residue within its H-box. The phosphoryl group is then either transferred directly to a conserved asparate within the REC domain of RsbY (route 1), or shuttled to RsbY indirectly (route 2) via RsbK’s own REC domain and a potential phosphotransferase protein (marked ‘H?’) (de Been et al., 2010). In the former scenario, the RsbK REC may play a role in fine-tuning RsbK kinase activity. Phosphoryl transfer within RsbK is therefore shown by a double arrow. Phosphorylation of RsbY most likely activates its PP2C domain, which dephosphorylates RsbV, ultimately resulting in the activation of $\sigma^B$ (van Schaik et al., 2005). An additional fine-tuning system may include CheR-mediated methylation processes of RsbK (this study). Other *B.*
general stress response, σB plays an important role in virulence in the human pathogens Listeria monocytogenes and Staphylococcus aureus (Chaturongakul et al., 2008; Novick, 2003), and to a lesser extent in Bacillus anthracis (Fouet et al., 2000). Sigma factors equivalent to σB have also been found in high-GC Gram-positive bacteria, including Mycobacterium tuberculosis and Streptomyces species (Mittenhuber, 2002). In Streptomyces coelicolor, σB acts in a complex network of several paralogous sigma factors, where it plays a role in osmotic and oxidative stress responses, as well as cellular differentiation and the production of antibiotics (Cho et al., 2001; Lee et al., 2005; Viollier et al., 2003).

The σB network has been studied best in the model low-GC Gram-positive B. subtilis. In B. subtilis, σB activity is controlled by RsbVW partner-switching, a mechanism that is highly conserved in species that contain σB (Fig. 1, bottom). Under non-stress conditions, σB is held in an inactive state complex by the anti-sigma factor RsbW. Release of σB from RsbW is accomplished by the anti-anti sigma factor RsbV, which, upon dephosphorylation, sequesters RsbW. In addition, RsbW acts as a kinase of σB, thereby providing a negative feedback on σB activation. Under stress conditions, RsbV is dephosphorylated by one or more specific PP2C-type phosphatases, resulting in the sequestration of RsbW and the activation of σB (Hecker et al., 2007; Price, 2002).

Whereas RsbVW-mediated control of σB is highly conserved, the N-terminal input domains of the PP2C-type phosphatases vary considerably across species (van Schaik & Abe, 2005). For example, B. subtilis contains two σB-activating PP2C-type phosphatases, RsbP and RsbU. Energy stress is probably signalled through RsbP, which contains an N-terminal PAS sensory domain (Brody et al., 2001, 2009; Vijay et al., 2000), while environmental stress (i.e. heat, osmolites, ethanol, low pH) is signalled through RsbU, which contains an N-terminus that interacts with the regulator RsbT, which in turn interacts with the RsbR- and RsbS-containing supramolecular ‘stressosome’ (Akbar et al., 2001; Chen et al., 2003; Delumeau et al., 2006; Dufour et al., 1996; Kim et al., 2004; Marles-Wright et al., 2008) (Fig. 1a).

In the human pathogen Bacillus cereus, the mechanism of σB activation has only been studied more recently (see Fig. 1b for the current model). It has been shown that σB activation is governed by a single PP2C-type phosphatase, RsbY, which carries an N-terminal REC domain (van Schaik et al., 2005). This suggested the existence of a partner HK acting on RsbY. Indeed, we have recently identified the hybrid kinase RsbK (BC1008) as a potential partner in the σB-mediated stress response of B. cereus (de Been et al., 2010). RsbK contains both HK and RR domains, and the rsbK gene is located close to sigB on the genome. A genome survey indicated that RsbK and RsbY should constitute one functional module for the control of σB activity in members of the B. cereus group, including the pathogens Bacillus thuringiensis and B. anthracis and the psychrotolerant B. weihenstephanensis. Orthologous RsbKY signalling modules were found in four other bacilli outside the B. cereus group. However, the RsbKY modules of these other bacilli were not genomically associated with sigB (de Been et al., 2010). To explore the occurrence of RsbK- and RsbY-like proteins outside the B. cereus group, we searched available microbial and eukaryotic genome sequences for the presence of RsbK- and RsbY-type signalling domains. Subsequent phylogenetic and gene context analyses revealed that signalling modules involving RsbK (and sometimes also RsbY) homologues are present in several other low-GC as well as high-GC Gram-positive bacteria and could potentially regulate σB-like sigma factors. Based on these results, we propose that, besides the well-characterized and conserved σB activation pathway of B. subtilis, the use of RsbK-type hybrid kinases is another common bacterial strategy to regulate stress-responsive σB(-like) sigma factors.

