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CONTROL OF GENE EXPRESSION IN GRAM-POSITIVE BACTERIA: EXTENSIONS OF AND DEPARTURES FROM ENTERIC PARADIGMS

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1. ABSTRACT

Our introduction to prokaryotic gene expression has always focused on the operon and regulatory mechanisms that operate within enteric bacteria such as *Escherichia coli*, *Salmonella* species, and their phages. While operon organization and many of the components of regulatory networks are conserved in Gram-positive species, there exists unique features that set these organisms apart from the enterics. Two examples are presented herein: carbon catabolite control and regulation of RNA polymerase sigma subunit activity, are presented. The accompanying reviews highlight the diversity and novel aspects of genetic control in Gram-positive bacteria, with descriptions of quorum-sensing systems, transcriptional control, and RNA processing mechanisms.

2. INTRODUCTION

Students of the molecular biomedical sciences, as part of their post-graduate core curricular requirements, are introduced to prokaryotic gene expression and its regulation, a topic incorporated within the broader scope of their biochemistry and molecular biology courses. Emphasis is placed on the organization and control of the operon, with the focus of attention on the *lac* operon of *Escherichia coli*. With prior exposure to the structure and function of RNA polymerase and the mechanisms of transcription initiation, elongation, and termination., a detailed view of gene control emerges as students become familiar with the concepts of negative and positive control and the role of nucleotide sequence-specific DNA-binding proteins. Foundations for genetic analysis and explorations into gene expression were also established through the studies involving the *E. coli* temperate phage lambda and amino acid biosynthesis operons of enteric microorganisms (1, 2). Control systems operating at the levels of transcription initiation, termination, translation and protein stability all were brought to light by these studies. For decades, the original investigations of *E. coli* and phage operon structure and explorations into the control of operon expression have had an enormous influence on how we approached new systems of genetic regulation such as those of confounding complexity that govern eukaryotic gene expression.

Over the past several years, new paradigms of prokaryotic gene regulation have emerged and have found their way into the instruction received by students as they pursue careers in biomedical research. These, again, have their origins in studies of enteric and other Gram-negative bacteria. Two-component regulatory systems of signal transduction (3, 4) were initially characterized in studies of gene expression that is controlled in response to organic nitrogen availability, phosphate limitation, and osmotic stress. Now the sensor, histidine protein kinase and the

response regulator of the two component system are known to represent two vast protein families that extend over more than one hundred species and across kingdom boundaries. Chemical communication amongst individuals within a population of a bacterial species, termed quorum-sensing and originally studied in symbiotic *Vibrio* species, is a phenomenon that is now observed widely among microbial species (5, 6). Quorum-sensing mediated by modified homoserine lactones in Gram-negative bacteria profoundly affects the control of gene expression as it relates to the cell's response to changes in its environment. Cell-cell communication and its effect on the control of prokaryotic gene expression is a topic that has gradually found its way into molecular biology core curricula.

3. GRAM-POSITIVE BACTERIA: NEW PARADIGMS OR VARIATIONS ON ENTERIC THEMES?

Our overall view of operon structure and its expression changes little when attention is turned to Gram-positive bacteria. But in some cases, it has been the study of Gram-positive species that have revealed regulatory devices that were later found to be universal among prokaryotes. A notable example of this is the existence of alternative forms of RNA polymerase, originally discovered in *Bacillus subtilis* cells infected with the lytic phage, SP01 (7-9). It had been known that the sigma subunit conferred upon the RNA polymerase holoenzyme, promoter specificity while reducing its non-specific binding to DNA. But studies of SP01 phage infection revealed that the sigma subunit could be replaced with sigma species that confer entirely different promoter nucleotide sequence specificity. The early and middle genes of SPO1, named according to when during the infection cycle they are expressed, encoded sigma subunits that would interact with core and direct phage-, temporal-specific gene transcription. As predicted from these studies and earlier work, alternative sigma subunits were found that directed the transcription of stress-induced genes and genes required for developmental processes, such as sporulation in *B. subtilis* and motility/chemotaxis in both Gram-negative and Gram-positive species (10, 11). The discovery that heat shock factor of *E. coli* (12) was actually an RNA polymerase sigma subunit lent support to the growing realization that multiple sigma subunits exist within many if not all members of the procarya.

