MINIREVIEW

Escherichia coli Starvation Diets: Essential Nutrients Weigh in Distinctly

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Bacterial growth is often limited by availability of nutrients. Soil, water, and even host environments such as macrophages can be nutrient poor, lacking essential building blocks for growth, including carbon, nitrogen, and phosphorus. The ratios of these elements differ according to the local ecology, so each one of them is limiting in different environments (4, 28). When presented with any type of starvation, *Escherichia coli* passes into a dormant mode, known as stationary phase, which protects the cells against harsh conditions. The master regulator of this response is RpoS. This review summarizes how cells sense starvation for carbon (glucose), phosphorus (inorganic phosphate), and nitrogen (ammonia) and subsequently turn on RpoS to initiate stationary phase. It was commonly thought that a universal signal, such as a general reduction in growth or slowing of macromolecule synthesis, communicated all types of starvation (16, 19). Surprisingly, each type of starvation triggers the pathway to stationary phase in a distinct fashion. Insights into the nature of the various starvation signals have been obtained by comparing different starvation conditions.

BACKGROUND

Current views suggest a two-stage starvation protocol (28). The first response is scavenging: when a particular nutrient becomes limiting, *E. coli* increases the production of proteins that forage for the limiting nutrient. These scavenging regulons include CAP (catabolite activator protein)/Crp (cyclic AMP [cAMP] receptor protein), which allows for the use of alternative carbon sources, and the two-component regulatory systems NtrB/NtrC and PhoR/PhoB, which control scavenging for nitrogen and phosphorus, respectively. Both the CAP/Crp and Ntr systems survey nutrient status through intracellular metabolites; CAP/Crp recognizes cAMP, while NtrC responds to glutamine. The Pho system, on the other hand, monitors inorganic phosphate levels via the activity of the Pst transport system (44). In all three cases, if scavenging fails, the cells starve and enter stationary phase.

In the complete absence of any of the three essential nutrients, stationary phase induces a characteristic response. Using

two-dimensional gels to examine protein patterns in growing and starved cells, Groat and coworkers found a class of proteins whose synthesis increased under all three starvation conditions (13). In an insightful review of this work, Matin et al. proposed that proteins whose synthesis is increased by carbon starvation, for example, would enhance metabolic potential, whereas proteins whose synthesis increased under all starvation conditions would confer resistance to a variety of environmental insults (28).

The sigma factor responsible for the general stress resistance is called RpoS (σ^S , σ^{38}). Upon starvation, RpoS regulates the transcription of hundreds of stationary-phase genes. Given this global role, it is not surprising that it was discovered in multiple ways. It was originally discovered by groups studying the regulation of peroxide resistance (40) and acid resistance (42). Later, McCann et al. (30) showed that mutations in the RpoS regulatory gene prevent the induction of starvation-induced stress responses. In parallel, Lange and Hengge-Aronis (23) identified *rpoS* in a screen designed to find genes whose expression increased upon carbon starvation independent of the CAP-mediated carbon scavenging response and realized that the same gene had been found in all these different studies. Its product is homologous to RpoD (σ^{70}), the housekeeping sigma factor, and is even referred to as the second primary sigma factor (16). The similar sigma factors even recognize the same consensus promoter sequences in vitro (8).

RpoS regulates transcription of hundreds of genes whose products render the cell resistant to many different stresses. RpoS-regulated proteins alter every compartment in cells, including both membranes and peptidoglycan (11). Osmoprotectants are increased in the periplasm, and metabolism is redirected so that storage compounds, such as glycogen and polyphosphate, accumulate (37, 45). Cell shape changes, as stationary-phase *E. coli* cells are more spherical than logarithmic-phase cells. The cells are also smaller, since there is no cell growth before the last division and some autodigestion occurs (33). Because of all of these changes, stationary-phase cells are far more resistant to a variety of environmental insults, such as heat, oxidation, and prolonged starvation, than their exponentially growing counterparts. To use a sailing analogy, *E. coli* appears to “batten down the hatches” in response to starvation.

Stationary phase represents a critical developmental decision with multiple input signals, thus making regulation of RpoS complex. Indeed, the production of RpoS is regulated at each and every step of gene expression: transcription, transla-

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tion, protein stability, and activity. There are many known regulatory factors for RpoS, but in most cases there is little understanding of the environmental stimuli associated with these factors. A compendium of such factors can be found in a recent review (16).