RsbK-type hybrid kinases occur in a wide variety of bacterial species

To map the occurrence of RsbK and RsbY homologues in other species, a similar approach was followed as described previously (de Been et al., 2006, 2010). This approach included a straightforward BLAST search with the HK phosphotransferase (RsbK) and REC (RsbK and RsbY) domain sequences. As these types of domains are characteristic for all TCSs and are easily recognized, such a search should yield all potential candidates. In fact, it has been shown that these domains contain enough information density to enable their use in classification and evolutionary studies (Alm et al., 2006; Fabret et al., 1999; Grebe & Stock, 1999). For each of the three domains, their protein BLAST hits were aligned and a bootstrapped neighbour-joining tree was built (see Supplementary Figs S1–S3, available with the online version of this paper). For assigning potential RsbK and RsbY homologues, we used a minimal bootstrap support of 30%. In the case of RsbY, the procedure resulted in the identification of only six putative RsbY homologues outside the B. cereus group.
Novel SigB activation modules involve hybrid kinases

RsbK-type HKs display extremely variable sensory and C-terminal regions

Sequence analysis of the RsbK homologues revealed the presence of several N-terminal HK sensory domains (Fig. 2), including CHASE3, GAF and PAS/PAC domains, of which the latter two have been implicated in small ligand/cyclic nucleotide binding and redox/light/metabolite sensing, respectively (Galperin, 2004). The GAF sensory domain was highly conserved in the RsbK homologues and was always found next to, and N-terminally from, the HK phosphotransferase domain. In addition, almost all RsbK homologues contained one to several putative HAMP domains, which are thought to link N-terminal sensory domains with intracellular phosphotransferases (Hulko et al., 2006).

Based on the N-terminal sensory regions, a subdivision could be made into two RsbK-types: type I, containing transmembrane helices and putative membrane-associated extracellular sensory domains (this type includes B. cereus RsbK); and type II, lacking transmembrane helices and containing a multitude of HAMP linker regions (Fig. 2). Even within the two types, high variability was observed between the different N-terminal regions. For example, in Shewanella woodyi two type I RsbK-like HKs were identified (Swoo1960 and Swoo1961), which were highly related in terms of their phosphotransferase and GAF domains, but which displayed marked differences with respect to their N-terminal sensory domains. In type II RsbK homologues, the N-terminal regions showed extreme variability with respect to the number of detected HAMP domains per HK, which ranged from 4 to as many as 14. These findings are in agreement with a previous study in which it was shown that evolutionarily related HKS can contain very different N-terminal regions due to shufflings and duplications of sensory domains (Alm et al., 2006).
A more surprising variability was observed in the number of predicted C-terminal REC domains, which ranged from one in most of the RsbK homologues found in low- and high-GC Gram-positive bacteria to as many as three in some of the other species. When considering the homologues that contained two or three REC domains, the C-terminal REC domain always appeared to be most similar to RsbK REC (~50% identical), while the other REC domains were relatively dissimilar from RsbK REC (~25% identical), the only exception being Mmc1_1215 of Magnetococcus MC-1.

Connecting the RsbK homologues to cognate RR

In addition to RsbK of B. cereus, two of its homologues have been experimentally characterized. These include the type II homologues SCO5748 (OsaA) of Streptomyces coelicolor and MXAN_0712 of Myxococcus xanthus. OsaA of S. coelicolor and its putative cognate RR OsaB have been implicated in function to osmoadaptation, aerial mycelium formation and the coordination of antibiotic production (Bishop et al., 2004), while MXAN_0712 of M. xanthus was shown to be essential in fruiting body formation and sporulation (Shi et al., 2008). To obtain additional information about the potential biological role of the other RsbK homologues, especially with respect to the possible regulation of alternative sigma factors, we analysed the genomic regions surrounding RsbK-encoding genes. Genetic context, especially when found conserved across species, is a strong indicator of the biological role of a gene (Dandekar et al., 1998; Overbeek et al., 1999). Almost all RsbK homologues (~88%) were genomically connected to one or more genes encoding an RR (Fig. 2). The domain composition of these RRs appeared highly variable, ranging from the ‘classical’ composition, containing an N-terminal REC and a C-terminal DNA-binding domain, to ‘atypical’ composition, containing a single REC domain or putative C-terminal guanylate cyclase-, cyclic di-GMP phosphodiesterase- and kinase-type output domains in addition.

