Degradation of Stable RNA in Bacteria*

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At first glance, the title of this minireview might appear to be an oxymoron. How can “stable” RNAs be degraded? We have become accustomed to thinking about the stable RNAs, primarily rRNA and tRNA, as being stable in an absolute sense; however, this terminology really is correct only in comparison to the rapid turnover of mRNAs. In fact, although rRNA and tRNA are quite stable during exponential growth (11, 12), they have been known since the earliest studies of RNA metabolism that under certain physiological conditions these RNA molecules can be extensively degraded (2). Yet, in contrast to the many studies of mRNA decay (3–5), there has been relatively little attention in recent years to the study of the processes that result in degradation of stable RNAs despite the fact that these molecules account for ~98% of all cellular RNA (6).

Starvation, Stationary Phase, and Slow Growth

Degradation of stable RNA is most usually associated with conditions of starvation. Thus, depletion of any one of a number of nutrients including phosphate (7), nitrogen (8), carbon (9), or even Mg²⁺ (10) leads to a dramatic loss of RNA. It is not clear whether starvation for different nutrients leads to different rates of degradation, as data on this point have been inconsistent (e.g. Refs. 11 and 12). Inasmuch as ribosomes account for the bulk of cellular RNA (6), degradation during starvation is confined largely to rRNA. In fact, there is some evidence that tRNA may be stable under these conditions (11). Likewise, it appears that ribosomal proteins remain relatively stable (9, 12, 13) so ribosomes may be able to reassemble as soon as RNA is synthesized. This would be important for cells to recover from starvation more rapidly because if few ribosomes remained, resynthesis of ribosomal proteins would be expected to be slow. Because ribosomes represent such a large fraction of cellular mass (6), they are a major storehouse for nutrients, and the ability of cells to recover from starvation may be related to their capacity to generate nutrients from degraded ribosomes (12).

Degradation of ribosomes during starvation can be rapid and quite extensive, amounting to >95% in some studies (11, 13). Interestingly, ribosome degradation appears to be an “all or none” phenomenon in that once breakdown of a ribosome begins, it goes to completion, whereas residual ribosomes remain intact (9, 11, 12). Some evidence suggests that 30 S subunits may disappear more rapidly than 50 S (11), but this is not a uniform finding (9). Although not conclusively established, the pathway of ribosome degradation upon starvation appears to proceed from polysomes to monosomes to ribosome subunits (12). However, the signals controlling this progression are not known.

Most studies of starvation employ a regimen in which growing cells are resuspended in medium or buffer lacking a particular nutrient. However, it has been pointed out that this is unnatural and that cells normally would lose nutrients gradually, allowing for adaptive changes that might affect subsequent events (11). It is not understood to what extent these laboratory regimens for starvation may affect rates or extents of RNA degradation. Nevertheless, it is clear that RNA degradation begins as soon as nutrients become limiting and before growth ceases and cell viability begins to decrease (11). In Salmonella strains, rRNA degradation is taken to extremes. More than 90% of 23 S rRNA and ~50% of 16 S rRNA are degraded when cells reach stationary phase (14). The reason for this extensive rRNA degradation is not yet understood.

Starvation and stationary phases have in common a dramatic slowing or complete absence of growth. Consequently, other situations in which growth slows might also affect the stability of RNA, and such is the case following a nutritional downshift. In a relaxed mutant Escherichia coli strain, a substantial portion of newly synthesized rRNA is degraded during the first 30 min after the downshift (15). Confirmation that growth rate affects stability comes from direct measurement of stable RNA accumulation in cells growing over a wide range of rates. At low growth rates, in particular, the balance between the synthesis of rRNA and ribosomal proteins is disturbed such that excess RNA is produced and ultimately degraded (16, 17). At very low growth rates as much as 70% of the newly synthesized rRNA does not accumulate in ribosomes and apparently is degraded. Moreover, some excess of rRNA over ribosomal protein may be synthesized at all growth rates (16, 17), suggesting that mechanisms must exist for removing the excess RNA because free rRNA does not accumulate (18). Such quality control mechanisms will be discussed in more detail later. Some data suggest that at very slow growth rates a portion of newly made tRNA also may be degraded (16). However, this point has not been examined in detail.

