Biochimica et Biophysica Acta 1829 (2013) 742–747

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagrm

Review

Regulatory RNAs and target mRNA decay in prokaryotes ☆

David Lalaouna [a], Maxime Simoneau-Roy [a,b], Daniel Lafontaine [b], Eric Massé [a,*]

[a] Université de Sherbrooke, Faculty of Medicine and Health Sciences, Department of Biochemistry, RNA Group, 3201 Jean Mignault Street, Sherbrooke, Quebec J1E 4K8, Canada
[b] Université de Sherbrooke, Faculty of Sciences, Department of Biology, RNA Group, 2500 Blvd Université, Sherbrooke, Quebec J1K 2R1, Canada

ARTICLE INFO

Article history:
Received 19 November 2012
Received in revised form 22 February 2013
Accepted 25 February 2013
Available online 14 March 2013

Keywords:
Small RNA
mRNA translation
mRNA degradation
RNase E
Ribonuclease
Riboswitch

ABSTRACT

Recent advances in prokaryote genetics have highlighted the important and complex roles of small regulatory RNAs (sRNAs). Although blocking mRNA translation is often the main function of sRNAs, these molecules can also induce the degradation of target mRNAs using a mechanism that drastically differs from eukaryotic RNA interference (RNAi). Whereas RNAi relies on RNase III-like machinery that is specific to double-strand RNAs, sRNA-mediated mRNA degradation in *Escherichia coli* and *Samonella typhimurium* depends on RNase E, a single-strand specific endoribonuclease. Surprisingly, the latest descriptions of sRNA-mediated mRNA degradation in various bacteria suggest a variety of previously unsuspected mechanisms. In this review, we focus on recently characterized mechanisms in which sRNAs can bind to target mRNAs to induce decay. These new mechanisms illustrate how sRNAs and mRNA structures, including riboswitches, act cooperatively with protein partners to initiate the decay of mRNAs. This article is part of a Special Issue entitled: RNA Decay mechanisms.

1. Introduction

Post-transcriptional gene regulation mediated by small regulatory RNAs (sRNAs) is commonly found in both prokaryotic and eukaryotic kingdoms. Small RNAs in these systems act to down-regulate target genes by decreasing translation and/or increasing mRNA turnover [1–3]. Eukaryotic microRNAs (miRNA) or small interfering RNAs (siRNA) are assembled into ribonucleoprotein complexes known as RNA-induced silencing complex (RISC) [1,2]. RISCs are composed of a variety of proteins such as RNA-binding proteins, RNA helicases, and nucleases. These characteristics are reminiscent of bacterial sRNAs and RNA-binding protein Hfq, both of which form ribonucleoprotein complexes with the endoribonuclease RNase E [4]. Although there are multiple functional similarities between eukaryote and prokaryote processes, this review will focus on prokaryotic systems of mRNA decay, notably in *Escherichia coli*.

In bacteria, sRNAs are usually non-coding and smaller than 300 nucleotides. At present, ~100 sRNAs have been identified, located either on *E. coli* plasmid or its chromosome [3,5]. Antisense sRNAs, which act by base-pairing with mRNA to inhibit translation of their targets, represent the major class of sRNAs in bacteria. This group can be subdivided as true antisense RNAs or *cis*-encoded sRNAs, synthesized from the strand complementary to the mRNA they regulate, or *trans*-encoded sRNAs, synthesized at a different genomic location. The latter type of sRNA possesses limited complementarity with mRNA targets (about 7 to 12 bases) that enables *trans*-encoded sRNAs to modulate the activity and stability of multiple mRNAs [3]. The segment of contiguous base-pairing is called “seed region” by comparison to eukaryotic microRNA system [6]. Basically, base-pairing between sRNA and mRNA targets can lead to the activation or inhibition of mRNA translation (RNAIII, [7]), mRNA stabilization (GadY, [8]) or mRNA degradation (RyhB, [9]).