As detailed knowledge of gene expression control in enteric, Gram-negative bacteria accumulated, were there reasons to expect the existence of unique systems of control in Gram-positive bacteria? The distinguishing structural features of the Gram-negative cell envelope and Gram-positve cell wall would suggest that there are substances from the environment that gain access to the cytoplasmic membrane of Gram-positive species that might be excluded by the outer membrane of Gram-negative cells. Hence, Gram-positive species have distinctly different contacts with their environment when compared to Gram-negative bacteria and, very likely as a result, have evolved different capabilities in dealing with environmental change. Even so, as signal transduction networks have been uncovered from a variety of Gram-positive organisms, universal systems like those composed of two-component regulatory proteins, are found to figure prominently in the organization of regulatory networks that are in place to sense environmental changes and activate appropriate responses ((13), See review by Ogura and Tanaka). Nevertheless, unique systems of gene control in Gram-positive organisms have been revealed and characterized in considerable detail. The first example to be described herein is carbon catabolite control, which utilizes similar components as that uncovered in the study of enteric Gram-negatives, but which are employed in distinctly different ways. The second example is the signal transduction system that controls sigma factor activity through protein-protein interaction and O-phosphotransfer, a system that is uniquely Gram-positive but involves reactions that are similar to those observed in eukaryotic signal transduction systems.

4. CARBON CATABOLITE REGULATION

Gram-negative enteric bacteria and several low GC-content Gram-positive species utilize glucose preferentially above other carbon sources. Glucose-6-phosphate is produced when the hexose is transported into the cell via the sugar phosphotransferase system (PTS) (14). When glucose is present, alternative carbon sources are not transported and catabolized. Thus, the transport of glucose via the PTS, has the dual effect of introducing glucose carbon into the glycolytic pathway and participating in the control of other systems of carbon/energy source acquisition. If glucose is not available to undergo import and phosphorylation in *E. coli*, then accumulated phosphorylated $EIIA^{Glc}$ activates adenyl cyclase. The product of the adenyl cyclase-catalyzed reaction, cAMP, accumulates and combines with the CRP (cAMP-receptor protein) forming a complex that interacts with the regulatory sequences of operons whose products function in the utilization of alternative carbon sources. CRP-cAMP recruits RNA polymerase to the promoters, thus stimulating operon transcription. Inducer exclusion, which prevents import of alternative carbon sources, again involves the activity of $EIIA^{Glc}$, as it inhibits transporter by direct protein-protein interaction.

Phosphate that is used to form glucose-6-phosphate and to activate adenyl cyclase is derived from phosphoenolpyruvate and is transferred to the PTS Hpr protein by a reaction catalyzed by PTS enzyme I. Hpr-phosphate interacts with PTS Enzyme II domains A and B, and the phosphate is transferred from Hpr to enzyme II, which utilizes the phosphate to generate glucose-6-phosphate. Enzyme II also contains domain C (and sometimes D), a membrane spanning domain that functions in the transport of glucose. Analysis of the *E. coli* genome reveals at least 21 enzyme II complexes with presumably distinct carbohydrate specificity (15). Three PTS-like domains, encoded by the nitrogen control operon containing *ptsP* gene, the dihydroxyacetone phosphate *dha* operon, and the *bglG* gene encoding the antiterminator for *bgl* operon expression, are believed to serve regulatory roles. The *E. coli* PTS itself is regulated by the transcriptional repressor, Mlc. The *ptsG* gene is subject to