The breakdown of ribosomes and degradation of stable RNA under conditions of starvation, stationary phase, and slow growth would appear to be of major importance to bacterial cells under natural conditions. Enteric bacteria, such as E. coli, live under “feast or famine” conditions, and processes that release the stores of nutrients present in ribosomes would thus represent an important survival strategy. Understanding how this is accomplished and identifying the regulatory signals that underlie these degradative processes will be of considerable interest.

Agents Affecting RNA Stability

Treatment of bacteria with any one of a variety of agents leads to extensive breakdown of cellular RNA, in some cases approaching the entire RNA content. Among the compounds promoting RNA degradation are antibiotics such as streptomycin (19), mitomycin C (20), and polymixin E (21), membrane-damaging reagents such as toluene (22) and dodecyl diethanoldiamine (23), and Hg²⁺ ion (24). A likely explanation for the action of many of these agents is an effect on the cell membrane leading to alterations in permeability. These changes affect the internal environment because of the loss of ions, including
Mg\textsuperscript{2+}, and as a consequence, ribosome structure may be altered, rendering the rRNA more accessible to the action of a degradative RNase.

That this scenario probably is correct comes from evidence that RNA degradation in many of these situations is because of action of the nonspecific endoribonuclease, RNase I (21, 23, 24). In cells lacking RNase I, the extensive RNA breakdown does not occur (23, 24). Moreover, 3′-mononucleotides are among the degradation products (24), as expected for RNase I action. RNase I is thought to be present largely in the periplasmic space (25), but membrane damage would allow entry of active RNase I into the cell. In addition, the loss of Mg\textsuperscript{2+}, an inhibitor of RNase I, and the more exposed rRNA all combine to result in extensive RNA degradation. An interesting feature of the RNA breakdown induced by Hg\textsuperscript{2+} is that it occurs only in cells in exponential growth; cells in stationary phase are insensitive (24). It is thought that changes in the cell membrane, known to occur upon entry into stationary phase (25), may affect the entry of RNase I into the cytoplasm.

An additional feature of the Hg\textsuperscript{2+} ion activation of RNase I also needs to be considered. A portion of cellular RNase I resides in the cytoplasm, most likely in an inactive form (25, 26). This raises the possibility that bacteria may contain a Hg\textsuperscript{2+}-ion-sensitive inhibitor (24, 27), as is known to be present in eukaryotic cells (28). Upon addition of Hg\textsuperscript{2+}, the inhibitor would be inactivated, turning on the intracellular pool of RNase I. Circumstantial evidence for such a bacterial RNase I inhibitor exists (24, 27), and by analogy with eukaryotes, would be an interesting mechanism by which the activity of RNase I could be modulated under appropriate physiological conditions.

Mutations That Affect RNA Stability

One can imagine a wide range of mutations that would have the potential to affect RNA stability. For example, one class of mutations could alter the mechanisms that must exist for protecting stable RNAs against cellular RNases during exponential growth and for eliminating this protection when conditions require RNA degradation. A second class could interfere with maturation of RNA or tRNA or disrupt ribosome assembly; ultimately leading to altered or damaged RNAs that would need to be eliminated. A third class of mutations could directly eliminate an RNase activity and thereby stabilize RNAs that otherwise would be removed, such as was found with mutations lacking RNase I. Detailed examination of these many types of mutants undoubtedly could provide valuable information on the various processes and factors that influence RNA stability, and in fact, many studies along these lines have been undertaken.