2. sRNAs as mRNA translation modulators

Most sRNAs characterized to date block translation by direct binding to the ribosome-binding site (RBS) in the 5′-UTR (UnTranslated Region) of target mRNAs (Fig. 1A). Basically, sRNA sequester and mask the RBS through interactions involving short regions (7–12 bases) of imperfect complementarity, to prevent 30S ribosome binding and translation initiation.

In contrast, some sRNAs activate translation by binding to the 5′-untranslated region (5′-UTR) of the target mRNA. Usually, these target mRNAs harbor an intrinsic secondary structure in the 5′-UTR that inhibits ribosome binding. Thus, when a sRNA binds to the inhibitory sequence in the 5′-UTR, the RBS becomes available, allowing initiation of translation (Fig. 1D). For instance, this regulation mechanism was shown for both DsrA and RyhB sRNAs, which stimulate RpoS [10] and *shiA* translation initiation in *E. coli* [11,12], respectively. Another example is the activation of *hla* mRNA translation by the

☆ This article is part of a Special Issue entitled: RNA Decay mechanisms.

* Corresponding author. Tel.: +1 819 821 8000x75475.
E-mail address: eric.masse@usherbrooke.ca (E. Massé).

1874-9399/$ – see front matter.
http://dx.doi.org/10.1016/j.bbagrm.2013.02.013

5′-end of RNAIII sRNA in *Staphylococcus aureus* [7]. One can speculate that the number of sRNAs activating mRNA translation is most likely underestimated as the effect on targeted mRNAs is often too subtle to be detected by microarrays or Northern blots. Remarkably, whether the target mRNAs are activated or repressed by sRNAs, they require the RNA chaperone Hfq for the full extent of regulation at least in *E. coli* and *Samonella*.

3. The RNA chaperone Hfq and mRNA translation repression

In *E. coli*, most sRNAs that bind to mRNAs depend on the 11 kDa RNA chaperone Hfq. *In vivo*, Hfq monomers assemble to form hexamers and dodecamers, which stabilize sRNAs and modulate base-pairing with target mRNAs [13–15]. Several studies have shown similarities in both protein sequence and structure between bacterial Hfq and eukaryotic Sm proteins, which bind small nucleolar RNAs and are components of the spliceosome in eukaryotes [16]. Recently, a number of studies, using Hfq as bait, have identified a few dozen sRNAs bound to this chaperone protein in *E. coli* [17,18] and *Salmonella* [19–21]. Based on the fact that Hfq binds to so many sRNAs, it has become the focus of intensive research aimed at a better understanding of its cellular role. The chaperone Hfq likely helps binding through remodeling RNA structures and by increasing local concentrations of the sRNA and target mRNA [13–15,22].

A recent report has provided evidence that Hfq is recruited by sRNA Spot42 and directly represses mRNA translation [23]. According to this novel mechanism, Spot42 is exclusively involved in Hfq recruitment and does not contribute directly to mRNA regulation. This is the first example of a "role reversal" between a sRNA and Hfq where Hfq is directly involved in the translational repression of the target mRNA and where the sRNA acts only as a recruitment factor. Furthermore, several groups have shown that Hfq can also bind target mRNAs such as *sodB*, *iscS*, and *sdhC* even in the absence of sRNA [22,24]. This direct binding on target mRNAs suggests that Hfq may help to recruit the ribonucleoprotein silencing complex on specific mRNAs.

4. Hfq antagonizes RNase E activity

Hfq is also a key player in the modulation of mRNA stability. In fact, Hfq can protect transcripts against ribonuclease E (RNase E) attacks due to coincident Hfq binding sites and RNase E cleavage sites on mRNA (AU-rich single-strand regions) [4]. RNase E is a single-strand-specific endoribonuclease that initiates the decay of many mRNAs in *E. coli*. Subsequently to RNase E-dependent cleavage, the resulting intermediate products are degraded by endo- and exoribonucleases (*e.g.* polynucleotide phosphorylase (PNPase), RNase II, and RNase R). RNase E is part of a multiprotein complex called RNA degradosome that is composed of a 3′-exoribonuclease (polynucleotide phosphorylase or PNPase), a DEAD-box RNA helicase (RhlB), a glycolytic enzyme (enolase), and other proteins, depending on physiological conditions [25,26].