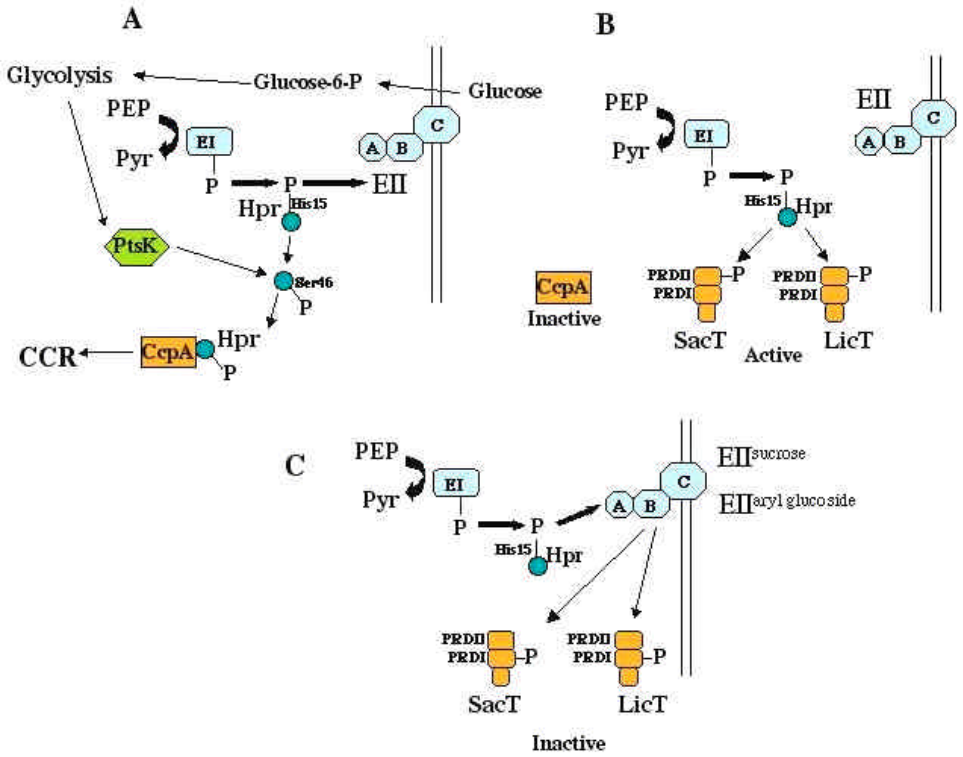

Figure 1. Examples of carbon catabolite control systems in B. subtilis. A. When glucose is present, the PTS system EI,Hpr, EIIABC, function to phosphorylate and transport glucose. Glucose-6-phosphate (Glucose-6-P) enters the glycolytic pathway, intermediates of which activate PtsK, the Hpr kinase/phospatase (PtK). PtsK phosphorylates the conserved Ser of Hpr,which then combines with catabolite control protein (CcpA) to repress the transcription of operons that function in alternative carbon source utilization. B. In the absence of glucose, Hpr phosphate is transferred from the conserved His residue to the PRDII's of the antiterminators LicT and SacT, a reaction that promotes active dimer formation. C. When the inducers of aryl-glucoside or sucrose utilization are not present, the substrate specific EIIA subunits serve to phosphorylate the PRDI's of LicT and SacT, thereby rendering them inactive.

repression by Mlc, which is relieved by glucose-6-phosphate and by sequestration of Mlc which involves the EIIB and C components of PTS (16, 17).

Analysis of the *B. subtilis* genome has uncovered 16 operons encoding PTS systems, indicative of the versatile carbon acquisition capabilities of the soil-inhabiting microorganism (18). In several ways, the glucose-specific PTS of Gram-positives resembles that of enteric organisms. The import of glucose involves the transfer of phosphate from PEP via an enzyme EI-catalyzed reaction, to Hpr. Phosphate is then transferred to EIIAB and finally to glucose. But important differences from the *E. coli* systems have been uncovered that relate to the regulation of carbon source utilization. It has long been known that Gram-positive organisms do not produce cAMP as a cofactor for carbon catabolite control. While CRP homologs exist in Gram-positive bacteria (19), none of these function in regulating carbon source utilization. There are three features that distinguish low GC Gram positive organisms from the enteric, Gram-negatives with respect to carbon catabolite control. First, the Hpr protein is modified by an Hpr kinase/phosphatase at a conserved Ser residue in response to active glycolysis (20). This generates a form of Hpr that can participate directly in the transcriptional control of carbon-utilization operons and in inducer exclusion 21-23). Secondly, many of the operons whose products are required for alternative carbon source uptake and catabolism are under direct negative control of a LacI/GalR homolog, CcpA (24), the activity of which appears to be enhanced by the direct interaction with Hpr(Ser46)-phosphate (21, 22) (Figure 1A). And third, there are numerous carbon catabolite regulators controlling several utilization systems that contain PTS-like regulatory domains, or PRD's (25). These share homology with PTS EII domains and are the targets of PTS-dependent phosphorylation.

