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Strategies to adapt cellular processes to nutrient availability in bacteria

Elodie Foulquier[1], Thierry Doan[1], Frederique Pompeo[1], Anne Galinier[1]

[1]From Laboratoire de Chimie Bacterienne, UPR 9043, IFR 88, CNRS, Universite de la Mediterranee, 31 chemin Joseph Aiguier, 13402 Marseille Cedex 20, France

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1. ABSTRACT

Bacteria are able to adapt to nutrient availability in the environment. For example, when nutritional conditions are not favorable, bacterial size can be reduced and duplication time can be significantly extended in comparison to rich growth conditions. These observations suggest that essential cellular processes like cell division, morphogenesis and chromosome dynamics are highly coordinated with central metabolism to ensure the production of fit progeny. The aim of this review is to provide an overview extending from physiological observations done more than fifty years ago to recent discoveries showing strategies to control essential functions in relation with metabolism in the model bacterium *Bacillus subtilis.*

2. INTRODUCTION

Our understanding of the molecular mechanisms driving cell-wide processes in bacteria has exploded in the past decade, fueled by technological advances in global approaches like genomics, proteomics, high-resolution fluorescence microscopy and high-throughput techniques (1, 2). These processes include how cells generate and maintain their shape, how they divide, and how chromosome replication and segregation are coordinated with division. Thus, bacteria have progressed from the status of "bags of enzymes" to "highly organized organisms" in which processes are spatially and temporally controlled along the cell cycle.

To ensure the production of viable descendants, key cellular processes, like cell division, cell elongation, and chromosome replication and segregation all have to be directly or indirectly coupled to nutrient availability (3). Bacterial cells have developed a variety of strategies to adjust metabolism and key cellular processes in response to changes of nutritional conditions. These changes affect the pools of metabolic precursors and the synthesis of cellular macromolecules. One well-established strategy used by the cell to compensate for these differences is by limiting their effects through feedback inhibition mechanisms like the inhibition or the absence of activation of gene expression. For example, in response to high glucose concentration, global transcriptional regulators, such as CRP in *Escherichia coli* or CcpA in *Bacillus subtilis*, regulate the expression of many genes (4). In particular, they inhibit or do not activate the expression of genes involved in utilization of others carbon sources. Furthermore, in response to carbon, nitrogen, phosphate or amino acid deprivation, bacteria synthesize the alarmones pppGpp and ppGpp. These small molecules repress ribosomal RNA synthesis and DNA replication, and regulate the transcription of many genes in the cell in order to coordinate a global response to these stringent conditions and thus to promote survival until nutrient conditions improve (5). The molecular mechanisms involved in all the adaptation responses mentioned in this introduction section will be developed below.

To transmit environmental signals within the cell, bacteria can sense variations in the concentration of metabolic intermediates, like fructose-1,6-bisphophate in *B. subtilis* (6), or nucleotides used as second messengers (7). For example, the level of cAMP controls carbon catabolite repression (CCR) in *E. coli.* Similarly, the molecule (p)ppGpp drives the stringent response in many bacteria (8, 9). The function of all these molecules can be intimately connected. For example, in *E. coli*, the control of motility (versus adhesion) mainly involves a second messenger, c-di-GMP but also involves ppGpp and cAMP at different points of a regulatory network (10).

Global mechanisms of adaptation, such as CCR or the stringent response, mainly affect the level of protein synthesis within the cell and are relatively well described. However, in the past five years, alternative mechanisms employed in bacteria have been discovered. These mechanisms involve the direct regulation of cellular processes by metabolic sensor proteins. These regulators are often metabolic enzymes that are able to sense different metabolic conditions, and in turn, directly modulate the activity of key proteins involved in cellular processes. Few evidence supporting the role of these metabolic coordinators have been revealed so far. It was known for a long time that doubling time varies drastically from a rich growth medium, typically 20 to 25 min for *B. subtilis*, to several hours in nutrient limited conditions. In a less manifest manner, cell size is also dependent on carbon availability: *B. subtilis* cells are longer in a rich medium even though division rate is high (11). In fact, division appears slowed down relative to cell elongation in rich medium. It has recently been discovered that the UgtP protein delays cell division in rich medium by inhibiting the assembly of the division apparatus (12).