One interesting mutant strain was found to rapidly degrade its rRNA and tRNA population upon cessation of RNA synthesis at 42 °C (29). Extensive analysis revealed that the phenotype was due to a gene, srnB, located on the F-plasmid, whose product, a 12-kDa protein, increases membrane permeability (30). As a consequence, RNase I, present in the periplasm, enters the cytoplasm, and as already noted, leads to massive RNA degradation. Under normal conditions, the srnB gene is turned off, and this is influenced by a chromosomal gene, srnA. Mutation of srnA or overexpression of srnB promotes degradation. Unraveling the phenotype of this mutant strain emphasizes how important it is for cells to exclude active RNase I from the cytoplasm. Mechanisms for ensuring this must be highly efficient because overexpression of RNase I by as much as 20–100-fold has little effect on cell growth (27). Thus, by sequencing most RNase I in the periplasm and keeping the cytoplasmic pool in an inactive state, cells keep this destructive enzyme under control.

A variety of mutations that affect ribosome assembly or rRNA processing also lead to RNA degradation. As an example, mutations of this type could affect a ribosomal protein. One such mutation, which results in an alteration of ribosomal protein S10 (30), leads to 50–60% degradation of 16 S rRNA. Possibly, this change in S10 affects ribosome structure or assembly such that the small subunit RNA is not sufficiently protected against nuclease action. It would be expected that mutations in many other proteins would have similar consequences. Alternatively, because protein S10 also serves as the antitermination factor, NusE, other more indirect effects also may be involved.

Mutations in rRNA itself may affect stability, particularly if these changes impact on ribosome assembly. For example, mutations in the leader sequence of rRNA operons affect synthesis of mature 16 S rRNA and 30 S subunit formation and ultimately 16 S RNA stability (31), despite that fact that the leader region is removed during maturation. Examination of a series of deletions of 23 S rRNA revealed that some of them lead to instability (32). RNAs with certain internal deletions are incorporated into stable RNP\textsuperscript{1} particles, whereas those in which the RNA termini are missing do not form particles and the RNA is ultimately degraded. These types of studies indicate that cells possess quality control mechanisms for assessing the accuracy of ribosome assembly (see below).

Mutations that directly eliminate RNase activity have proven particularly informative. Those mutations that remove an RNase involved in degradation will lead to stabilization of the RNA substrate. As noted earlier, many examples of this phenomenon related to RNase I removal have been documented. A similar situation was reported recently for cells lacking polynucleotide phosphorylase (PNPase) and RNase R (33). In the absence of these two exoribonucleases, mutant cells accumulate massive amounts of rRNA fragments that normally would be removed if either of the two RNases were present. Removal of other RNases may alter RNA maturation or ribosome assembly and lead to degradation of the affected RNA. Such is the case in a double mutant strain defective in RNase III and rho factor (34). In these cells, newly synthesized rRNA does not accumulate. Likewise, in cells lacking the phosphate-dependent exoribonucleases, PNPase and RNase PH, 50 S ribosomal subunits are dramatically reduced at 31 °C, and 23 S rRNA is degraded (35). The basis for these mutant phenotypes is not yet understood.

Quality Control of RNA

The synthesis, maturation, and assembly of RNA molecules into RNP particles are carried out in cells with a high degree of accuracy. However, these complex processes are not perfect, and as a consequence, a certain level of defective RNAs or misassembled RNPs continually is produced. In many cases, these “bad” RNAs have the potential to interfere with the function of their normal counterparts, and therefore, it might be expected that they would be repaired or eliminated. It has been known for some time that eukaryotic mRNAs with premature nonsense codons are degraded by a nonsense-mediated quality control process (36). However, until recently it was unclear whether similar mechanisms might be present for removing defective stable RNAs. Hints that such processes probably exist have come from studies already mentioned in which it was found that mutations affecting ribosome assembly lead to degradation of the rRNA (30–32), implying that RNA in incorrectly assembled particles is unstable. More direct evidence for RNA quality control, both for tRNA (37) and for rRNA (33), has been reported recently.