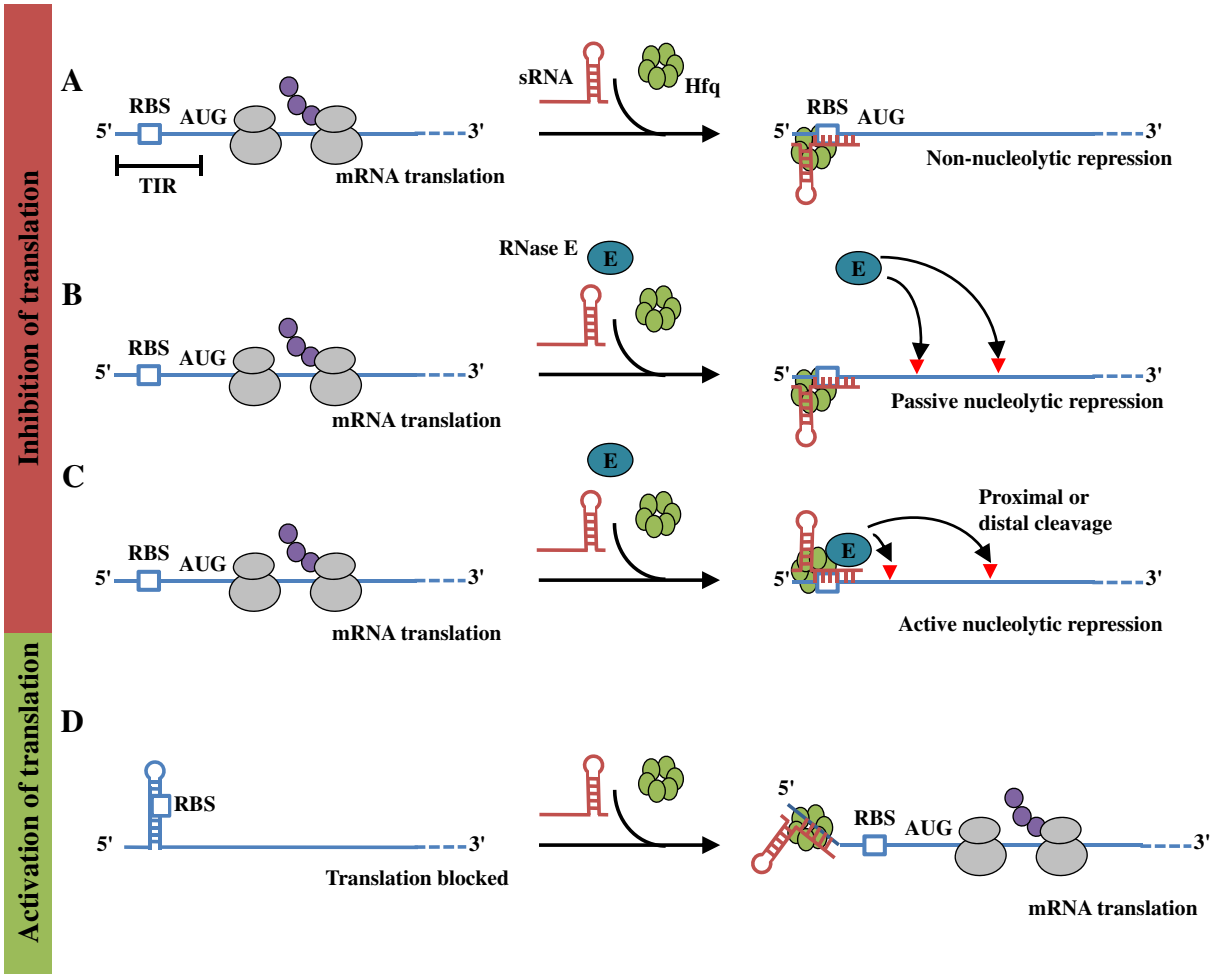

Fig. 1. Small RNA-based regulatory mechanisms of mRNA expression.