Glucose is imported via the glucose PTS resulting in the passage of a high energy phosphate from PEP through Hpr and enzyme II, where it is used to generate the first metabolite to enter the glycolytic pathway, glucose-6-phosphate. Hpr is phosphorylated by EI at the highly conserved His15 residue, but the phosphate is rapidly transferred to EII. In the nonphosphorylated form, Hpr can undergo phosphorylation at Ser46 by Hpr kinase/phosphatase (Figure 1A). During active glycolysis, the intermediates, notably fructose-1,6-bisphosphate and

glycerate-2-phosphate, activate the Hpr kinase/phosphatase (26), Hpr(Ser46)-phosphate has been shown to interact with the transcriptional repressor, CcpA, thus stimulating its non-cooperative interaction with target DNA. While Hpr(Ser46)-phosphate is thought to be the CcpA cofactor, certain glycolytic intermediates and NADP have been implicated in the modulation of CcpA activity (27, 28).

Several operons that function in the utilization of alternative carbon sources are subject to CcpA-dependent repression in Gram-positive microorganisms. Each one bears a catabolite-responsive element or *cre* within their transcription initiation regions (24, 29). The *cre* is a conserved sequence of approximate dyad symmetry that interacts with the N-terminal helix-turn-helix domains of CcpA dimers (30, 31). Thus, the *bglPH* (β-glucoside), *acu* (acetoin utilization), and *amyE* (amylase) operons all have cre's within the promoter regions, where CcpA interaction reduces access to the promoter by RNA polymerase holoenzyme. Activated CcpA can also stimulate transcription from operons that function in the formation of glycolytic endproducts, such as acetic acid and lactic acid, which are produced during "overflow" metabolism of glucose carbon (32-34). The *cre*'s of the *pta* (phospo transacetylase) and *ackA* (acetate kinase) genes are situated upstream of the promoters, where CcpA binding assists in RNA polymerase promoter interaction.

There are also operon-specific regulatory factors whose activity is influenced by elements of the glucose-PTS system. Both *sacPA* (sucrose) and *bglPH* (β-glucoside) are controlled at the level of transcriptional antitermination by two RNA binding proteins, SacT and LicT, respectively (35-38) (Figure 1B). In the 5' leader regions of *sacPA* and *bglPH* RNA's are rho-independent terminators, the formation of which is controlled by RAT (ribonucleic antiterminator) sequences (39, 40). The RAT sequence is the target of the cognate antiterminator proteins, which prevent terminator formation, thus allowing transcription to proceed through the downstream ORFs. Both antiterminators have two PRDs, one of which, PRDII, is the EII-like domain that is the direct target of phosphorylation by Hpr(His15)-phosphate (35, 41, 42) (Figure 1B). When glucose concentration is low, Hpr(His15)-phosphate accumulates, which increases the frequency of productive interactions with the SacT and LicT antiterminators resulting in phosphorylation at conserved histidine residues. When glucose becomes available, Hpr(His15)-phosphate is diverted to the glucosePTS EII for the import and phosphorylation of glucose, thereby reducing the Hpr-phosphate available for activating SacT and LicT (43-45). The PRD-I of the antiterminator is the site of carbon source-specific negative control that is targeted by enzyme II-dependent phosphorylation (45). Thus, $PTS^{sucrose}$ EII, when sucrose is not available, donates a phosphate to a conserved His residue of SacT PRD-1, which inactivates SacT and allows the terminator to form in the *sacPA* leader RNA. Likewise, LicT is inactivated by the aryl-β glucoside PTS component EIIB by phosphorylation of the PRD1 of the antiterminator (Figure 1C). The phosphorylation is thought to also facilitate interaction of LicT with EII^{Bgl} resulting in the sequestration of the antiterminator in an inactive complex . Other PRD-containing regulators do not fit this model of control, however. The SacY, an antiterminator that activates *sacB*, encoding the enzyme levanase, and *sacXY* which encode components of a sucrose PTS, does not require Hpr-mediated phosphorylation for activity (46).