\textsuperscript{1}The abbreviations used are: RNP, ribonucleoprotein; PNPase, polynucleotide phosphorylase.
Precursors of stable RNAs that cannot be converted to their mature forms because of the absence of processing exoribonucleases become polyadenylated (38). Because polyadenylation is a signal for RNA degradation in bacteria (3, 5), this observation raised the possibility that polyadenylation of stable RNA precursors might serve a physiological role, i.e., a means to remove defective precursors that are poorly converted to mature species. This idea was tested using a temperature-sensitive mutant of tRNA\textsubscript{Trp} that is more susceptible to denaturation \textit{in vivo} than the wild type (39), making it a useful model for a defective tRNA. The mutant tRNA accumulates in cells to only 15% of the level of its wild type counterpart because of the fact that it is degraded (37). Most importantly, this degradation occurs primarily at the precursor level and is dependent on polyadenylation. Removal of poly(A) polymerase, the enzyme responsible for polyadenylation, and PNPase, an RNase responsible for at least some of the degradation, results in accumulation of large amounts of precursor of the defective tRNA. These data demonstrate that \textit{E. coli} has a quality control mechanism for the specific elimination of a defective tRNA and may explain why stable RNAs are initially synthesized in precursor forms.

Evidence for quality control of rRNA comes from studies of a mutant strain lacking the exoribonucleases, PNPase and RNase R (33). As discussed earlier, these cells accumulate large amounts of fragments of 16 and 23 S rRNA that normally would be degraded by the RNases. How the fragments arise in the first place has not yet been ascertained. However, considering that rRNA may always be synthesized in excess of ribosomal protein (16, 17) and that a certain frequency of errors in rRNA synthesis or assembly undoubtedly occur, an ample supply of potential rRNA substrate for generation of the fragments is continually being produced. The rRNA fragments would likely be deleterious to the cell, for example, by binding to the limited supply of ribosomal proteins; in fact, cells in which the rRNA fragments are not removed ultimately lose viability (33). Thus, quality control of stable RNA metabolism would appear to be an important function for cell survival.

\textbf{RNases Contributing to Stable RNA Degradation}

Currently, at least 15 RNases are known in \textit{E. coli} and at least 10 in \textit{Bacillus subtilis} (40). However, although considerable information has accumulated about the roles of these enzymes in mRNA decay and stable RNA maturation, we know relatively little about their involvement in the degradation of stable RNA. A few studies directly dealing with this issue were carried out years ago (e.g., Refs. 12 and 41), but at that time only a small number of the currently known RNases had been identified, and many of the mutant strains used in that work retained partial RNAse activity. The conclusion from such studies was that stable RNA degradation was initiated by endonuclease cleavage followed by exoribonuclease action to generate mononucleotides (42), a sequence of events remarkably similar to how we currently view mRNA breakdown (3–5). The endonuclease, RNase I, and the exoribonucleases, PNPase and RNase II, were implicated in the degradation that occurred following nutrient deprivation (41, 42). However, further analysis of the products of RNA degradation indicated that the role of RNase I was primarily at elevated temperatures (45–50 °C) and that although 5’-mononucleotides were produced, an enzyme other than RNase II was probably responsible (43). Thus, the identity of the RNases involved remained uncertain.

One possibility suggested for the endoribonuclease was an enzyme termed RNase N, which cleaved rRNA, poly(U), and poly(C) to small oligonucleotides and 5’-mononucleotides (44). RNase N was reported to be active on all types of RNAs, to be intracellular, and to be a large protein of 120 kDa (45). Unfortunately, mutant strains lacking this activity were not obtained, so that its actual role \textit{in vivo} was not established. More recent attempts to identify and isolate this enzyme have proven unsuccessful,\(^2\) leaving the status of RNase N unclear.

On the other hand, a role for RNase I in at least some aspects of stable RNA degradation seems likely, particularly in those instances in which damage to the cell membrane occurs, which would allow for entry of active enzyme into the cytoplasm (21, 23, 24). As noted earlier, the fact that certain types of RNA degradation can be eliminated in RNase I mutants and that 3’-phosphorylated products are found, which are generated only by RNase I, supports the involvement of this enzyme. However, it is also clear that at least one additional endoribonuclease will be required to initiate the stable RNA degradation that occurs during starvation or quality control of ribosome assembly.