5. sRNA-mediated mRNA decay

A new family of sRNAs with a more complex mechanism of action was first characterized ten years ago [9]. This group of sRNAs, which quickly became a paradigm in sRNA mechanism, was shown to base-pair with target mRNAs to trigger their degradation by RNase E (Fig. 1B and C). Incidently, RNA-binding Hfq was also shown to be involved in the recruitment of RNase E and sRNA-mediated mRNA decay [27,28]. The first example of sRNA involved in sRNA-mediated mRNA degradation was RyhB, which coordinates bacterial response to iron starvation. The sRNA RyhB is essential for the iron-sparing response that redistributes scarce amounts of intracellular iron and allows growth during severe iron-limitation [29–31]. RyhB induces the rapid degradation (within 10 min) of at least 18 mRNAs, which all encode iron-using proteins, to redirect iron to essential regions of the cell [9,32]. A similar mechanism of fast mRNA decay was recently confirmed for additional sRNAs such as SgrS [33], MicC [34], GcvB [35], OmrA and OmrB [36–38], and RybB [39].

The rapidity of sRNA-mediated mRNA degradation suggests that target mRNAs have to be silenced as soon as possible under conditions where RyhB is expressed (low iron). Remarkably, Morita et al. [40] showed that translational repression occurs in the absence of sRNA-mediated mRNA degradation for the SgrS/*ptsG* and RyhB/*sodB* duplexes. Thus, in most cases, translational repression is sufficient for gene silencing. One possible physiological role of mRNA degradation mediated by sRNAs is to make gene silencing irreversible. It has been observed that during the process of sRNA-mediated mRNA degradation, the sRNA is degraded stochiometrically together with its target [4,9,41]. However, recent data suggest that the stoichiometric cleavage of sRNA and target mRNA may not be concomitant in the case of all sRNAs. Indeed, whereas sRNA MicC in *Salmonella* induces the degradation of *ompD* mRNA, MicC itself becomes degraded in a sequential manner, possibly when it is liberated from the degraded target [42].

The mechanism by which sRNAs/Hfq association leads to the degradation of target mRNAs by RNase E remains unclear. Two pathways can be proposed to explain mRNA destabilization. According to one pathway, mRNAs may become more sensitive to RNase E attacks after base-pairing with sRNA, as a result of the loss of protection conferred by translating ribosomes (Fig. 1B, passive nucleolytic repression) [43]. According to the other pathway, recruitment of RNase E on the target mRNA triggers formation of a sRNA/Hfq/RNase E complex that favors RNase E attacks; this complex then becomes a specialized RNA decay machine (Fig. 1C, active nucleolytic repression). In fact, in some cases such as MicC/*ompD* duplex, it cannot be assumed that mRNA decay is due to an indirect effect of mRNA translation inhibition. The sRNA MicC has been first identified as a repressor of the major porin OmpC synthesis in *E. coli*. MicC blocks *ompC* translation by competing with ribosome binding [44]. In *Salmonella typhimurium*, MicC sRNA also pairs within the coding sequence (CDS) of *ompD* mRNA [34]. Due to the fact that MicC binds the *ompD* mRNA far downstream of the RBS, MicC is unable to directly block *ompD* translation initiation. In order to abrogate OmpD synthesis, MicC has to induce a specific RNase E-dependent cleavage in the CDS of *ompD* [34]. In *S. typhimurium*, a similar mechanism is observed in *lpxR* mRNA regulation by MicF sRNA [45]. Furthermore, a recent study [46] has shown that the pairing of RyhB to target mRNA *sodB* initiates mRNA degradation even in the absence of translation of mRNA target. In fact, even if RyhB pairs at RBS, RyhB induces mRNA cleavage at a distal site located hundreds of nucleotides downstream, in the coding sequence of *sodB* mRNA. Despite these observations, the mechanism by which sRNAs induce distal mRNA cleavage remains obscure. To expand on these findings, Bandyra et al. [42] have suggested that sRNA/mRNA duplexes could actively stimulate RNase E attacks, contrasting with a simple and passive model of RNase E recruitment.