The bacterium *B. subtilis* aim of this review is to summarize old and new findings concerning the strategies developed by the gram-positive to generate a global cellular response and to keep key cellular processes in tune with metabolism.

3. THE FIRST DISCOVERED REGULATORY MECHANISMS OF ADAPTATION TO NUTRIENT VARIATIONS

To adapt to environmental changes, bacteria have developed mechanisms that permit coordinated responses. The common feature of a global response is the modulation of protein synthesis or transcription of multiple genes involved in a variety of cellular processes using pleiotropic regulators. This review is not aimed at describing all these global responses and the mechanisms of their corresponding regulators; we chose to focus on the transcriptional regulator CcpA (13), that mediates CCR. To cap it all, some of these global transcriptional regulators (CcpA, TnrA and CodY), whose activity is mediated by signaling metabolites (fructose-1,6-bisphosphate, citrate, GTP and isoleucine or valine), are integrated into a large regulatory network (the interested reader can find more information in (14)). Our understanding of these networks has increased in the last ten years with the advent of transcriptomic and proteomic approaches. In particular, these tools are useful to determine the extent of these global responses (15, 16). In *B. subtilis*, these “omic” approaches were used to study CCR and glucose starvation (17-19) and the stringent response (20).

3.1. Carbon catabolite regulation

CCR allows bacteria to use carbon sources in a hierarchical manner. In other words, when bacteria are exposed to two or more carbon sources, one of them is often preferentially utilized, frequently glucose (4). This serves to optimize metabolism by regulating sugar transport and metabolic pathways. Thus, waste is limited and bacteria improve their competitiveness.

CCR is often mediated by several regulatory mechanisms, including transcriptional regulation and control of translation by RNA-binding proteins (21). It was discovered in the early 1940s in *B. subtilis* and termed “diauxic phenomenon” by Jacques Monod (22) but the general CCR machineries were deciphered in the 1970s in *E. coli* (23) and in the 1990s in *B. subtilis* (24, 25). In fact, the molecular mechanism driving CCR in Enterobacteria and in Firmicutes are different. In particular, the metabolites, whose intracellular levels regulate CCR, are cAMP in *E. coli* and fructose-1,6-bisphosphate (FBP) in *B. subtilis*. In both species, CCR involves a global mechanism and several operon-specific regulatory mechanisms. In *E. coli*, CCR is mediated by the prevention of transcriptional activation of catabolic genes in the presence of glucose. By contrast, in *B. subtilis*, CCR is mediated by negative regulation through a repressor protein in the presence of glucose. Although the mechanisms of CCR differ in these

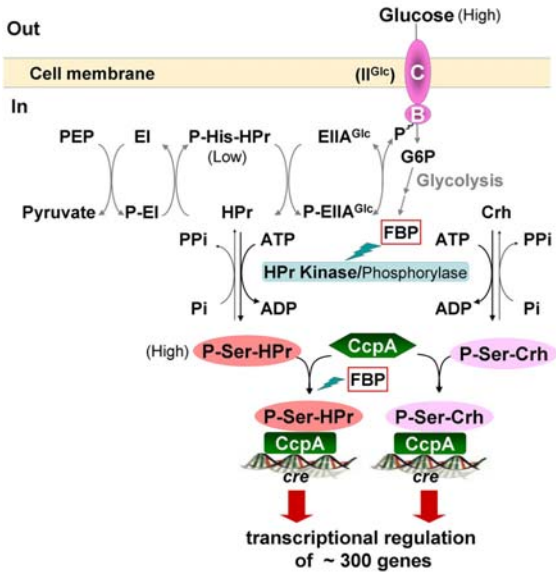

Figure 1. The main mechanism of catabolite regulation in *B. subtilis*. The uptake of rapidly carbon sources like glucose induces an increase of intracellular pool of fructose-1,6-bisphosphate (71). This metabolite stimulates the ATP dependent phosphorylation of HPr and Crh by the HPr kinase/phosphorylase (26) and the interaction between P-Ser-HPr and CcpA (29). Only these phosphorylated forms of Crh and HPr can interact to CcpA (6). The two protein complexes (P-Ser-HPr/CcpA and P-Ser-Crh/CcpA) can interact with the *cre* sequences and then control expression of many genes (17).