Connections of RsbK homologues with CheR and CheB homologues

Interestingly, many RsbK homologues appeared to be genomically associated with genes encoding putative CheR (~60% of the HKs) and CheB homologues (~42%) (Fig. 2 and Supplementary Fig. S5). CheR and CheB have been extensively studied in E. coli and B. subtilis, where they play a role in the adaptation (i.e. sensitization and desensitization) of the chemotaxis machinery to persisting stimuli. CheR is a methyltransferase that methylates specific glutamate residues within methyl-accepting chemotaxis proteins (MCPs), while the methylesterase/deamidase CheB removes methyl groups from these proteins. MCPs function as stimulus receptors that transduce their signals to the chemotaxis regulator CheA. The methylation state of the MCPs influences this signalling activity and consequently influences flagellar rotation (Hazelbauer & Lai, 2010). The observed genomic association between RsbK-type HKs and the CheR/B homologues could imply a role for these HKs in bacterial chemotaxis. However, no evidence for such a role has been found so far. Therefore it is much more likely that the hybrid kinases themselves are the main target of these CheR/B homologues. In MCPs, methylation sites generally appear as glutamate (E) or glutamine (Q) pairs that are located in tandemly repeated heptads within coiled-coil regions. In the case of glutamine, the side chain is deamidated by CheB prior to its participation in the methylation cycle (Hazelbauer & Lai, 2010). Interestingly, sequence analysis of the RsbK homologues indeed revealed the presence of conserved glutamate and glutamine pairs. These conserved pairs were always found between the cytoplasmic GAF domain and the H-box and always occurred in tandemly repeated heptads (Supplementary Fig. S6). In fact, some of these heptads have recently been predicted to constitute a conserved helical domain (Anantharaman et al., 2006). In a previous comparative study of bacterial MCPs (Le Moual & Koshland, 1996), predicted and confirmed methylation sites were assigned to positions ‘b’ and ‘c’ of the ‘a-b-c-d-e-f-g’ heptad repeat, according to the scheme of McLachlan & Stewart (1975). Similarly, we could assign the detected glutamate and glutamine pairs of the RsbK homologues to these positions, which were followed almost invariably by a leucine (L) at position ‘d’ (Fig. 3 and Supplementary Fig. S6). As compared to established methylation heptads in MCPs from E. coli, Salmonella enterica and B. subtilis (Le Moual & Koshland, 1996; Zimmer et al., 2000), the heptads found in the RsbK homologues appeared to be different at positions ‘a-d-e-f-g’. However, a recent study on Thermotoga maritima MCPs has revealed that CheR-mediated methylation heptads can indeed be distinct from the E. coli, S. enterica and B. subtilis consensus (Perez et al., 2006) (Fig. 3).

On the basis of the above data, we conclude that the sensitivity of RsbK-type HKs to environmental signals probably can be modulated via CheB/B-homologue-mediated methylation/demethylation. This hypothesis is supported by the fact that the RsbK homologues that are genomically associated with the CheR/B homologues generally contain more putative methylatable pairs at the ‘b-c’ positions than those that are not associated with the CheR/B homologues (an average of 4.7 pairs per protein versus 2.2 pairs per protein, respectively; Supplementary Fig. S5).