The elements and trans-acting factors of carbon catabolite control show some conservation among low GC content Gram-positive bacteria. The RNA binding domain, catabolite antiterminator or CAT domain, is shared among at least 12 proteins from both Gram-positive and Gram-negative species (40). The CAT domains can dimerize without PRDI and II. Each monomer is composed of 4 antiparallel β strands, and the dimer forms an eight-stranded β-barrel. The residues within the loops connecting the β-strands contact the nucleotides within the minor groove in a part of the RAT hairpin helix that lies between two nucleotide bulges. Phosphorylation of the PRDII of LicT results in dimer closure and stabilization both at the opposing CAT and PRDI domains (41). Phosphorylation at the PRDI domains result in opening at the CAT dimer interface and disruption of the RAT-binding surface.

5. SIGNAL TRANSDUCTION AND ALTERNATIVE FORMS OF RNA POLYMERASE

The role of alternative sigma subunits in global transcriptional regulation has been described more fully in studies of the *Bacillus subtilis* system (47). Genetics and genomic analysis has expanded the estimated number of sigma subunits encoded by the *B. subtilis* genome to seventeen. While some have not been assigned a regulatory function, those required for the transcription of motility genes as well as those required for sporulation and the general stress response have been characterized in some detail.

5.1. Activation of sigma-F in *B. subtilis* sporulation

Five sigma subunits are required for sporulation in *B. subtilis*, with sigma(H) (SigH) being necessary for the transcription of genes at the earliest stage, stage 0; a time when the comparment-specific transcription of sporulation genes begins to be established (48, 49). The formation of the forespore compartment, which will develop into the mature spore, is initiated by the assembly of the sporulation septum, a cell division septum that is positioned at one end of the cell. SigH specific transcription is necessary for the production of gene products that direct the assembly of the sporulation division septum, and is also required for the production of sigma(F) (SigF) encoded by the *spoIIA* operon (50, 51). SigF is active only in the forespore compartment as its activity is inhibited by the anti sigma factor, SpoIIAB, also encoded by the *spoIIA* operon (52, 53) (Figure 2A). SpoIIAB binds to sigma(F) as a dimer (54) but is itself subject to negative control by an inhibitor, the anti-anti sigma factor SpoIIAA, which through its interaction with SpoIIAB releases SigF so that it can associate with core RNAP (55). SpoIIAB can bind to either SigF or SpoIIAA, the decision being influenced by the phosphorylated state of SpoIIAA. SpoIIAB is a member of a family of serine kinases that function in controlling sigma

