PERSPECTIVE

Degradation of targeted mRNAs in *Escherichia coli*: regulation by a small antisense RNA

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In this issue of *Genes & Development*, Massé et al. (2003a) show that a small antisense RNA (saRNA) triggers mRNA degradation via a pathway in which the saRNA is also consumed. The stoichiometric binding of the saRNA to its mRNA target thus appears to activate the degradation of both RNAs (coupled degradation).

The physical interaction of complementary polynucleotides is arguably the fundamental chemical principle underlying molecular genetics. It is the most important feature of the structure of double-stranded DNA, and it is at the heart of the mechanism by which tRNA decodes mRNA to synthesize protein. The article by Massé et al. (2003a) reports novel findings on the action of a chromosome-encoded saRNA in the regulation of gene expression. They show that RyhB, an saRNA, triggers mRNA degradation via a pathway in which RyhB is degraded together with its target mRNA. Similar results were obtained with two other saRNAs. Thus, it seems likely that RyhB will serve as a model for saRNAs that activate mRNA degradation.

Biological regulatory mechanisms involving antisense RNA have been recognized for many years in *Escherichia coli*. However, until recently, the known antisense RNAs were encoded by extrachromosomal elements such as transposons, plasmids, and bacteriophage. With the current renaissance in interest in small noncoding RNAs, a surprising number of putative small regulatory RNAs (50–100), encoded on the *E. coli* chromosome, have recently been described. An important factor in the discovery of these RNAs was the availability of the complete genome sequence of *E. coli* and related bacteria such as *Salmonella*. This genomic information facilitated searches based, in part, on sequence conservation in noncoding regions of the chromosome. It is only now that the function of some of the newly dis-

covered RNAs is being elucidated. Although it seems reasonable to believe that the chromosome-encoded saRNAs and the classical antisense RNAs from transposons, plasmids, and bacteriophage act by similar mechanisms, I will argue that there could be some significant differences.

This perspective is based on the accompanying research article by Massé et al. (2003a). As a reference for recent developments on small regulatory RNAs in *E. coli*, I highly recommend the review by Susan Gottesman that was published in *Genes & Development* last year (Gottesman 2002). In this perspective, I will describe the antisense RNAs from transposons, plasmids, and bacteriophage that have been characterized over the past twenty years (classical antisense), then introduce the chromosome-encoded antisense RNAs that have been discovered recently (renaissance antisense). After that, I will briefly discuss some differences between these two families of antisense RNA, then discuss the work in the Massé et al. (2003a) article and its implications for the role of the chromosome-encoded antisense RNAs in mRNA degradation.

Classical antisense

Antisense RNAs have been known in *E. coli* for over twenty years. As has often been the case in molecular genetics, their discovery stemmed from the study of relative simple systems such as transposons, plasmids, and bacteriophage. Perhaps the best known antisense RNAs are those involving the control of plasmid replication. ColE1 plasmid copy number is controlled by the interaction between an antisense RNA, RNAI, and an RNA primer, which is involved in initiating DNA replication, RNAII (Polisky 1988; Eguchi et al. 1991). RI plasmid copy number is controlled by an interaction between an antisense RNA, CopA, and an mRNA encoding the RepA protein (Wagner and Simons 1994; Wagner et al. 2002). Other well studied systems include the control of RI plasmid postsegregational killing by Sok RNA, the

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control of *Tn10* transposition by RNA-OUT, and the control of bacteriophage lambda lysogeny by OOP RNA (Wagner and Simons 1994; Gerdes et al. 1997; Gottesman 2002; Wagner et al. 2002).