RsbK homologues found in Gram-positive bacteria are connected to σB

The gene context analysis revealed that besides rsbK in the B. cereus group, several rsbK homologues found in low- and high-GC Gram-positive bacteria are located in gene clusters encoding one to several proteins related to the σB-mediated stress response. The clusters included genes...
encoding PP2C-type phosphatases, RsbV, RsbW, RsbR, RsbS and RsbT. Moreover, four of these gene clusters (excluding \textit{B. cereus}) also encode a putative $\sigma^B$-like sigma factor (Fig. 2). Some of the \textit{rsbK} homologues, such as \textit{fraa}l6455 in \textit{Frankia alni} ACN14a, were found in gene clusters that encode a single putative $\sigma^R$-related regulator, while other \textit{rsbK} homologues are located in gene clusters that encode multiple partner-switching proteins for the potential control of $\sigma^B$ activity. For example, in \textit{Streptomyces coelicolor} the \textit{rsbK} homologue \textit{isco}7327 is located in a gene cluster that encodes as many as three potential PP2C-type phosphatases, an anti-sigma factor antagonist (RsbV), an RsbRST module and the alternative sigma factor $\sigma^M$, which is related to $\sigma^B$ (Lee et al., 2005). In addition, one of the PP2C phosphatases was found to be fused to an N-terminal ATPase and thus could function as an anti-sigma factor.

Another interesting gene cluster is present in \textit{Geobacillus Y412MC10}, where the \textit{rsbK} homologue \textit{gymc}10\_5554 directly flanks an \textit{rsbY}-like gene, similar to what is found in the \textit{B. cereus} group. Other genes in its direct neighbourhood are \textit{rsbV}, \textit{rsbW} and \textit{sigB}, but also yflT and \textit{corA}. The latter two genes encode a putative general stress protein and an Mg$^{2+}$/Co$^{2+}$ transporter, respectively. In fact, the orthologues of these genes in \textit{B. cereus} (\textit{bc}9998 and \textit{bc}3129, respectively) have been implicated previously in the $\sigma^B$-mediated stress response (de Been et al., 2010). Finally, the \textit{rsbK} homologue \textit{Pjdr2\_1827} of \textit{Paenibacillus JDR-2} is likely to be involved in $\sigma^B$ regulation because it is associated with \textit{rsbW} and \textit{sigB} and because the \textit{Paenibacillus} genome harbours an operon encoding \textit{RsbY} (\textit{Pjdr2\_1863}), \textit{RsbV}, \textit{RsbW} and \textit{YflT}. This operon has probably ‘jumped’ to another location in the genome, as it is flanked by putative transposase- and integrase-encoding elements.

**Novel activation routes for $\sigma^B$ in Gram-positive bacteria**

As described above, the \textit{RsbK}-type HK OsaA and its putative cognate RR OsaB of \textit{Streptomyces coelicolor} have been implicated in osmoadaptation, cellular differentiation and the production of antibiotics (Bishop et al., 2004). In \textit{S. coelicolor}, these processes are also controlled by a seemingly complex network of $\sigma^B$-like sigma factors (Cho et al., 2001; Lee et al., 2005; Viollier et al., 2003). Indeed, experimental support for a functional link between OsaAB and a $\sigma^B$-like sigma factor (in this case $\sigma^B$ itself) was recently provided (Fernández Martínez et al., 2009). It was shown that \textit{osaC}, which flanks \textit{osaA} and \textit{osaB} and is divergently transcribed from \textit{osaA}, encodes a regulatory protein that contains an N-terminal RsbW-like domain, followed by PAS and GAF sensory domains and a PP2C-type phosphatase domain. The OsaC RsbW-like domain was demonstrated to interact with $\sigma^B$ and to function as a $\sigma^B$ anti-sigma factor. Furthermore, it was found that \textit{osaB} is induced upon osmotic shock in a $\sigma^B$-dependent manner and that OsaC is essential for returning \textit{osaB} and \textit{sigB} expression levels back to ‘normal’ after osmotic shock (Fernández Martínez et al., 2009).

Besides OsaC, another ‘more classical’ \textit{RsbW} protein has been characterized in \textit{S. coelicolor}. This protein (RsbA) acts in an RsbVVW-like partner-switching module for the control of $\sigma^B$ (Lee et al., 2004). Whereas \textit{rsbA} is located in the \textit{sigB} operon, \textit{rsbV} is located in a gene cluster encoding multiple putative sigma factor regulators as well as the $\sigma^B$ parologue, $\sigma^M$. Interestingly, this gene cluster also
includes sco7327, the second rsbK homologue of S. coelicolor next to osaA (Fig. 2). These findings indicate a complex regulatory connection between $\sigma^B$ and $\sigma^M$, a connection that has been partly confirmed (Lee et al., 2005). It is possible that SCO7327 controls $\sigma^M$ activity, in conjunction with the genomically associated RsbRST module. However, the fact that it is genomically linked to rsbV may also suggest a role for this RsbK homologue in controlling $\sigma^B$ activity.