two microorganisms, components of the phosphoenolpyruvate: carbohydrate phosphotransferase system (PTS) and protein phosphorylation play an essential role in CCR (4).

In *B. subtilis*, the main mechanism of CCR is pleiotropic and is mediated by the global transcriptional regulator CcpA (13) (see below). Several operon-specific regulatory mechanisms also exist but they only concern operons or genes involved in carbohydrate utilization (4, 21). We will not describe these specific mechanisms since the topic of this review concerns the strategies that *B. subtilis* use to generate a global adaptation in response to the variation of nutrient availability.

In addition to CcpA, the main CCR mechanism requires the phosphorylation of HPr, a component of the PTS, and of its homolog Crh (Figure 1). The level of phosphorylation of HPr and Crh is directly connected to the concentration of FBP in the cell. This metabolite activates the HPr kinase/phosphorylase responsible of the phosphorylation/dephosphorylation of HPr or Crh (26). Then, in a seryl-phosphorylated form, HPr or Crh interacts with CcpA and this complex binds to catabolite responsive elements (*cre*) of target operons to control their expression (27, 28). In addition, FBP was shown to increase the affinity of seryl-phosphorylated HPr to CcpA (29). An *in silico* search for *cre* sequences in the *B. subtilis* genome suggested the presence of 126 (predicted and characterized) *cre* sequences (30). Furthermore, a transcriptomic comparison between a *ccpA* mutant and a wild-type strain suggested that glucose-dependent regulation via CcpA affects the expression of about 300 genes (17, 18, 31), about 10% of the *B. subtilis* whole genome. Most of these genes are involved in carbon source utilization, however, interestingly, CCR is also regulates several other genes that are involved in different processes. Indeed genes implicated in nitrogen or phosphate metabolism, biosynthesis of branched-chain amino acids, respiration, and stress responses are also regulated by CcpA in response of the presence of glucose (31, 32). The extend of the CCR was surprising because it is not only confined to a hierarchical sugar utilization, as it was initially described, but also to a coordinated cellular response that largely influences several key cellular processes.

3.2. The stringent response

Bacteria possess another global regulatory mechanism that operates in response to carbon, nitrogen, phosphate or amino acid deprivation: the stringent response (9). In summary, this nutritional stress response consists in growth arrest and activation of survival processes. It is controlled by the rapid synthesis of the alarmones pppGpp and ppGpp (8, 33, 34). Almost all bacteria are capable of a stringent response and possess (p)ppGpp synthetases (35). However, the molecular mechanisms involved in (p)ppGpp synthesis and degradation, and the molecular function of (p)ppGpp differ, especially between Firmicutes and Proteobacteria (36).

In all bacteria, (p)ppGpp is synthesized under conditions of amino acid deprivation. In Proteobacteria, it can be synthesized by the bifunctional SpoT enzyme (37). Otherwise, accumulation of uncharged tRNAs at the ribosome activates the (p)ppGpp synthase RelA (38). In Firmicutes, (p)ppGpp is synthesized by the Rsh enzyme (for RelA SpoT homologue) whose putative regulation by ribosomes/uncharged tRNA interaction is unclear. (p)ppGpp can additionally be provided by small alarmone synthetases (SASs) RelP and RelQ (39). These enzymes lack a signaling domain and thus regulation presumably occurs at the transcriptional level.