These systems have a number of common features. The antisense RNAs are *cis*-encoded; that is, they are transcribed from the same loci, but in the sense opposite from the target RNA. Thus, the *cis*-encoded antisense RNAs have perfect complementarity to large stretches of the target RNA. Although the interaction of these RNAs can ultimately lead to the formation of extended double-stranded RNAs, as might be expected, the antisense RNA and its target exist as folded molecules containing RNA stem-loops. Their initial interaction involves the pairing of a few bases between complementarity loops, in an interaction that is not that much different from the decoding of mRNA by tRNA (Zeiler and Simons 1998). This weak interaction occurs in an initial step in which the antisense RNA scans a large number of possible targets. In a subsequent step, interacting RNAs with extended complementarity can isomerize into stable double-stranded RNA structures.

The formation of a complex between the antisense RNA and its target can have a variety of biological effects. In the case of ColE1 plasmid replication, the interaction of RNAI with RNAII prevents a conformational change in RNAII that is required for priming DNA synthesis. High levels of RNAI block plasmid replication, whereas low levels permit plasmid replication. In the case of RI plasmid replication, CopA represses the translation of the mRNA encoding the RepA protein, which is required for initiating DNA synthesis. Other antisense RNAs have been reported to affect processes that include transcription, translation, and mRNA stability (Gottesman 2002; Wagner et al. 2002).

The study of the antisense RNA regulating ColE1 plasmid replication, RNAI, has contributed significantly to our understanding of RNA degradation in *E. coli*. RNAI, which is 108 nt in length, has a tRNA-like secondary structure in the sense that it can be drawn as a cloverleaf containing three stem-loops. However, unlike tRNA, it is short-lived with a 2-min half-life, which is comparable to that of an mRNA (Cohen 1995). The similarity to mRNA does not end there. Its degradation involves many of the same enzymes in the general pathway for mRNA turnover in *E. coli* including RNase E, polynucleotide phosphorylase (PNPase), and poly(A) polymerase (PAP). Indeed, the gene encoding PAP in *E. coli* is named *pcnB* (plasmid copy number B) because it was first identified due to its effect on ColE1 plasmid copy number (Cao and Sarkar 1992). Degradation of the antisense RNAs CopA and Sok has also been shown to follow a pathway comparable to that of RNAI. In the case of these antisense RNAs, their short lifetime is an important property permitting timely responses that are necessary for proper regulation (Gerdes et al. 1997; Gottesman 2002; Wagner et al. 2002). It should be mentioned that the degradation of RNAI, CopA, and Sok in an mRNA-like pathway has generally been regarded as the turnover of free antisense RNA, that is, not in a complex

with its target RNA. In light of the work by Massé et al. (2003a), this point perhaps deserves re-examination.

Renaissance antisense

A renewal of interest in small RNAs in *E. coli* was sparked by the recent discovery of a large number of chromosome-encoded noncoding RNAs (Argaman et al. 2001; Rivas et al. 2001; Wassarman et al. 2001; Gottesman 2002). For the purpose of this perspective, I am focusing on those RNAs that act by an antisense mechanism. As described above, I will refer to them as saRNAs (small antisense RNAs). However, not all chromosome-encoded noncoding RNAs are antisense RNAs, and there is not yet a consensus as to how these RNAs should be named. In contrast to the classical antisense RNAs described above, the chromosome-encoded saRNAs are *trans*-encoded; that is, they are transcribed from loci that are distinct from the genes encoding their targets. Furthermore, the complementarity of the saRNAs to their targets is imperfect. The structure of the complexes formed between the chromosome-encoded saRNAs and their targets has not yet been investigated in any detail, and it is not known whether there are any conserved features in the structure of these imperfectly paired RNAs. Some of the *trans*-encoded saRNAs are now known to interact with multiple targets. Thus, they can regulate a set of mRNAs that are encoded by unlinked genes. The saRNAs regulating mRNA, which have been characterized to date, all appear to interact with the 5' untranslated region (UTR) of their targets.