Our understanding of exoribonuclease involvement is somewhat more advanced. Nucleoside diphosphates are one of the degradation products found as a result of carbon starvation and are not present in mutant strains lacking PNPase (43). PNPase has also been shown to be involved in quality control processes that result in degradation of defective tRNA (37) and in removal of RNA fragments derived from rRNA (33). Based on these observations, PNPase undoubtedly contributes to pathways degrading stable RNAs. Interestingly, PNPase is also a major participant in mRNA degradation (3, 5). A portion of the cell’s population of PNPase is found as part of the degradosome, a complex that also contains the endonuclease, RNase E, and an RNA helicase (3, 5). Although the degradosome is thought to be primarily an important component of mRNA decay, fragments of rRNA have been found associated with it, and it can degrade rRNAs \textit{in vitro} (46). Whether RNase E and/or the degradosome might play a role in stable RNA degradation \textit{in vivo} remains to be established. It is already known that RNase E participates in maturation of rRNA (47, 48) and tRNA (49, 50).

Evidence suggests that the exoribonuclease, RNase R, participates in some types of stable RNA degradation. As already noted, either RNase R or PNPase are required to degrade the fragments of rRNA that are generated during quality control of rRNA metabolism (33). Likewise, RNase R may participate in the degradation of defective tRNAs.\(^3\) Inasmuch as 5’-mononucleotides are generated upon RNA degradation during carbon starvation (43) and RNase II is not involved, RNase R is a strong candidate, particularly as it is known to be able to digest rRNA (33, 51). Whether RNase R acts during starvation for other types of nutrients as well remains to be determined. If these conclusions are correct, it may be that the exoribonuclease components of the stable RNA degradation machinery already have been identified.\(^4\)

\section*{Regulation}

Of critical importance to our understanding of stable RNA degradation is clarifying how these processes are regulated. In particular, one would want to know how RNA stability is maintained during exponential growth and what are the signals and mechanisms that trigger degradation in other situations. The simplest model would be that RNAs are degraded unless they are somehow protected against the action of RNases. Thus, in growing cells, the stability of rRNA would most likely be a consequence of its incorporation into ribosomes and protection by ribosomal proteins. It is known that synthesis of rRNA and of ribosomal proteins is closely coordinated over a range of growth rates (16–18). When this coordination is disrupted, for

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\(^2\) P. R. Subbarayan and M. P. Deutscher, unpublished observations.

\(^3\) C. Kim, S. Reimers, and M. P. Deutscher, unpublished observations.
example, by overexpression of rRNA (52) or by its more rapid synthesis compared with ribosomal proteins (53), then the unprotected rRNA molecules become subject to degradation. Likewise, if an error takes place during ribosome assembly that results in incomplete protection of the rRNA, degradation also would follow, but in this instance that would be considered to be a quality control process (53).

In the case of tRNA molecules, their resistance to RNase action would derive from extensive secondary and tertiary structure and from their transient associations with acyl-tRNA synthetases, elongation factor, and ribosomes. The 3' terminus would be protected against exoribonucleases by aminocacylation. In fact, when aminocacylation is inhibited or during the short periods that a tRNA might be uncharged, it can be acted on by RNase T leading to removal of the 3'-terminal A residue of the CCA sequence (54). Because RNase T works very poorly at CC sequences (55), it would then fall off allowing for repair by tRNA nucleotidyltransferase. This continual removal and repair of the 3'-end of tRNA is the well known tRNA end-turnover process (56).

Outstanding Questions and Future Directions

What the proposed model fails to explain, and what is ripe for future work, is the mechanism of stable RNA degradation under starvation conditions. Either the structure of the ribosome is somehow altered to allow attack by certain intracellular RNases or an RNase activity is elevated. The latter could be accomplished either by increasing the activity of an existing RNase or by turning on an additional RNase in response to the starvation condition. Understanding how this is accomplished would be of considerable interest and may provide new insights into RNA metabolism. Likewise, identifying conclusively the RNases responsible for stable RNA degradation is of prime importance. With our current knowledge of bacterial RNases and the availability of mutant strains lacking one or more of these enzymes, such studies are waiting to be done. Additionally, the information gleaned from such work will make it possible to compare the machinery of stable RNA degradation to that of mRNA decay to help understand the similarities and differences between these processes.

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