CARBON STARVATION

Carbon starvation is one of the strongest inducers of RpoS. While this sigma factor is not essential during exponential growth, it is required for survival during carbon starvation (6, 23, 30). Regulation of RpoS upon carbon starvation occurs at the level of proteolysis (35). Schweder and colleagues showed that in exponentially growing cells, the ClpXP protease rapidly degrades RpoS (41). This is an energy-dependent process by which ClpX unfolds the substrate for complete degradation by ClpP (46).

Control of proteolysis is solely responsible for RpoS accumulation upon carbon starvation. Zgurskaya and colleagues (47) calculated the rate of RpoS protein synthesis in stationary phase and found it to be lower than that in logarithmic growth phase. The overall decrease in synthesis, combined with an increased stability of 7- to 16-fold, led the authors to conclude that protein stability is the only level of regulation during carbon starvation. A recent study has confirmed this by expressing the *rpoS* open reading frame from heterologous *cis*-regulatory elements to eliminate the native transcriptional and translational control mechanisms operating on wild-type *rpoS*. Results with this construct demonstrate that stabilization of RpoS protein alone is sufficient to account for its accumulation upon carbon starvation (26).

The discovery that RpoS is regulated at the level of protein stability upon carbon starvation raised the obvious question of how this process is regulated. The gene *sprE*, which encodes a novel response regulator, was identified in a screen looking for factors that modulate RpoS-dependent repression of *ompF'-lacZ*⁺ (35). (SprE has also been called RssB, but in this review the SprE nomenclature will be used.) SprE is unusual because, unlike most response regulators, it is not involved in transcriptional regulation, and its C terminus does not share homology with known response regulators. It was shown that SprE directs RpoS for degradation by ClpXP *in vivo*, making it the first response regulator implicated in control of protein stability (32, 35). This has since been confirmed in a reconstituted *in vitro* system containing only SprE, RpoS, ClpXP, and ATP (21, 48). This biochemical work demonstrated that SprE and RpoS form a stoichiometric 1:1 complex with no oligomerization. Furthermore, it showed that SprE acts catalytically, since it is recycled rather than degraded after chaperoning RpoS to the protease.

There is evidence that the carbon starvation stabilization of RpoS is achieved via the SprE signal transduction pathway. Pratt and Silhavy (35) showed that a *sprE* null strain is blind to this starvation signal; there is no increase in the already high RpoS levels. The levels of SprE and ClpXP do not decrease upon starvation, and the protease has been shown to be active for other substrates under these conditions (5, 10, 36, 38, 41). This suggests that SprE activity must be regulated.

By homology, SprE belongs to the response regulator family of proteins which, with sensor kinases, comprise two-compo-

nent systems, the most common type of signal transduction system in bacteria. Typically, two-component systems contain a sensor kinase that autophosphorylates at a conserved histidine upon receiving an environmental signal. The kinase then phosphorylates the response regulator at a conserved aspartate. This phosphorylation event activates the response regulator. Mutations that alter the conserved histidine in the sensor kinase or the conserved aspartate in the response regulator disrupt signal transduction (18).

Since SprE has a conserved N-terminal response regulator domain, it has long been assumed that the activity of SprE would be controlled by phosphorylation (2, 16, 31, 35). These models rested on site-directed mutagenesis studies in which the conserved Asp residue, which is the only site of phosphorylation *in vitro*, was changed to other amino acids (2, 31). However, these studies did not examine the abilities of any of the mutant SprE proteins to carry out signal transduction in response to carbon starvation. Moreover, repeated attempts to identify the gene for the cognate kinase have been unsuccessful. Accordingly, models to explain the regulation of SprE activity had become more and more complex, involving multiple kinases and small-molecule phosphate donors (16).

Recently, we rigorously addressed the question of SprE phosphorylation by mutating the conserved Asp codon in the *sprE* gene present at its native chromosomal location (34). This mutation, *sprED58A*, has no effect on the carbon starvation signal transduction pathway; RpoS is still degraded during logarithmic growth and becomes stabilized upon starvation. The overall rate of RpoS degradation is slightly reduced in the mutant, indicating that phosphorylation may contribute to the basal activity of SprE. While it is possible that the phosphorylation of SprE is important for relaying some other environmental signal, it is not involved in signaling carbon starvation (34).