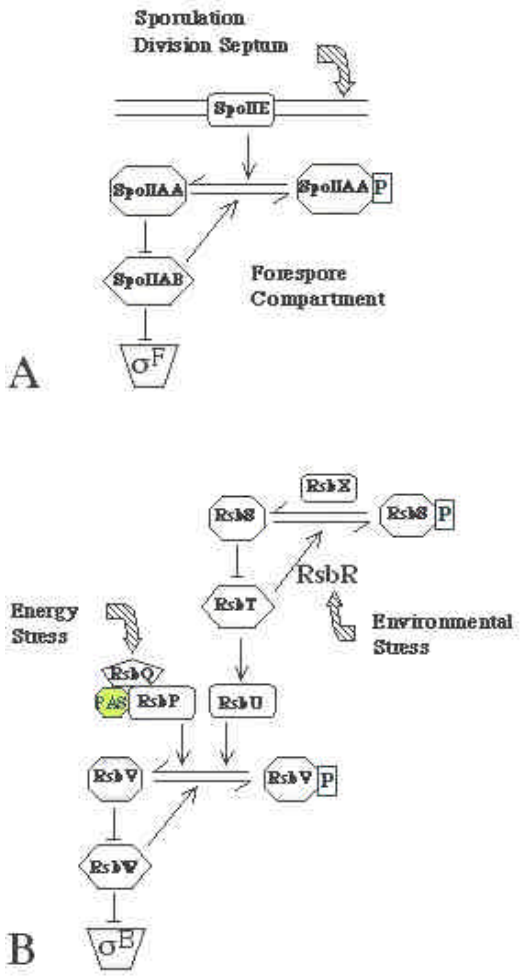

Figure 2. Signal transduction and phospho-transfer reactions that modulate anti-Sigma/Sigma factor interactions. A. Sigma factor F (σF) is inactive due to the interaction with the anti-sigma factor SpoIIAB. Anti-sigma/Sigma F interaction is prevented by the anti-anti-sigma protein SpoIIAA, but SpoIIAB is also a kinase and SpoIIAA is inactivated by SpoIIAB-dependent phosphorylation. Formation of the sporulation septum results in the membrane localization of the SpoIIE protein, a phosphatase specific for SpoIIAA. Dephosphorylation promotes SpoIIAA/SpoIIAB interaction and release of active Sigma F. B. Two separate pathways of activation for the Sigma factor B, which mediates part of the stress response in Gram-positive bacteria. RsbW is the anti-sigma that renders Sigma B (σB) inactive. The anti-anti-Sigma RsbV prevents RsbW/Sigma B interaction. RsbW, also a protein kinase, inactivates RsbV, but RsbV can be reactivated by dephosphorylation that is catalyzed by one of two protein phosphatases, RsbP and RsbU. RsbP is activated in response to energy stress and bears an N-terminal PAS domain. It requires the interaction of RsbQ. RsbU activity is stimulated by RsbT, which is subject to negative control by the interaction of RsbS. RsbT is also a protein kinase that inactivates RsbS. RsbT kinase activity is modulated by a family of regulatory proteins, homologs of RsbR, that function in the cell's response to stress.

factor activity. SpoIIAA is a substrate for SpoIIAB-catalyzed phosphorylation, resulting in its inactivation. Thus, when ATP is abundant, SpoIIAB is able to inactivate its inhibitor, SpoIIAA, freeing itself to complex with SigF. But SpoIIAA can be dephosphorylated when the sporulation septum is erected. This morphological checkpoint is made possible by a membrane bound phosphatase, SpoIIE, that is anchored to the septal membrane (56, 57) (Figure 2A). The phosphatase is specific to SpoIIAA-phosphate, and catalyzes dephosphorylation to convert SpoIIAA to an active form, able to bind to SpoIIAB. SpoIIAB itself is subject to proteolytic control by the ATP-dependent protease ClpCP, but only when it is not complexed with either SpoIIAA or SigF. ClpCP is known to participate in proteolytic control during the process of competence development (58). In the forespore compartment, one can imagine that it degrades SpoIIAB when SpoIIAA-phosphate is released from the SpoIIAB-AA complex (59).