Our review focuses on *B. subtilis*. In this bacterium, the bifunctional enzyme Rsh can both synthesize and degrade (p)ppGpp, whereas RelP and RelQ are only responsible of (p)ppGpp production. Elevated concentrations of these signaling molecules regulate many aspects of microbial physiology, including growth, adaptation, secondary metabolism, cell division and competence (9). However, despite 40 years of research on these molecules, some molecular functions of (p)ppGpp remain unclear. Upon amino acid deprivation, (p)ppGpp is synthesized and accumulates in the cell, causing many intracellular adaptative responses (Figure 2). Transcriptomic and proteomic studies have confirmed that the stringent response affects many cellular processes. In particular, it inhibits reactions specifically involved in growth like ribosome synthesis, DNA synthesis and cell wall synthesis (20). Below, we describe how ppGpp regulates these essential cellular biological processes in *B.*

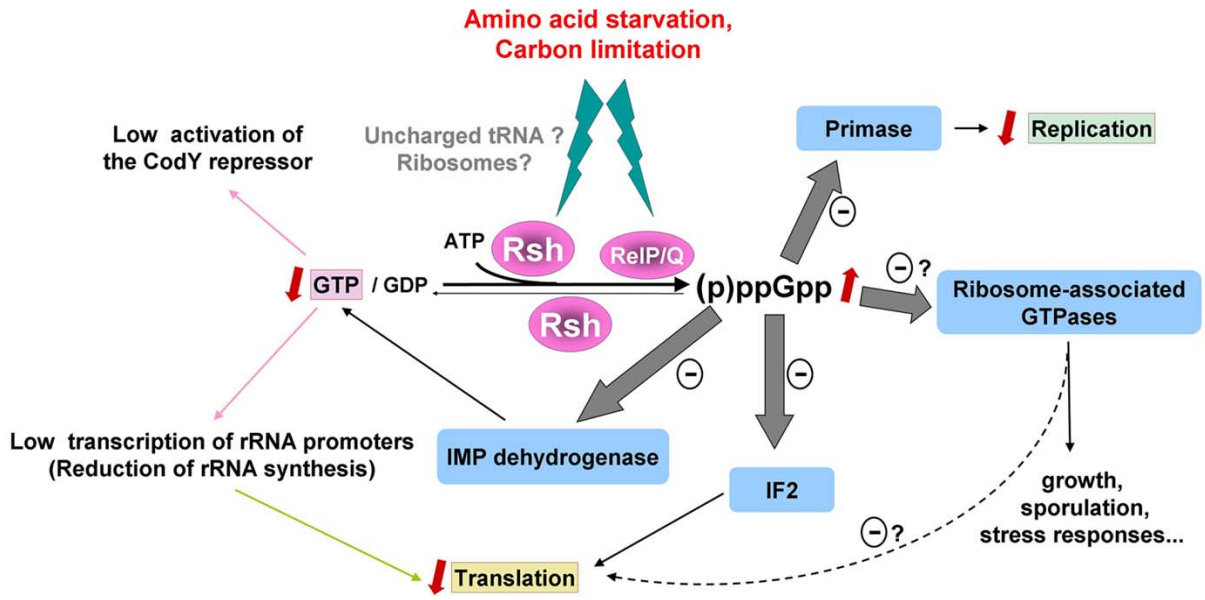

Figure 2. Major effects of (p)ppGpp during stringent response in *B. subtilis*. Under stresses or amino acid starvation, (p)ppGpp is synthesized by the Rsh enzyme or, additionally by the PelP/Q enzymes. Rsh also degrades (p)ppGpp. Contrarily to *E. coli*, the role of an interaction of Rsh with ribosomes/uncharged tRNA is not clear. The presence of (p)ppGpp has many effects. It binds to essential ribosome-associated GTPase to probably affect different cellular processes. It binds also the translation factor IF2, and thus probably inhibits protein synthesis (46). It interacts with the primase and inhibits DNA elongation during replication (50). It also inhibits IMP dehydrogenase and thus the intracellular GTP pool droops (72). The consequence is no activation of CodY repressor (73) and an indirect effect on transcription since guanine is essential as +1 nucleotide of *rrn* (42).

subtilis. Concerning cell wall synthesis, few data were obtained on the influence of stringent response on it but, it was shown that the expression of genes involved in peptidoglycan (PG) biosynthesis (*gcaD* and *murE*) and in lipoteichoic acid biosynthesis (*dltA* gene) was repressed during stringent response (20).