The molecular signal for carbon starvation thus remains elusive. Some obvious metabolic signaling candidates have been ruled out, since they act at the level of RpoS synthesis rather than degradation. These factors include CAP-cAMP, magic spot (ppGpp), and the functional EIIA(Glc) component of the glucose-specific phosphotransferase system (9, 17, 22, 23, 29, 43).

PHOSPHORUS STARVATION

E. coli cells also enter stationary phase upon phosphorus limitation. Under these conditions, RpoS levels increase to a degree similar to that seen with carbon starvation, and RpoS-dependent gene expression follows accordingly (13, 34, 39). This occurs despite continuing slow growth, which we suspect results from the mobilization of intracellular polyphosphate stores. Despite the same output, this starvation input is quite distinct from that with carbon starvation. First, RpoS is still unstable during phosphorus limitation, whereas it is stable during carbon limitation (34). Second, the cellular physiologies are quite different in these different conditions. Ballesteros and colleagues monitored metabolism via heat production, CO₂ production, and O₂ consumption. While carbon starvation shuts down central metabolism completely, metabolism continues robustly upon phosphorus starvation (1).

E. coli has two low-affinity transporters, PitA and PitB (15),

and one high-affinity transport system (Pst) for inorganic phosphate, the preferred source of phosphorus. The Pst system is an ABC transporter composed of the periplasmic binding protein PstS, the two inner membrane proteins PstA and PstC, and the cytoplasmic ATPase PstB (44). The PhoR/PhoB two-component regulatory system assesses phosphate availability by monitoring the activity of the Pst transporter. Low activity of this transporter causes autophosphorylation of the sensor kinase PhoR, which then phosphorylates PhoB to activate the Pho regulon. Mutations that compromise the Pst transporter also activate the Pho regulon by the same mechanism (44). These mutant strains “think” they are starving for phosphate all of the time.

Ruiz and Silhavy (39) discovered that *pst* mutations greatly elevate levels of RpoS in a PhoRB-dependent manner. Epistasis tests showed that the effect of the *pst* mutations are independent of *sprE*, suggesting that the *pst* mutations do not affect RpoS stability but rather affect some other aspect of *rpoS* regulation. Using transcriptional and translation *rpoS-lacZ* fusions, they showed that the *pst* mutations specifically increase the translation of *rpoS* mRNA. Thus, the PhoRB two-component system, either directly or indirectly, regulates the translation of *rpoS* mRNA (39). In contrast to nitrogen and carbon starvation, this is a case where there is clear relationship between scavenging and starvation responses.

Because PhoB is a transcriptional regulator, it was suspected that its effects on *rpoS* translation were indirect. Small non-coding RNAs (sRNAs) are important regulators of translation and mRNA stability. The *rpoS* mRNA has a long leader region that can form stem-loop structures that block the ribosome-binding site (Shine-Dalgarno sequence), diminishing translational efficiency (3). sRNAs can relieve this inhibition by pairing with the mRNA leader and preventing formation of the stem-loop structures (12, 24). The sRNAs require the RNA chaperone Hfq for the formation of the RNA-RNA duplex, and there are at least three sRNAs known to affect *rpoS* translation (3, 12, 24, 25). Genetic analysis suggests that the effect of the *pst* mutations on *rpoS* is Hfq dependent; however, all known sRNA regulators of *rpoS* were tested and ruled out. It was predicted that a PhoR/PhoB-regulated novel sRNA controls translation of *rpoS* (39).

The current model for the phosphorus starvation signal transduction pathway is as follows. Impending phosphorus starvation is sensed as diminished activity of the Pst transporter. This causes autophosphorylation of PhoR, which then phosphorylates PhoB. PhoB-P directly or indirectly activates transcription of an sRNA that stimulates translation of *rpoS* mRNA, thus elevating levels of RpoS to initiate the stationary phase response. One complication for this model is that during true phosphorus starvation, RpoS levels increase in the absence of PhoR/PhoB. Phosphorus starvation may be signaled in ways more complex than that involving the *pst* mutant, and it will not be possible to test this hypothesis directly until the sRNA has been found (39).