Another feature of the chromosome-encoded saRNAs is that many of them are ribonucleoproteins formed by an interaction with Hfq, which is an RNA-binding protein related to the Sm proteins in eukaryotes. There is also evidence that some of the target mRNAs interact with Hfq. The *hfq* gene was originally discovered as a host factor necessary for the propagation of the RNA phage QB. It was only recently that the relationship between the prokaryotic Hfq protein and the eukaryotic Sm proteins was established (Moller et al. 2002; Zhang et al. 2002). This ubiquitous family of RNA-binding proteins is believed to act as chaperones in RNA-RNA interactions. Indeed, Hfq has been shown to promote RNA-RNA annealing in vitro. Recent work shows that the coimmunoprecipitation of small RNAs with Hfq can be used as a means of isolating and identifying putative saRNAs (Zhang et al. 2003).

RyhB, the saRNA characterized in the article by Massé et al. (2003a), is a good model demonstrating many of the characteristics described in the previous paragraph. RyhB transcription is under the control of the Fur (ferric uptake regulation) repressor, which regulates transcription in response to iron levels (Massé and Gottesman 2002; Massé et al. 2003b). When RyhB transcription is derepressed by iron depletion, the newly synthesized RyhB binds to a variety of mRNA targets involved in iron binding and storage, inhibiting the synthesis of the corresponding proteins. The genes in this regulatory circuit are not linked. RyhB acts as a repressor, although

there are examples of activators such as DsrA, which stimulates translation of the *spoS* mRNA (Majdalani et al. 1998). In contrast to the classical antisense RNAs discussed above (RNAI, CopA, and Sok), the half-life of RyhB is greater than 30 min. Similar stability has been observed for the DsrA, OxyS, and Spot 42 saRNAs (Altuvia et al. 1997; Majdalani et al. 2001; Repoila and Gottesman 2001; Moller et al. 2002). It has been pointed out previously that the long lifetime of these antisense RNAs appears to be at odds with their function as a reversible switch in gene regulation (Gottesman 2002). I will return to this point below.

Enlightened antisense

The distinctions that I have made between classical antisense RNA, which is *cis*-encoded, and renaissance antisense RNA, which is *trans*-encoded, could be misleading. In the case of extrachromosomal elements, *trans*-encoded saRNAs may not yet have been identified, because genomic approaches have not been used. For instance, it has been established over the past decade that the bacteriophage T4 of *E. coli* is founder of a large family of related phage, some of which grow on bacteria that are only distantly related to *E. coli* (Desplats and Krisch 2003). The systematic sequencing of the genomes of T4-related phages has only recently begun. Thus, it is possible that new genomic information will eventually lead to the identification of *trans*-encoded saRNAs in bacteriophage. The lack of examples of *cis*-encoded antisense RNAs in the *E. coli* genome could be due to the methods that have recently been used to find small regulatory RNAs. These screens were based on the analysis of non-coding regions of the chromosome. Thus, *cis*-encoded antisense RNAs with extensive complementarity to coding regions would have been missed.

If, however, there is a real distinction between *cis*-encoded antisense RNA in extrachromosomal elements and *trans*-encoded antisense RNA in the chromosome, then this might reflect differences in selective pressure on the evolution of the genes encoding antisense RNA. In the case of the extrachromosomal elements, which are often small and mobile, selective pressure might keep the gene encoding an saRNA tightly linked to the gene encoding the target. This would favor *cis*-encoded antisense RNA (Gottesman 2002). In the case of the bacterial chromosome, this pressure might be relaxed, thus permitting the evolution of *trans*-encoded saRNAs that act on multiple, unlinked targets.

Degradation of targeted mRNAs

The striking result of the work in the article by Massé et al. (2003a) is that RyhB triggers the degradation of its target mRNA via a pathway in which the saRNA is also degraded. Furthermore, similar results were obtained with two other saRNAs, DsrA and OxyS, leading to the proposal of a "coupled degradation" pathway. The rapid degradation of the saRNA together with the target

mRNA suggests that previous measurements, showing that the free saRNAs are quite stable, are misleading. In the presence of their mRNA targets, the saRNAs turn over rapidly. Whether the activation of RNA degradation is a direct consequence of saRNA binding or is due to the inhibition of mRNA translation is a question that remains to be addressed (see below).