RNase E is known to be involved in two mRNA decay pathways: a first and direct pathway allowing cleavage of triphosphorylated primary transcripts (described above) and a 5′-end-dependent mRNA degradation pathway which requires prior conversion of the 5′-triphosphate extremity to a 5′-monophosphate by the RNA pyrophosphohydrolase RppH, in a manner similar to decapping of mRNAs in eukaryotes [47]. In fact, RNase E favors binding on a monophosphorylated 5′-end (5′-P end), which can bind in a discrete pocket on the surface of RNase E, facilitating mRNA cleavage at a downstream location by the RNase E active site [48–51]. Bandyra et al. [42] showed that the interaction of the 5′-P end of sRNA with a sensor pocket of RNase E favors closure of the catalytic domain to enhance nucleolytic activity (Fig. 1C). Evidence for this mechanism was obtained by studying artificial RNA duplexes and naturally occurring MicC/*ompD* duplexes. In the specific case of MicC/*ompD*, the sRNA/mRNA/Hfq complex not only recruits RNase E but also directly activates mRNA cleavage. Therefore, it can be suggested that an initial cleavage could induce RNase E activity by generation of a 5′-P end sRNA.

6. RNase III can replace RNase E

RNase E is not the only RNase involved in mRNA decay. Other RNases directly process and degrade mRNA transcripts like RNase III, which cleaves double-stranded RNA [52]. For example, *S. aureus* sRNA RNAIII is involved in the control of virulence by regulating several mRNAs encoding exotoxins and exoproteases [53]. RNAIII base-pairs with a couple of mRNA target independently of Hfq and induce degradation by RNase III instead of RNase E [54]. A same mechanism is observed for *tisAB* mRNA translational repression by IstR-1 sRNA [55].

In *S. typhimurium*, RNase III has also been shown to regulate MicA, a sRNA involved in porin control, in a target-coupled way [56]. Of note, RNase E is responsible for the control of free MicA levels in the cell.

7. Modulation of RNA stability is a widespread regulatory mechanism for sRNAs

The sRNA GadY is a member of the *cis*-encoded RNA class. GadY positively regulates the levels of *gadW* and *gadX* mRNA that are involved in response to acid stress [57]. Base-pairing of GadY with the intergenic region of the *gadX-gadW* mRNA results in targeted cleavage within the region of complementarity and in the stabilization of each transcript [58–60]. In *E. coli*, the activity of the pleiotropic/global regulator CsrA (carbon storage regulator) is regulated by two sRNAs CsrB and CsrC, which act by sequestering multiple CsrA dimers [61,62]. Suzuki et al. [63] have published that CsrB and CsrC degradation is mediated by a specific factor, termed CsrD. CsrD is not a nuclease but targets CsrB and CsrC for degradation by RNase E.

Whereas the RNA binding protein Hfq is frequently described as being involved in sRNA/mRNA duplex stabilization, it also stabilizes sRNA that acts by sequestration of regulatory proteins. For example, the Rsm sRNA family in *Pseudomonas aeruginosa*, which is homolog to the Csr sRNA family in *E. coli* (for reviews: [64,65]). Sonnleitner et al. [66] have shown that in *P. aeruginosa* RsmY sRNA is specifically stabilized by Hfq protein. Hfq could protect RsmY against RNase E attacks by masking the cleavage site of the enzyme [67].