NITROGEN STARVATION

Nitrogen starvation signal transduction to RpoS has received little attention relative to that accorded to carbon and phosphorus starvation. ppGpp levels were known to increase

upon nitrogen starvation (20), and Gentry et al. (9) demonstrated strong correlations between levels of ppGpp and RpoS levels. There are no reported connections between the stringent response (ppGpp) and RpoS stability control via SprE/ClpXP. Therefore, ppGpp is unlikely to represent a key shared signal that underlies regulation of RpoS upon starvation for carbon, phosphorus, and nitrogen. Moreover, ppGpp has been reported to affect baseline levels of RpoS in rich medium but not the increase observed in stationary phase (17). This raised the question of whether RpoS synthesis or stability is controlled upon nitrogen starvation.

Examination of RpoS levels directly during nitrogen starvation revealed another possibility. Cells starved for nitrogen increase their levels of RpoS only twofold, which is reduced by an order of magnitude compared with the levels observed during carbon starvation (26). This modest increase in RpoS levels is observed both in a relaxed strain which carries the *relA1* allele and in a stringent wild-type strain (26). Furthermore, RpoS is not stabilized upon nitrogen starvation like it is upon carbon starvation, indicating that SprE is still active under nitrogen starvation conditions (26). Therefore, nitrogen starvation represents a state truly distinct from both carbon starvation and phosphorus starvation.

Unlike phosphorus limitation, when cell growth continues slowly, nitrogen-starved and carbon-starved cells stop growing immediately upon starvation (26). Since growth ceases upon both carbon and nitrogen starvations yet SprE is active in the latter but not the former, growth arrest cannot be the signal that regulates SprE activity.

Although RpoS levels do not change significantly upon nitrogen starvation, this does not seem to diminish the role that the general stress response plays during nitrogen deprivation. Similar proteins are induced following starvation for carbon, nitrogen, and phosphorus (13, 27). RpoS is required for survival following nitrogen starvation and in nitrogen downshifts (14, 30), and RpoS-dependent genes are induced upon starvation for carbon, phosphorus, or nitrogen (7). Furthermore, the Kustu laboratory has observed RpoS-dependent gene expression during nitrogen downshifts (14). Therefore, although the levels of RpoS are similar in terms of logarithmic phase and nitrogen starvation, we suggest that an increase in the activity of RpoS is the critical response to nitrogen starvation. There are numerous players that affect the competition between RpoS and RpoD, including Rsd, 6S RNA, and ppGpp. It will be interesting to see if any of these candidates have important signaling functions during nitrogen starvation.

The role that the NtrB/C nitrogen scavenging system plays in regulating RpoS is unclear. Analysis of the supplementary data provided in the work of Zimmer et al. (49) failed to identify a significant increase in RpoS-dependent gene expression upon genetic activation of NtrB/C scavenging, and this has been interpreted as evidence for the independence of the RpoS and NtrB/C pathways (26). We note, however, that these studies were conducted under various culture conditions in which nitrogen starvation was not complete. Now that research on the RpoS response under nitrogen starvation is focused on activity, it is possible to investigate connections with other signaling pathways.

FIG. 1. A model to explain how starvation for different nutrients regulates RpoS by different mechanisms. The *rpoS* mRNA is translated at low levels due to its 5' untranslated region forming a hairpin structure and occluding the Shine-Dalgarno sequence. Translation of the message is significantly enhanced in an Hfq-dependent manner in response to perceived phosphorus limitation, presumably by binding of a heretofore-uncharacterized small RNA. This causes significant increase in RpoS protein levels, though the protein is not as stable as it is under carbon starvation. Carbon starvation inhibits SprE (RssB)-mediated degradation of RpoS through the ClpXP protease. This leads to accumulation of highly stable RpoS protein. Nitrogen starvation shows only a modest increase in RpoS levels during starvation, so it is expected that its primary effect on RpoS regulation is at the level of activity, since RpoS plays an important role under nitrogen starvation. By influencing different elements of the pathway, each starvation signal activates RpoS regardless of the status—starvation level or excess—of the other nutrients. Thus, the signals act independently and do not interfere with each other.

CONCLUSION

Upon starvation for any of the three nutrients—carbon, phosphorus, or nitrogen—*E. coli* activates the RpoS response and enters stationary phase for survival. However, each type of starvation is sensed differently, and activation of the RpoS regulon occurs in a unique way with each type of starvation (Fig. 1). In carbon-starved cells, RpoS levels increase because degradation stops. In phosphorus-starved cells, RpoS levels increase because translation of *rpoS* mRNA increases. In nitrogen-starved cells, RpoS levels change little, but RpoS activity increases.