Coupled degradation has some notable features. If the saRNA acts directly, then it is limited only by the rate of complex formation with the target mRNA. If the saRNA is degraded together with the mRNA, then the arrest of the synthesis of the saRNA should rapidly restore the expression by newly synthesized mRNA. Formally, the activity of RyhB is similar to a protein repressor of mRNA translation, but with two important differences. First, the transcription of the *ryhB* gene yields the repressor with no requirement for protein synthesis. Second, coupled degradation destroys RyhB, whereas protein repressors are usually stable. Many protein repressors of translation in *E. coli* are involved in feedback regulation that assures appropriate levels of synthesis of specific proteins. These proteins are only depleted by their assembly into a structure such as the ribosome or by dilution upon growth. Thus, it seems reasonable to suggest that stable protein repressors are best suited for feedback systems that maintain balanced levels of expression, whereas saRNAs that are degraded with their mRNA target are best suited for reversible switches responding to changes in the environment.

The overall pathway for mRNA degradation in *E. coli* is now well established (Coburn and Mackie 1999; Grunberg-Manago 1999; Régner and Arraiano 2000; Steege 2000). Transcription and translation are coupled, and mRNAs are often polycistronic. Message lifetime depends on the specific transcript: it varies from ~1 to 20 min under normal conditions of laboratory growth. In the case of large polycistronic messages, cistrons in the 5' end of a message can be degraded before the synthesis of the 3' end is completed. Bacterial mRNAs are not modified at the 5' end (i.e., no cap structures), and there are no known 5' → 3' exoribonucleases. The 3' ends of bacterial mRNAs are often protected from 3' → 5' exonucleases, either as part of the transcription elongation complex (nascent transcripts) or by RNA stem-loops that are formed upon transcription termination. It is now widely accepted that mRNA degradation is initiated by endoribonucleolytic cleavage in a pathway producing mRNA fragments, which are then degraded to nucleotides by the 3' → 5' exonucleases. Thus, the attack of an mRNA by an endoribonuclease is usually the initial step in mRNA degradation.

The principal endoribonuclease in *E. coli* mRNA decay is generally believed to be RNase E, which is a single-strand specific enzyme (Kushner 2002). However, in a limited number of cases, RNase III, which is double-strand-specific, has been implicated in mRNA decay. The principal exonucleases in mRNA decay are PNPase and RNase II. PNPase and RNase E are associated in a multienzyme complex, called the RNA degradosome, that also contains a DEAD-box RNA helicase and the

glycolytic enzyme enolase (Carpousis et al. 1994, 1999; Miczak et al. 1996; Py et al. 1996). RNase E is a large, multidomain protein with a noncatalytic C-terminal half that contains RNA-binding sites as well as protein-binding sites for interactions with RhlB, enolase, and PNPase (Kaberdin et al. 1998; Vanzo et al. 1998).

The enzymatic activity of RNase E is essential for viability, but strains with deletions of the noncatalytic regions of RNase E, which disrupt the RNA degradosome, are viable (Kido et al. 1996; Vanzo et al. 1998). In the study by Massé et al. (2003a), several different mutants of RNase E were used: the *rne-3071* allele encodes a temperature-sensitive RNase E that can be inactivated by shifting the cells from 30°C to 43.5°C, whereas the other mutants encode RNase E in which part or all of the noncatalytic region has been deleted. Taken together, the experiments with these mutants shows that degradation of both the mRNA target and RyhB depends on the enzymatic activity of RNase E and is slowed when the noncatalytic part of RNase E is disrupted. Thus, RNase E is necessary for coupled degradation, and the RNA degradosome appears to be implicated in this process.