The changes induced by the accumulation of (p)ppGpp operate both at transcriptional and post-transcriptional levels. They are very often due to the reduction in intracellular GTP levels, probably by the inhibition of IMP dehydrogenase, the first enzyme in GTP biosynthesis (40). For example, it induces derepression of genes that are regulated by the metabolic repressor CodY (14). GTP enhances the affinity of CodY to a conserved binding motif in the promoter region of target genes that are mainly involved in nitrogen metabolism and transport. Thus, in conditions of stringent response, CodY target genes are derepressed (41). Furthermore, reduction in the GTP pool has a major influence on *rrn* promoter activity. Indeed, rrn promoters in *B. subtilis* initiate with GTP and a change in the identity of the base at position +1 results in a loss of regulation by (p)ppGpp and GTP. Consequently, rRNA synthesis is immediately derepressed (42), thus leading to the decrease in ribosome content per cell. By contrast, *E. coli* rRNA transcription can begin with ATP, GTP or CTP and thus is not specially affected by a drop of GTP pools. However, it is also regulated by (p)ppGpp. Indeed, the alarmone directly interacts with RNA polymerase (43) and, in concert with the cofactor protein DksA, specifically inhibits promoters for rRNAs and most tRNAs (44, 45). How this binding alters transcription initiation remains unresolved. Thus, *E. coli* and *B. subtilis* both use (p)ppGpp to reduce their ribosome production in response to aminoacid deprivation, but use different mechanisms.

(p)ppGpp might influence translation by directly binding to the initiation factor IF2 or by binding to essential ribosome-associated GTP-binding proteins. Since binding of GTP to IF2 activates translation, it was proposed that the replacement of GTP by (p)ppGpp in the interaction with IF2 might inhibit the translation machinery (46). However, the relevance of this mechanism remains to be determined in vivo. In addition to IF2, ribosome-associated GTPase were found to be regulated by (p)ppGpp. For example, the ribosome-associated GTP-binding protein Obg binds to (p)ppGpp (47). This essential protein has undefined roles in growth, sporulation, and stress responses (48). It was shown that its interaction with the ribosome is stabilized by GTP (49) and we can hypothesize that (p)ppGpp affects the interaction of Obg with the ribosome.

Furthermore, it was recently shown that the stringent response also directly regulates DNA replication. In starved *B. subtilis* cells, high (p)ppGpp concentrations inhibit DnaG, which is the primase of the replication machinery. Binding of (p)ppGpp to DnaG leads to an arrest of DNA replication elongation (50). Contrary to the previous cases where (p)ppGpp action was correlated to GTP levels, this inhibition of DnaG by (p)ppGpp is direct and independent of GTP. In *E. coli,* DNA replication is also

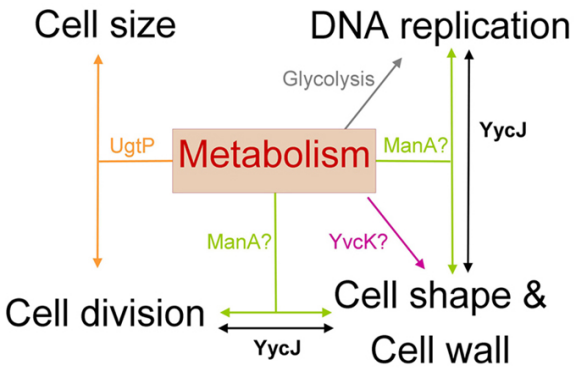

Figure 3. Main metabolic sensors that have be recently unrevealed in *B. subtilis*. This scheme resumes the interconnections that have been recently revealed between cellular processes and metabolism. This scheme could rapidly be obsolete with the growing list of metabolic proteins that have enzymatic signatures and that act on cellular processes but is at present the first metabolic sensors identified in *B. subtilis*.