5.2. Sigma activation and the stress response

In prokaryotic cells, the stress response, the collection of processes that are induced under harsh environmental conditions, is characterized by global changes in the transcriptional "cross-section" and the accumulation of gene products that are required to eliminate or repair damaged and denatured protein. Situations that induce the stress response include encounters with toxic chemical and physical agents, but the most thoroughly studied condition, as related to the bacterial stress response, is heat shock. Here, again, significant differences exist when enteric Gram-negative and Gram-positive bacterial species are compared, but in both groups the regulation of genes required for the heat shock response involves changes to the composition of RNA polymerase holoenzyme. In *E. coli*, the product of *rpoH*, the RNA polymerase sigma subunit, SigH, becomes active when the chaperone proteins (DnaK, DnaJ, GrpE) that sequester it are titrated by denatured proteins which accumulate upon exposure to elevated temperatures (60). The transcription of *rpoH* is also stimulated when another sigma subunit, SigE, becomes active. SigE is released from a membrane-associated inhibitory complex when heat shock causes protein damage in the periplasm (61-64). The dual effects of heightened *rpoH* transcriptional activity and the release of active SigH results in the SigH-dependent transcriptional activation of genes whose products function in the repair and disposal of damaged protein. Such genes encode ATP-dependent proteases that eliminate damaged proteins and molecular chaperones that dissociate inactive aggregates of proteins and allow proper refolding of polypeptide chains.

The general stress sigma factor, SigB, is regulated by a complex collection of SpoIIAA-, AB-, and SpoIIE-like proteins in Gram-positive bacteria (65). In *B. subtilis*, the *sigB* gene resides in an operon with *rsbR*, *S*, *T*, *U*, *V*, *W* and *X*, all of which function in the regulation of SigB (66, 67). RsbW is the anti-SigB that is inhibited by the anti-anti-sigma factor RsbV (68, 69). As in the case with the SigF control system, RsbW is a kinase that catalyzes the phosphorylation of RsbV, a SpoIIAA

homolog, rendering it inactive (Figure 2B). But a phosphatase, RsbU, in a manner similar to that of SpoIIE, can remove the phosphate from RsbV, allowing it to target the anti sigma factor RsbW (70, 71). It is the control of the RsbV phosphorylation state in response to energy, physical or chemical stress that is focal point for SigB control.

Two converging pathways exert control over RsbU activity (72). RsbT stimulates RsbU but it is subject to inhibition by RsbS. Here again, RsbT is a kinase that can inactivate RsbS by phosphorylation (70, 71) (Figure 2B). The kinase activity of RsbT is controlled by RsbR, and possibly by a collection of RsbR homologs, genes for which were identified through analysis of the *B. subtilis* genome (73, 74). These proteins are thought to participate in sensing encounters with harsh physical or chemical agents, or the biochemical consequences of such encounters. Might there be a structure in the cell where stress is “felt”? Studies from Haldenwang’s group have provided evidence that the ribosome might be the location where cells perceive the consequences of harsh environmental conditions (75, 76). The essential GTPase, Obg, is required for the activation of SigB, a requirement that can be overcome by overexpressing *rsbT*. Obg is bound to ribosomal protein L13 of the 50S subunit, in which L11, another protein required for SigB activation, resides. All three proteins co-localize with the ribosome and with RsbR, suggesting an interaction amongst RsbR proteins, Obg, and the ribosome. This complex stimulates RsbT kinase activity, resulting in the inactivation of RsbS. Active RsbT would now accumulate and stimulate, through direct protein-protein interaction, the RsbU phosphatase.

Energy stress, the depletion of intracellular ATP, also stimulates SigB activity but through a system that is distinct from the RsbRSTU pathway. Energy stress activates a PAS domain protein RsbP that, like RsbU, dephosphorylates RsbV so that the RsbV-RsbW complex can form, thereby releasing SigB (77, 78) (Figure 2B). The PAS domain (Period circadian protein, Ah receptor nuclear translocator protein, Single-minded protein) superfamily transducers function in cells' responses to light, O_2, and redox potential and exist in both eukaryotes and prokaryotes (79). RsbP activity requires a member of the α/β hydrolase family, RsbQ, which directly interacts with RsbP (80). It is not known at present how ATP concentration affects the operation of the RsbPQ system.

The SigF and SigB activating systems utilize members of the PPM family of Mn2+/Mg2+-requiring protein phosphatases, specifically those of the low molecular weight PP2C group (81). RsbP and RsbU and the sporulation-specific SpoIIE proteins are all PP2C members and target the Ser O-phosphorylation sites of their substrates, RsbV and SpoIIAA, respectively.