Based on the above findings, it seems likely that osaABC encodes one functional module for the (post-osmotic shock) control of $\sigma^B$ and perhaps other related sigma factors. Further support for OsaABC being one functional module comes from the fact that an osaC deletion mutant displayed a phenotype comparable to that of the osaA and osaB deletion mutants, at least with respect to osmoadaptation and cellular differentiation (Fernández Martínez et al., 2009). One question that needs answering is how signals are transferred to OsaC. It has been suggested that OsaB may interact with other proteins via its C-terminal coiled-coil region (Fernández Martínez et al., 2009). Considering this, we propose that after osmotic shock, the RsbK homologue OsaA triggers its partner RR OsaB to transduce its signals to OsaC via direct or indirect protein–protein interactions. In turn, this would activate the OsaC RsbW domain, thus preventing continued activation of $\sigma^B$ (Fig. 1c). Another important question is what the C-terminal PP2C-type phosphatase domain of OsaC is doing. Since the osaC deletion mutant was not disturbed in its induction of $\sigma^B$ upon osmotic shock, the PP2C-type phosphatase domain at least does not seem to dephosphorylate RsbV under those conditions (Fernández Martínez et al., 2009).

The proposed model for $\sigma^B$ regulation in S. coelicolor A3(2) also holds for the high-GC Gram-positive bacteria Streptomyces avermitilis, Streptomyces griseus, Thermobifida fusca, Salinispora tropica, Salinispora arenicola, and several Frankia species, which all contain the OsaABC module. As pointed out in this study, the above actinobacterial modules display strong similarities to the $\sigma^B$-regulating RsbKY module of the B. cereus group and possible other $\sigma^B$-regulating modules of Gram-positive bacteria. This strongly suggests that the use of RsbK/OsaA-type hybrid HKs is a common strategy for Gram-positive bacteria to control the activity of (sigma-like) alternative sigma factors. As summarized in Fig. 1, this strategy is altogether different from the well-characterized $\sigma^B$ activation pathway in B. subtilis.

Conclusions

Based on conserved gene context analysis, we suggest that RsbK(Y)-mediated regulation of alternative sigma factors is not restricted to members of the B. cereus group, but is used by several other low- as well as high-GC Gram-positive bacteria. In addition, we show that RsbK-like hybrid kinases are not restricted to Gram-positive bacteria, but also occur in Proteobacteria, Cyanobacteria and Bacteroidetes. However, it seems that in these phyla the RsbK-type HKs are used for purposes other than the regulation of alternative sigma factors. This finding is similar to what has been observed for the RsbRST-like modules which occur in a wide variety of bacteria, where they appear to interact with different types of downstream signalling modules (Pané-Farré et al., 2005). Most of these downstream modules were found to include hybrid HKs (unrelated to RsbK) with up to two REC domains, indicating complex phophorelays. Interestingly, a universal feature of these downstream modules was the presence of a PP2C-type phosphatase, related to RsbX (Fig. 1a). These findings indicated that the stressosome together with its cognate PP2C-type phosphatase protein function as a ‘core’ module for gathering signals and conveying these to diverse downstream signalling modules (Pané-Farré et al., 2005). As shown in this study, RsbK-type HKs are also often connected to potential complex downstream signalling modules, including different types of RR with additional C-terminal signalling domains. Apparently, RsbRST- and RsbK-like modules provide a common solution to the problem of signal integration in bacteria. However, despite the apparently universal use of these signalling modules across bacteria, considerable variability may arise within these modules. In the case of the RsbK-type HKs, the variability even occurs between homologues that are potentially involved in the same process, as is demonstrated by the difference in N-terminal sensory domains between RsbK and OsaA. The observed variation reflects the different niches in which the associated organisms reside and may illustrate the common yet specific solutions these organisms have evolved for the same process: the control of a stress-responsive alternative sigma factor. Finally, our findings further demonstrate the highly modular nature of sigma factor activation routes and signal transduction routes in general.

References