The challenge for the future is to identify the signal transduction mechanisms that mediate the various starvation signals. At present, our knowledge is incomplete. In carbon starvation, SprE is the effector molecule, but the signal is unknown. In phosphorus-starved cells, at least one of the signals is known, but the effector is not. In nitrogen-starved cells, both the signal and the effector remain elusive.

Much of the literature on stationary phase concerns comparisons of stationary-phase cells to exponentially growing cells. The differences between stationary-phase cells and exponentially growing cells are profound, and it is extremely difficult to distinguish the differences that are relevant for RpoS from those that are not. We suggest that significant insights into starvation signaling can be made by comparing cells that have been starved for one nutrient with cells that have been

starved for another. This comparative approach offers a more appropriate control for rates of macromolecular synthesis, cell cycle, and RpoS-dependent gene expression. It has the advantage that all cells are in a stable state and thus can be easily manipulated without affecting their physiology. For these reasons, comparing differentially starved cells may reveal key differences in starvation signal transduction.

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REFERENCES

- Ballesteros, M., A. Fredriksson, J. Henriksson, and T. Nystrom. 2001. Bacterial senescence: protein oxidation in non-proliferating cells is dictated by the accuracy of the ribosomes. *EMBO J.* **20**:5280–5289.
- Becker, G., E. Klauck, and R. Hengge-Aronis. 2000. The response regulator RssB, a recognition factor for σ^S proteolysis in *Escherichia coli*, can act like an anti- σ^S factor. *Mol. Microbiol.* **35**:657–666.
- Brown, L., and T. Elliott. 1997. Mutations that increase expression of the *rpoS* gene and decrease its dependence on *hfq* function in *Salmonella typhimurium*. *J. Bacteriol.* **179**:656–662.
- Codispoti, L. 1989. Phosphorous vs. nitrogen limitation of new and export production, p. 377–394. In W. Berger, V. Smetacek, and G. Wefer (ed.), *Productivity of the ocean: present and past*. Wiley & Sons, Chichester, United Kingdom.
- Damerau, K., and A. C. St. John. 1993. Role of Clp protease subunits in degradation of carbon starvation proteins in *Escherichia coli*. *J. Bacteriol.* **175**:53–63.
- Fang, F. C., S. J. Libby, N. A. Buchmeier, P. C. Loewen, J. Switala, J. Harwood, and D. G. Guiney. 1992. The alternative sigma factor *katF* (*rpoS*) regulates *Salmonella* virulence. *Proc. Natl. Acad. Sci. USA* **89**:11978–11982.
- Farewell, A., K. Kvint, and T. Nystrom. 1998. *uspB*, a new σ^S -regulated gene in *Escherichia coli* which is required for stationary-phase resistance to ethanol. *J. Bacteriol.* **180**:6140–6147.
- Gaal, T., W. Ross, S. T. Estrem, L. H. Nguyen, R. R. Burgess, and R. L. Gourse. 2001. Promoter recognition and discrimination by $E\sigma^S$ RNA polymerase. *Mol. Microbiol.* **42**:939–954.
- Gentry, D. R., V. J. Hernandez, L. H. Nguyen, D. B. Jensen, and M. Cashel. 1993. Synthesis of the stationary-phase sigma factor σ^S is positively regulated by ppGpp. *J. Bacteriol.* **175**:7982–7989.
- Gibson, K. E., and T. J. Silhavy. 2000. SprE levels are growth phase regulated in a σ^S -dependent manner at the level of translation. *J. Bacteriol.* **182**:4117–4120.
- Goodrich-Blair, H., M. Uria-Nickelsen, and R. Kolter. 1996. Regulation of gene expression in stationary phase, p. 571–583. In E. C. C. Lin and A. S. Lynch (ed.), *Regulation of gene expression in Escherichia coli*. Chapman and Hall, New York, N.Y.
- Gottesman, S. 2004. The small RNA regulators of *Escherichia coli*: roles and mechanisms. *Annu. Rev. Microbiol.* **58**:303–328.
- Groat, R. G., J. E. Schultz, E. Zychlinsky, A. Bockman, and A. Martin. 1986. Starvation proteins in *Escherichia coli*: kinetics of synthesis and role in starvation survival. *J. Bacteriol.* **168**:486–493.
- Gyaneshwar, P., O. Paliy, J. McAuliffe, A. Jones, M. I. Jordan, and S. Kustu. 2005. Lessons from *Escherichia coli* genes similarly regulated in response to nitrogen and sulfur limitation. *Proc. Natl. Acad. Sci. USA* **102**:3453–3458.
- Harris, R. M., D. C. Webb, S. M. Howitt, and G. B. Cox. 2001. Characterization of PitA and PitB from *Escherichia coli*. *J. Bacteriol.* **183**:5008–5014.
- Hengge-Aronis, R. 2002. Signal transduction and regulatory mechanisms involved in control of the σ^S (RpoS) subunit of RNA polymerase. *Microbiol. Mol. Biol. Rev.* **66**:373–395.
- Hirsch, M., and T. Elliott. 2002. Role of ppGpp in *rpoS* stationary-phase regulation in *Escherichia coli*. *J. Bacteriol.* **184**:5077–5087.
- Hoch, J. A., and T. J. Silhavy. 1995. Two-component signal transduction. American Society for Microbiology, Washington, D.C.
- Huisman, G. W., and R. Kolter. 1994. Sensing starvation: a homoserine lactone-dependent signaling pathway in *Escherichia coli*. *Science* **265**:537–539.
- Irr, J. D. 1972. Control of nucleotide metabolism and ribosomal ribonucleic acid synthesis during nitrogen starvation of *Escherichia coli*. *J. Bacteriol.* **110**:554–561.
- Klauck, E., M. Lingnau, and R. Hengge-Aronis. 2001. Role of the response regulator RssB in σ^S recognition and initiation of σ^S proteolysis in *Escherichia coli*. *Mol. Microbiol.* **40**:1381–1390.