inhibited by (p)ppGpp. However, whereas the target of (p)ppGpp is replication elongation in *B. subtilis*, the initiation phase is inhibited in *E. coli* (51). We conclude that, independently of the molecular mechanisms developed by the bacteria, these regulatory mechanisms may be important for cells to maintain genomic integrity upon a nutritional stress. Thus, while it was thought that metabolism regulates cellular processes mainly at transcriptional and translational levels, there are also direct links between metabolism and the activity of proteins involved in key cellular processes.

4. RECENT DISCOVERIES ON LINKS BETWEEN METABOLISM, CELL GROWTH AND THE CELL CYCLE

The discovery of the direct inhibition of a key replication enzyme by (p)ppGpp supports the idea of a specific and direct link between DNA replication and nutrient availability. Another unexpected observation also suggests a direct connection between DNA synthesis and metabolism in *B. subtilis*. During an analysis of suppressors of thermosensitive mutants of genes encoding the DnaE polymerase, the DnaG primase and the DnaC helicase (52), Jannière and co-workers observed that several mutations in glycolytic genes (*gapA, pgK, pgm* and *pykA*) restored the viability of the replication mutants. The underlying mechanism of this rescue is still unresolved but it suggests a direct connection between DNA chain elongation and glycolysis. This coupling mechanism could serve to adjust DNA synthesis depending on the energy provided by the environment (52). A correlation between central carbon metabolism and DNA replication was also recently observed in *E. coli* (53), suggesting that this link might be conserved in bacteria.

Other direct links between metabolism and cellular processes have recently been observed. For example, recent results are consistent with the idea that cell division and cell size are tightly coupled to nutrient availability at the level of the key division protein FtsZ (12) (see below). Thus, to connect metabolism and the different cellular processes, bacteria also directly transmit nutritional and growth rate information to DNA replication and cell division machineries. The underlying mechanism of this link remains to be elucidated but some clues to the nature of these connections have been discovered in *B. subtilis*.

4.1. Nutrient availability determines cell size

Bacteria are able to modulate size and growth rate in a nutrient-dependent manner. *B. subtilis* is a rod shaped bacterium that grows by elongation in its long axis. Cell division occurs after a doubling in size to produce two equally sized daughter cells. Importantly, it has long been observed that cell division and cell size depend on growth conditions. During growth in a poor medium, bacterial cell size can be reduced to half the length in comparison to growth in a rich medium (54). Thus, cell length varies according to growth rate. In addition, DNA replication and segregation is closely associated to division along the cell cycle (55). Thus, it is consistent with the idea that cell division, cell size, and chromosome dynamics are tightly coordinated with metabolism. Bacteria have to detect, depending of nutrient availability, when they have reached the correct mass for a given growth rate and transmit this information to the division apparatus. A metabolic sensor that couples nutritional conditions to division in *B. subtilis* was recently identified (12).

At the heart of the division machinery resides the FtsZ tubulin-like protein that assembles into a cytoskeletal scaffold known as the FtsZ-ring (or Z-ring) (56, 57). At midcell (at the division site), the Z-ring initiates and coordinates the invagination of the cell wall, leading to the formation of the septum (58). Weart and coworkers discovered a growth rate-dependent inhibitor of Z-ring assembly. The authors showed that the UDP-glucose diacylglycerol glucosyltransferase UgtP, an enzyme involved in the synthesis of glycolipids and the anchoring of lipoteichoic acid (59), inhibits FtsZ assembly in vitro. Furthermore, UgtP was shown to localize at midcell in a nutrient-dependent manner. Indeed, under rich condition, UgtP was concentrated at midcell whereas, under poor conditions, UgtP appeared to be sequestered in randomly distributed foci where it is presumably unable to modulate FtsZ assembly. The change in UgtP localization (midcell versus random foci) is controlled by the availability of UDP–glucose, a substrate of UgtP that is supplied by the upstream enzymes of the pathway, GtaB and PgcA. In rich condition (high level of UDP-glucose), UgtP is concentrated at midcell and then acts as a potent inhibitor of FtsZ assembly. This inhibition of FtsZ polymerization is probably due to a disruption of the stabilizing lateral interactions between protofilaments. The authors proposed that, under rich conditions, UgtP localizes at midcell to inhibit Z-ring formation and to allow completion of multi-fork DNA replication that is typical of rapidly growing cells. This induces a delay of cell division. It remains unclear how UgtP inhibition is relieved and whether or not it is directly coupled to the completion of DNA replication, but the authors observed that when cells reached a