The current model for describing the activation of SigB is incomplete and some of what has been assembled is still awaiting experimental confirmation. But homologs of the proteins that function in SigB regulation are found in other Gram-positive bacteria in which SigB is known to function. For example, all of the *rsb* genes are present in the food-borne pathogen, *Listeria monocytogenes* (82), where they function in processes associated with the stress response, including the uptake of osmoprotectants under conditions of high osmotic strength (82-84). In *Staphylococcus aureus*, only the genes encoding RsbU, RsbV, RsbW, and SigB are present (85-88). RsbU is a major regulator of RsbV, but as in the case of *Bacillus subtilis*, there likely exists an RsbU-independent mechanism of controlling the phosphorylation state of RsbV (89). Acidic pH was observed to stimulate SigB activity, which was in keeping with the previously established association of SigB activity with the cell's stress response (89). By examining the phenotype of *sigB* and *rsb* mutants and controlling the level of SigB using a tetracycline inducible system (90), it was shown that *sigB* is necessary for micro-colony formation on solid surfaces, a prerequisite for biofilm development. SigB also exerts negative control over the production of alpha-hemolysin, which is a result of SigB-dependent transcription of *sarA* that encodes a global transcriptional regulator (see review by Cheung and Zhang). Both pigment and virulence associated protease production require SigB activity. Studies of *S. epidermidis sigB* showed that deletion of the *sigB* gene resulted in profound changes to the profile of exoproteins as revealed by SDS-PAGE and assay of exoprotease and lipase activities (87, 91).

Somewhat surprisingly, *Bacillus anthracis* possesses a *sigB* operon that resembles the *spoIIA* operon, with only the *rsbV* and *W* genes contained within (92). Thus, it more closely resembles the operon of *S. aureus* than that of *B. subtilis*. A homolog of *rsbP* is present in the *B. anthracis* genome, suggesting that SigB is regulated by energy stress in this organism. Examination of *sigB* and *sigB*-dependent expression shows that SigB is active in stationary phase and upon exposure to high temperature, in accordance with the conserved role of SigB in participating in the cell's stress response. But the absence of *rsbX* and *rsbR* homologs suggests different mechanisms controlling the RsbV phosphorylation state.

6. CONCLUSION

The continued investigation of gene expression and its control in Gram-positive bacteria will no doubt uncover more novel and interesting mechanisms of genetic regulation. The reviews included in this compendium for Frontiers in Bioscience cover several unique systems of regulation that share little with the enteric organisms which we have historically associated with the universal systems of gene control. Three of the articles deal directly with extracellular control mediated by low molecular weight signaling molecules. The review by Horinouchi summarizes recent progress in uncovering the signaling pathway activated by A-factor, or butyrolactone, in *Streptomyces* sp. Havarstein and Claverys report the recent findings from studies of the classic *Streptococcus pneumoniae* genetic transformation system, the establishment of which is controlled by extracellular signaling peptides. Pottathil and Lazazzera examine the unique phosphatase/peptide Rap/Phr system of extracellular control that has been uncovered in *Bacillus*. The article by

Cheung and Zhang outlines the complex array of signal transduction systems governing virulence determinants in *Staphylococcus aureus.* Ogura and Tanaka provide a glimpse of the two-component regulatory systems of *Bacillus subtilis* that were characterized through genomic and microarray analyses. The systems described in the above mentioned articles exert their effects primarily on transcription initiation, but the last two the articles focus on post-transcription initiation events. Grundy and Henkin review their characterization of the T- and S-box transcription antitermination control mechanisms found in the amino acid biosynthesis operons of several low GC content Gram-positive species. Klein and Dunny remind us that introns of the group II variety exist in the genes of certain prokaryotic species. Their review focuses on those of the Gram-positive Lactococci. They further describe their unique function as transposable elements. Collectively the articles confirm what many of us believed for some time that the Gram positive group of bacteria is a rich source of novel and interesting systems of genetic regulation deserving the same attention as that which had been paid to *Escherichia coli* and *Salmonella*.

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