22. Lange, R., D. Fischer, and R. Hengge-Aronis. 1995. Identification of transcriptional start sites and the role of ppGpp in the expression of *rpoS*, the structural gene for the σ^S subunit of RNA polymerase in *Escherichia coli*. *J. Bacteriol.* **177**:4676–4680.
23. Lange, R., and R. Hengge-Aronis. 1991. Identification of a central regulator of stationary-phase gene expression in *Escherichia coli*. *Mol. Microbiol.* **5**:49–59.
24. Majdalani, N., C. Cunniff, D. Sledjeski, T. Elliott, and S. Gottesman. 1998. DsrA RNA regulates translation of RpoS message by an anti-antisense mechanism, independent of its action as an antisilencer of transcription. *Proc. Natl. Acad. Sci. USA* **95**:12462–12467.
25. Majdalani, N., D. Hernandez, and S. Gottesman. 2002. Regulation and mode of action of the second small RNA activator of RpoS translation, RprA. *Mol. Microbiol.* **46**:813–826.
26. Mandel, M. J., and T. J. Silhavy. 2005. Starvation for different nutrients in *Escherichia coli* results in differential modulation of RpoS levels and stability. *J. Bacteriol.* **187**:434–442.
27. Matin, A. 1991. The molecular basis of carbon-starvation-induced general resistance in *Escherichia coli*. *Mol. Microbiol.* **5**:3–10.
28. Matin, A., E. A. Auger, P. H. Blum, and J. E. Schultz. 1989. Genetic basis of starvation survival in nondifferentiating bacteria. *Annu. Rev. Microbiol.* **43**:293–316.
29. McCann, M. P., C. D. Fraley, and A. Matin. 1993. The putative sigma factor KatF is regulated posttranscriptionally during carbon starvation. *J. Bacteriol.* **175**:2143–2149.
30. McCann, M. P., J. P. Kidwell, and A. Matin. 1991. The putative sigma factor KatF has a central role in development of starvation-mediated general resistance in *Escherichia coli*. *J. Bacteriol.* **173**:4188–4194.
31. Moreno, M., J. P. Audia, S. M. Bearson, C. Webb, and J. W. Foster. 2000. Regulation of σ^S degradation in *Salmonella enterica* var typhimurium: *in vivo* interactions between σ^S , the response regulator MviA(RssB) and ClpX. *J. Mol. Microbiol. Biotechnol.* **2**:245–254.
32. Muffler, A., D. Fischer, S. Altuvia, G. Storz, and R. Hengge-Aronis. 1996. The response regulator RssB controls stability of the σ^S subunit of RNA polymerase in *Escherichia coli*. *EMBO J.* **15**:1333–1339.
33. Nystrom, T. 2004. Stationary-phase physiology. *Annu. Rev. Microbiol.* **58**:161–181.
34. Peterson, C. N., N. Ruiz, and T. J. Silhavy. 2004. RpoS proteolysis is regulated by a mechanism that does not require the SprE (RssB) response regulator phosphorylation site. *J. Bacteriol.* **186**:7403–7410.
35. Pratt, L. A., and T. J. Silhavy. 1996. The response regulator SprE controls the stability of RpoS. *Proc. Natl. Acad. Sci. USA* **93**:2488–2492.
36. Pruteanu, M., and R. Hengge-Aronis. 2002. The cellular level of the recognition factor RssB is rate-limiting for σ^S proteolysis: implications for RssB regulation and signal transduction in σ^S turnover in *Escherichia coli*. *Mol. Microbiol.* **45**:1701–1713.