sufficient length, cell division is activated. The role of UgtP seems to keep a constant ratio of FtsZ rings to cell length independently of growth rate. A similar cell length phenotype was observed in *E. coli* cells lacking the PgcA homologue, Pgm (12). This observation suggests that this mechanism might be conserved throughout bacteria for coordinating cell size and division; it allows cells to reach the correct mass and length and to complete chromosome segregation prior to cytokinesis.

4.2. Metabolism, cell wall elongation and chromosome morphology

Recently, another putative metabolic sensor that may connect cell wall synthesis and DNA segregation was described in *B. subtilis* (60). This protein is ManA, a mannose 6-phosphate isomerase necessary for utilization of mannose. In *B. subtilis*, mannose uptake and its concomitant phosphorylation is carried out by a mannose-specific PTS transporter. The resulting mannose-6-phosphate is then converted to fructose-6-phosphate (Fru-6-P) by ManA (61). Fru-6-P is an intermediate of glycolysis/gluconeogenesis that is also used to synthesize precursors of PG or teichoic acids (WTA) (25). Surprisingly, ManA is not only involved in mannose utilization but also appears to be involved in cell wall construction. In addition, cells lacking ManA have defects in chromosome integrity when grown in rich medium, when mannose is not utilized as a carbon source (60).

To identify ManA, Ben-Yehuda and coworkers used transposon mutagenesis coupled to microscopy screening to isolate *B. subtilis* mutants exhibiting growth defects in a rich medium. They observed that *manA* mutant cells exhibited aberrant cell wall architecture, polyploidy and abnormal chromosome segregation (60). Importantly, the deletion of *pmi*, which encodes a second mannose phosphate isomerase (25), had no observable phenotype and unlike ManA, Pmi was undetectable in rich LB medium. The authors concluded that the two homologs have non-identical roles and, in addition to its traditional role of metabolic enzyme, ManA also plays a crucial role for cell integrity that is supported by its enzymatic activity. What could be ManA additional role? The absence of ManA could interfere with the equilibrium of several pathways producing nucleotide sugar reservoirs for synthesis of PG or WTA. In support of this idea, the deletion of *pgi*, a gene encoding an enzyme that produces Fru-6-P from Glucose-6-P (25), resulted in phenotypes similar to the defects observed upon deletion of *manA* (60). Despite this, the authors proposed that *manA* deletion has a specific effect on the composition of cell wall carbohydrates, and causes a decrease in components of the WTA pathway, without perturbing the levels of PG precursors. Indeed, the overall composition of PG components was shown to be unaffected in *manA* mutant cells, but visualization of the PG revealed a modified architecture. Altogether, these results suggest that ManA is specifically involved in WTA synthesis rather than in the PG synthesis. ManA is probably required to maintain not only a proper cell wall composition, particularly with respect to WTA constituents, but also the balance between PG and WTA; this equilibrium is crucial for proper cell wall construction. The absence of ManA leads to abnormal cell wall synthesis that causes asynchrony between cell wall elongation, division and nucleoid segregation (60).

