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MINIREVIEW

Life After Log

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A remarkable feature of bacterial species is their capacity for rapid growth when nutrients are available and conditions are appropriate for growth. Perhaps even more remarkable is their ability to remain viable under conditions not propitious for growth. Many bacteria have evolved highly sophisticated mechanisms that allow them to maintain cell viability during starvation and resume growth rapidly when nutrients again become available. Some species form dormant spores, while others form multicellular aggregates and fruiting bodies in response to starvation conditions (26, 34). But even without the formation of such elaborately differentiated cells, many bacteria, among them *Escherichia*, *Salmonella*, and *Vibrio* spp., enter a starvation-induced program that results in a metabolically less active and more resistant state.

Examination of starved cells using light microscopy reveals changes in cell morphology. *Escherichia coli* cells become much smaller and almost spherical when they enter stationary phase (22, 31). This phenomenon is even more striking for a number of marine bacteria which greatly decrease in size during starvation and form ultramicrocells, as small as 0.03 μm^3 (28). Ultramicrocells result from cells that undergo several cell divisions without an increase in biomass and then a further decrease in their size as a result of endogenous metabolism. One possible selective advantage of the reductive divisions seen in marine bacteria is to improve the survival of the clonal population by increasing the probability that some cells will encounter nutrients (38). In *E. coli*, these changes in cell size and shape are accompanied by changes in the subcellular compartments; the cytoplasm is condensed and the volume of the periplasm increases (48).

The surface properties of starved cells are also different from those of growing cells. The surface of many marine bacteria becomes increasingly hydrophobic and the cells become more adhesive during starvation (28). Changes in the fatty acid composition of the cell membranes have been seen during starvation of several species (28). For example, in *E. coli* there is a conversion of all unsaturated membrane fatty acids to the cyclopropyl derivatives as cells enter stationary phase (14). *Vibrio* sp. strain S14 acquires new fimbraelike structures and forms cellular aggregates or clumps after prolonged starvation (1). In *E. coli*, such starvation-induced aggregates appear to form as the result of a self-generated and secreted attractant that is sensed by the chemotaxis machinery (7).

The cell wall synthesized during amino acid starvation has a different structure from the cell wall synthesized during growth (46, 56). These changes in structure appear to protect cells against the autolysis induced by either penicillin or chaotropic agents. In *E. coli*, the increased resistance to autolysis is dependent on induction of the stringent response (29). It is likely that other starvation conditions such as carbon starvation, which increase the intracellular levels of the signal molecule ppGpp (9), may also induce resistance to autolysis.

Changes in the topology of the chromosome occur in starved cells. After several hours in stationary phase, changes in the negative superhelical density of reporter plasmids can be detected in *E. coli* (5). In addition, the nucleoid of starved *Vibrio* spp. is highly condensed (4, 39).

A general tenet in microbiology has been that the members of bacterial genera such as *Escherichia*, *Salmonella*, and *Vibrio* do not generate differentiated cells as a result of starvation. While it is evident that these species do not form classical spores, the foregoing description should make it clear that major structural changes do occur as a result of starvation. These changes are accompanied by changes in metabolism and physiology which, as will be discussed, confer on the cells some of the properties of classical spores.

As cells become starved their overall metabolic rate decreases, but some level of endogenous metabolism is maintained. This allows the starved cells to maintain some level of ATP (or other high-energy compounds) and the proton motive force across the membrane. One function of endogenous metabolism is to maintain the ability to transport substrates into the cell. If this ability is compromised, the starved cell will be unable to resume growth when nutrients become available in its environment. ATP levels and the energy charge, which is an indicator of the fraction of the adenylate pool that is available as ATP, decrease as cells go from the exponential growth phase into stationary phase but do not disappear (10, 22, 28). The proton motive force does not change significantly between growing and nongrowing cells. However, the contributions of ΔpH and $\Delta\Psi$ to the proton motive force change when cells are starved (27, 52).

Several adjustments are made in order to maintain some level of endogenous metabolism. For example, the rate of protein turnover increases approximately fivefold in starved *E. coli* cells (35). In the marine *Vibrio* sp. strain S14, the rate of proteolysis increases 16-fold during the first several hours of starvation (44). In rapidly growing *E. coli* cells, the bulk of the nucleic acid is stable (22). RNA stability decreases when cells enter stationary phase and 20 to 40% of total RNA is lost during the first several hours of starvation (35).