37. Rao, N. N., and A. Kornberg. 1996. Inorganic polyphosphate supports resistance and survival of stationary-phase *Escherichia coli*. *J. Bacteriol.* **178**:1394–1400.
38. Ruiz, N., C. N. Peterson, and T. J. Silhavy. 2001. RpoS-dependent transcriptional control of *sprE*: regulatory feedback loop. *J. Bacteriol.* **183**:5974–5981.
39. Ruiz, N., and T. J. Silhavy. 2003. Constitutive activation of the *Escherichia coli* Pho regulon upregulates *rpoS* translation in an Hfq-dependent fashion. *J. Bacteriol.* **185**:5984–5992.
40. Sak, B. D., A. Eisenstark, and D. Touati. 1989. Exonuclease III and the catalase hydroperoxidase II in *Escherichia coli* are both regulated by the *katF* gene product. *Proc. Natl. Acad. Sci. USA* **86**:3271–3275.
41. Schweder, T., K. H. Lee, O. Lomovskaya, and A. Matin. 1996. Regulation of *Escherichia coli* starvation sigma factor σ^S by ClpXP protease. *J. Bacteriol.* **178**:470–476.
42. Touati, E., E. Dassa, and P. L. Boquet. 1986. Pleiotropic mutations in *appR* reduce pH 2.5 acid phosphatase expression and restore succinate utilisation in CRP-deficient strains of *Escherichia coli*. *Mol. Gen. Genet.* **202**:257–264.
43. Ueguchi, C., N. Misonou, and T. Mizuno. 2001. Negative control of *rpoS* expression by phosphoenolpyruvate: carbohydrate phosphotransferase system in *Escherichia coli*. *J. Bacteriol.* **183**:520–527.
44. Wanner, B. L. 1996. Phosphorus assimilation and control of the phosphate regulon, p. 1357–1381. In F. C. Neidhardt, J. L. Ingraham, E. C. C. Lin, K. B. Low, B. Magasanik, W. S. Reznikoff, M. Riley, M. Schaechter, and H. E. Umbarger (ed.), *Escherichia coli* and *Salmonella*, 2nd ed., vol. 1. American Society for Microbiology, Washington D.C.
45. Wei, B., S. Shin, D. LaPorte, A. J. Wolfe, and T. Romeo. 2000. Global regulatory mutations in *csrA* and *rpoS* cause severe central carbon stress in *Escherichia coli* in the presence of acetate. *J. Bacteriol.* **182**:1632–1640.
46. Wickner, S., and M. R. Maurizi. 1999. Here's the hook: similar substrate binding sites in the chaperone domains of Clp and Lon. *Proc. Natl. Acad. Sci. USA* **96**:8318–8320.
47. Zgurskaya, H. I., M. Keyhan, and A. Matin. 1997. The σ^S level in starving *Escherichia coli* cells increases solely as a result of its increased stability, despite decreased synthesis. *Mol. Microbiol.* **24**:643–651.
48. Zhou, Y., S. Gottesman, J. R. Hoskins, M. R. Maurizi, and S. Wickner. 2001. The RssB response regulator directly targets σ^S for degradation by ClpXP. *Genes Dev.* **15**:627–637.
49. Zimmer, D. P., E. Soupe, H. L. Lee, V. F. Wendisch, A. B. Khodursky, B. J. Peter, R. A. Bender, and S. Kustu. 2000. Nitrogen regulatory protein C-controlled genes of *Escherichia coli*: scavenging as a defense against nitrogen limitation. *Proc. Natl. Acad. Sci. USA* **97**:14674–14679.