This study revealed an unexpected role of a metabolic enzyme in cell wall synthesis. However, the mechanism by which carbon source availability influences the connection between cell wall integrity and chromosome morphology has yet to be elucidated. Furthermore, it was demonstrated recently that the *B. subtilis* hydrolase YycJ is involved in the coordination of cell division with DNA replication by directly or indirectly affecting cell wall metabolism (62). These two different studies hint at an exciting and emerging link between cell wall synthesis and the cell cycle.

4.3. Metabolism and morphogenesis

Recently, a new connection was revealed between carbon metabolism and cell shape regulation in *B. subtilis* (63). The YvcK protein was shown to be required for morphogenesis only under gluconeogenic growth conditions. YvcK possesses a Rossmann fold (64), a structural motif often involved in NAD(P) binding. The enzymatic properties of YvcK are unknown, but *B. subtilis* needs YvcK for growth on Krebs cycle intermediates and substrates of the pentose phosphate pathway. A *yvcK* mutant grows normally on media containing glycolytic carbon sources but switching cells from glycolytic to gluconeogenetic growth conditions results in abnormal cell shape followed either by lysis or by growth arrest (65). Similar abnormal cell morphologies have been observed for mutants lacking MreB, an actin-like protein found in rod-shaped bacteria, that polymerizes to form helical filamentous structure in the cell to control the width of the bacteria (66).

Remarkably, YvcK is organized in a helical-like pattern in the cell independently of MreB (63). Strikingly, similarly to the *mreB* mutant, the shape and growth defects of the *yvcK* mutant are both suppressed by supplementing the medium with magnesium (65). In further support of the idea that YvcK plays a role in cell wall elongation/regulation, YvcK overproduction restores a normal morphology in an *mreB* mutant strain and reciprocally, an additional copy of *mreB* rescues a *yvcK* mutant strain grown on gluconeogenic carbon source (63). An explanation for this reciprocal complementation may lie in the localization of the PBP1 penicillin-binding protein. PBP enzymes are involved in the final stages of PG synthesis. Importantly, localization of PBP1 is dynamically linked to cell cycle. Specifically, PBP1 localizes with MreB during cell elongation and with FtsZ during cell division (67, 68). The current thinking is that MreB directly interacts with PBP1 in order to recruit it to the lateral cell wall (69). In the absence of MreB, PBP1 is mislocalized. Importantly, in the absence of YvcK, PBP1 is also mislocalized when bacteria are grown on gluconeogenic carbon sources (63). Thus, aberrant cell shape in a *yvcK* mutant could be caused by mislocalization and/or misregulation of PBP1. In support of this idea, YvcK overexpression restores proper localization of PBP1 and normal shape to mreB mutant cells. How YvcK influences the localization or activity of PBP1 is unknown. However, YvcK joins the increasing

number of proteins with an enzymatic signature that affect cellular processes (70). Our thesis is that these proteins sense changes in nutrients availability or in metabolism through interaction with a specific metabolite and translate these variations into an appropriate cellular response by directly regulating proteins involved in key cellular processes.

5. CONCLUSION

Bacteria coordinate various cellular processes not only through global regulatory mechanisms (CCR, stringent response or use of second messengers) that generally act at the transcriptional or translational level but also through metabolic sensor proteins that act directly on specific regulators of cellular processes. In various bacteria, recent findings show that metabolic enzymes are implicated in cell polarity, cell shape, DNA replication and chromosome segregation. Their ability to bind metabolites (or co-factors) or their role in metabolism predisposes some metabolic enzymes to evolve as metabolic sensors. With the recent technological advances in global approaches and in live cell imaging, the construction of interaction networks linking cellular processes and metabolism is opening a new field of research. A long-term objective for the study of interaction networks controlled by metabolic sensors is to understand how environmental changes in the broad sense that can lead to the adaptability of bacteria.

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Send correspondence to: Anne Galinier, From Laboratoire de Chimie Bacterienne, UPR 9043, IFR 88, CNRS, Universite de la Mediterranee, 31 chemin Joseph Aiguier, 13402 Marseille Cedex 20, France, Tel: 334- 911-64571, Fax: 334-917-18914, E-mail: galinier@ifr88.cnrs-mrs.fr

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