Thus, in the starved cell endogenous protein and RNA, mostly in the form of ribosomes, may provide a source of energy to support endogenous metabolism. However, the turnover of excess ribosomes must be controlled in some way because starved cells can resume high rates of protein synthesis immediately after the addition of nutrients (2).

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Perhaps the dimerization in stationary phase of a fraction of the ribosomes renders them resistant to degradation (57). The importance of protein turnover in cellular survival was demonstrated in studies with strains lacking multiple peptidases (49). These strains have a much lower rate of protein synthesis and have lower viability during carbon starvation than wild-type cells. Unlike RNA and protein, DNA remains stable in most bacteria, even during prolonged starvation. Teleologically, it makes sense to have evolved mechanisms of protecting the genome from degradation even under situations where other cellular components are being turned over.

One of the most striking features of spores is their extreme resistance to a variety of environmental assaults. Starvation induces the development of a more resistant state even in nonsporulating bacteria. Carbon-starved *E. coli* cells are more resistant to heat shock, oxidative stress, and osmotic challenge than exponential-phase cells (24, 25, 32). Exposure to nonlethal levels of heat, H_2O_2, or salt increases the resistance of growing cells to subsequent lethal challenges. However, the resistance produced by starvation is even more protective than preadaptation of growing cells.

The enhanced resistance that develops during starvation requires newly synthesized proteins. While bulk protein synthesis is turning off (15, 18, 47), the synthesis of 30 to 50 proteins is induced in response to starvation (18, 32, 45, 53). Part of the initial response to starvation for a particular nutrient, such as carbon, nitrogen, or phosphate, is to induce the expression of a group of genes whose functions are designed to help the cell cope with that particular starvation stress. Each of these systems appears to function via a sensor component that monitors the availability of a specific nutrient, either directly or indirectly. A decrease in the level of the nutrient leads to the activation of a transcriptional regulator that turns on expression of the genes in that regulon (42). For example, the nitrogen regulon is induced in response to limiting levels of NH_4^+, which is monitored by the protein NtrB. Transcription of the genes in the nitrogen regulon is controlled by an alternate sigma factor, σ^{54}, and the transcriptional activator NtrC. When ammonia levels are low, the kinase activity of the sensor NtrB is activated, leading to the phosphorylation and activation of NtrC, which in turn allows transcription of the Ntr regulon by RNA polymerase holoenzyme containing σ^{54} (30).

When even the induction of these regulons is not sufficient to secure enough of the limiting nutrient, growth ceases and cells enter stationary phase. All indications are that one or more new regulons are induced. The starved cell synthesizes proteins involved in maintaining viability during prolonged starvation and also synthesizes proteins needed for cells to recover from starvation and resume growth when nutrients become available. The existence of such proteins is demonstrated by observations that blocking protein synthesis at the same time that cells are starved leads to decreased viability (45, 48). In addition, there are *E. coli* mutants that, while appearing normal during logarithmic growth, fail to survive during stationary phase (54) or fail to exit stationary phase (51). The changes that occur under many or all starvation stresses is referred to here as the general starvation response.

How is the general starvation response regulated? It may be that each specific starvation condition leads to a long-term starvation response or there may be a common signal elicited regardless of the limiting nutrient. For example, subtle fluctuations in the ΔpH or $\Delta\Psi$ may provide a common signal that regulatory sensors can transduce to the cell's machinery signifying starvation. It has been proposed that the methylated form of elongation factor Tu, which is induced during starvation, could be a transducer of such a signal (58, 59).

A major regulator of the general starvation response has been identified in *E. coli* and is the product of the *katF* gene (32, 37). KatF is required for the synthesis of many of the proteins induced by carbon starvation. Several of the growth-phase-regulated genes that require *katF* for their induction have been identified. These genes include *katE*, which encodes HPII, a stationary-phase-induced catalase (33); *xthA*, which encodes exonuclease III (50); and *appA*, encoding an acid phosphatase (55). The change in cell shape that *E. coli* undergoes upon starvation is also *katF* dependent. Starved *katF* mutants remain rod shaped in stationary phase, perhaps as a result of failure to induce expression of the morphogene *bolA* (31). KatF mutants also fail to develop thermoresistance, osmoresistance, or resistance to H_2O_2 and have reduced viability under several starvation conditions (17, 32, 37).