A priori, the destabilization of an mRNA by an antisense RNA might be expected to involve RNase III, as this ribonuclease is double-strand-specific. Indeed, the characterization of RNA OOP (bacteriophage lambda) and RNA-OUT (Tn10) demonstrated the importance of RNase III in the destabilization of the mRNA targets of these antisense RNAs (Case et al. 1990; Krinke and Wulff 1990). Furthermore, in recent work on the regulation of *sodB*, which is a target of RyhB, both RNase E and RNase III were implicated in its repression (Dubrac and Touati 2002). In these experiments, a translation fusion between the 5' UTR of the *sodB* mRNA and *lacZ* was studied. Massé et al. (2003a) report no effect of RNase III on the turnover of authentic *sodB* mRNA. Whether the results of Dubrac and Touati are due to a direct or indirect effect of RNase III is an issue that should be addressed. If it turns out that the chromosome-encoded saRNAs work mainly by a coupled degradation pathway involving RNase E and the RNA degradosome, this would be significantly different from the RNase III-dependent decay pathway elucidated for RNA OOP and RNA-OUT. The difference between *cis*-encoded and *trans*-encoded saRNAs might reflect a difference between perfect versus imperfect complementarity. The thinking behind this suggestion is that *trans*-encoded RNAs with imperfect complementarity might not form good substrates for RNase III.

The remaining issue is whether RNase E and the RNA degradosome directly initiate the degradation of the RyhB/mRNA complex. Massé et al. (2003a) make the provocative suggestion that the binding of RyhB to its target mRNA could promote RNA degradation by recruiting RNase E or the RNA degradosome to the message. They point out that Hfq recognizes single-stranded, AU-rich regions and that this specificity is similar to that of RNase E. They suggest that coupled degradation could involve a rearrangement in which Hfq is released upon formation of an saRNA/mRNA complex, thus cre-

ating a target for RNase E. This model is supported to some extent by their observations that RyhB by itself is unstable in the absence of Hfq and the degradation of Hfq-free RyhB depends on RNase E. The role of the RNA degradosome in this model is unclear. The RNA helicase in the degradosome could be involved in RNA-RNA or RNA-protein rearrangements. The recruitment of PNPase, a component of the degradosome, to the complex could also be part of the coupled degradation pathway. However, the possibility that the mRNA destabilizing effect of RyhB is indirect needs to be considered. Ribosome-free mRNA is sensitive to degradation by RNase E, and this sensitivity requires the noncatalytic part of RNase E (Iost and Dreyfus 1995; Lopez et al. 1999; Leroy et al. 2002). Thus, if RyhB inhibits translation, this could be the principal reason for the destabilization of the mRNA. The difficulty with this viewpoint is that there is no obvious explanation for the degradation of the saRNA. Perhaps degradation of the translationally repressed mRNA releases RyhB in a form (Hfq free?) that is susceptible to degradation. It should be interesting to design new experiments that will permit discrimination between these possibilities.

It is evident that elucidating the pathway of coupled degradation will be an important challenge for future work on the chromosome-encoded saRNAs. Much needs to be learned about the formation and structure of the saRNA/mRNA complex. The reconstitution of the RyhB system in vitro should open approaches to a number of questions: (1) Does complex formation involve rearrangements and/or the release of Hfq? (2) Does complex formation prevent ribosome binding? (3) Does complex formation lead to a significant change in the sensitivity to ribonucleases? In addition to in vitro approaches, because the chromosomal saRNAs are *trans*-encoded, it is relatively simple to envision in vivo experiments in which the saRNA or the target mRNA are modified with the aim of elucidating the sequence and structural requirements for coupled degradation. The interplay between the in vitro and in vivo approaches should permit a detailed and accurate portrayal of how the chromosome-encoded saRNAs work. This research is not without interest in terms of practical applications in biotechnology, and it might yield clues regarding the function of natural and artificial saRNAs in other organisms.

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