The *katF* gene was cloned and sequenced and the predicted amino acid sequence found to have strong similarity to σ^{70}, the major sigma factor in *E. coli* (40). It is likely that *katF* encodes a stationary-phase- or starvation-specific sigma factor and it has been proposed that the *katF* locus be renamed *rpoS* (32). However, it has not yet been shown biochemically that the KatF protein functions as a sigma factor. It is also not known how the activity of KatF is regulated. Transcription of the *katF* regulon could be controlled by changes in the level and/or activity of the KatF protein. Expression of the *katF* gene increases upon entry into stationary phase (41), but whether this is sufficient to account for the induction of stationary-phase-induced genes remains to be shown. Ultimately the activity of KatF must be responsive to whatever signal(s) initiate the cellular response to starvation.

There is evidence that *katF* is not the only regulatory molecule involved in the general starvation response. Stationary-phase induction of the promoter of the microcin B17 (*mcb*) operon is independent of *katF* and transcription of the *mcb* promoter in vitro requires σ^{70} (6, 31). Interestingly, the sequence of the *bolA* promoter, whose stationary-phase induction is *katF* dependent, is nearly identical to that of the *mcb* promoter (3, 11, 31). These two promoters may be transcribed by RNA polymerase containing two different σ factors. Alternatively, if the *bolA* promoter were also transcribed by holoenzyme containing σ^{70}, the effect of *katF* mutations on *bolA* transcription may be indirect. Further evidence of the involvement of other regulatory molecules in the general starvation response is the observation that induction of approximately 20 of the proteins induced by carbon starvation is *katF* independent (37). This group includes three heat shock proteins (DnaK, GroEL, and HtpG) whose induction during starvation is dependent on σ^{32} rather than KatF (23).

During growth, cells have the capacity to respond rapidly to environmental challenges by turning on expression of sets of genes in response to stress, such as regulons controlled by σ^{32} or OxyR (16, 43). In a starved cell, such a rapid response requiring transcription and new protein synthesis is not likely to be possible. Therefore, cells must prepare in advance to deal with the possibility of eventual environmental challenges such as heat, osmotic, or oxidative stress. Indeed the starvation response includes expression of a catalase, HPII, to protect against oxidative damage (33). Starvation-specific thermotolerance and osmoprotection in-

volve the accumulation of trehalose (21). Expression of the trehalose-synthesizing enzymes (encoded by *otsA* and *otsB*) is induced upon carbon starvation as well as upon osmotic challenge; induction under both conditions is *katF* dependent.

Another response of cells to starvation stress is to increase their spontaneous mutation rate. This is observed under conditions where postselection mutations accumulate (8, 19, 20, 54). The biochemical mechanisms responsible for this increased mutagenesis are yet to be defined. The topic of postselection mutations will be the subject of a future minireview. Two observations that may prove relevant to this phenomenon are (i) mutations that block the hypermodification of some tRNAs increase the rate of spontaneous mutation and (ii) the level of modification decreases during carbon starvation (12, 13). These findings suggest that the level of tRNA modification could be one signal that triggers whatever process leads to the appearance of postselection mutations.

This review has focused on how bacterial cells survive prolonged starvation, but what about the cells that die during starvation? What are the causes of cell death? There is no definitive answer to this question, but loss of cell viability has been found to correlate with changes in several parameters. These include complete degradation of ribosomes, decrease in energy charge and ATP levels, and decrease in proton motive force (15, 28, 36). It is not clear, however, which of these is the cause, rather than the effect. One interesting question that is raised is this: under conditions where only a fraction of the cells in a population survive what, if anything, is different about the survivors? It is possible that death is a stochastic process and the survivors are a random sample of the population. Alternatively, it may be that the survivors represent a fraction of the population that entered on a different pathway at the onset of starvation. Perhaps these cells were at a particular point in the cell cycle that enabled them to respond differently to the starvation stress.

In order to survive in their natural environments, bacteria must constantly adapt to changing conditions and shift between states of growth and nongrowth. The molecular approaches to studying stationary phase that have been reviewed here are beginning to provide a picture of the mechanisms that cells use to maintain the living state during prolonged starvation.

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