8. Small RNAs and the termination factor Rho

A Rho-dependent mechanism of transcriptional termination by trans-acting sRNAs has recently been proposed [68]. In bacteria, there are two types of transcriptional termination, Rho-dependent and Rho-independent termination. In the case of Rho-independent termination, the mRNA generally presents a stem–loop structure

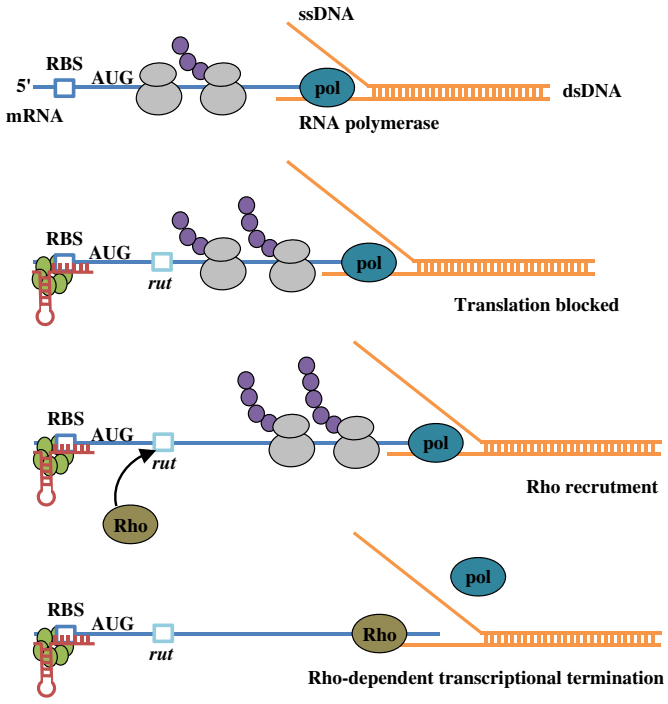

Fig. 2. Rho-dependent transcriptional termination mediated by a sRNA.

followed by a poly-uracil sequence, which facilitates dissociation of RNA polymerase from the DNA template. In this connection, Rho-independent transcription termination is a frequent mechanism used by riboswitches [69]. In the case of Rho-dependent termination, the transcription termination factor Rho is assumed to sequentially bind newly synthesized RNA through Rho utilization (*rut*) sites, to move in an ATP-dependent manner, towards the RNA 3′-end and to reach the transcription elongation complex in order to detach it from template DNA [70]. In *Salmonella*, Bossi et al. [68] have reported that ChiX sRNA indirectly exposes internal *rut* sites normally hidden by translating ribosomes by inhibition of *chiPQ* mRNA translation. In fact, ChiX down-regulates the distal portion of the bicistronic *chiPQ* operon by inducing early Rho-dependent transcription termination (Fig. 2). Recently, Rabhi et al. [71] have shown that, in *E. coli*, Hfq is able to bind Rho and to interfere with its activity. Thus, a Rho-dependent transcriptional termination mediated by a sRNA or the sRNA-Hfq complex, may be involved in the regulation of other target mRNAs.

9. Riboswitches

Riboswitches are RNA structures located within the 5′-UTR of mRNAs that regulate gene expression at the level of transcription, translation or splicing [72,73]. These RNA structures can change conformation by directly binding intracellular metabolites (*e.g.* vitamins or amino acids). Depending on the concentration of the metabolite, riboswitches will adopt either activating (ON) or repressing (OFF) conformations (Fig. 3A). Whereas riboswitches normally regulate in *cis*, recent results suggest that at least one riboswitch can also regulate in *trans*, similarly to sRNAs [74]. In this case, the riboswitch functions either in *cis*, as a conventional riboswitch, or in *trans*, as a sRNA. The sRNA is processed from the longer transcript by an unknown mechanism.

10. Riboswitches as targets for RNase E-based mRNA decay

Although every riboswitch is known, to date, to regulate either transcription elongation, translation initiation or splicing, it was recently shown that the *E. coli lysC* riboswitch controls both translation initiation and mRNA decay (Fig. 3B). When bound to the amino acid lysine, the *lysC* riboswitch adopts the OFF conformation, which simultaneously blocks translation initiation and rapidly induces RNase E degradation [75]. This rapid degradation suggests an active

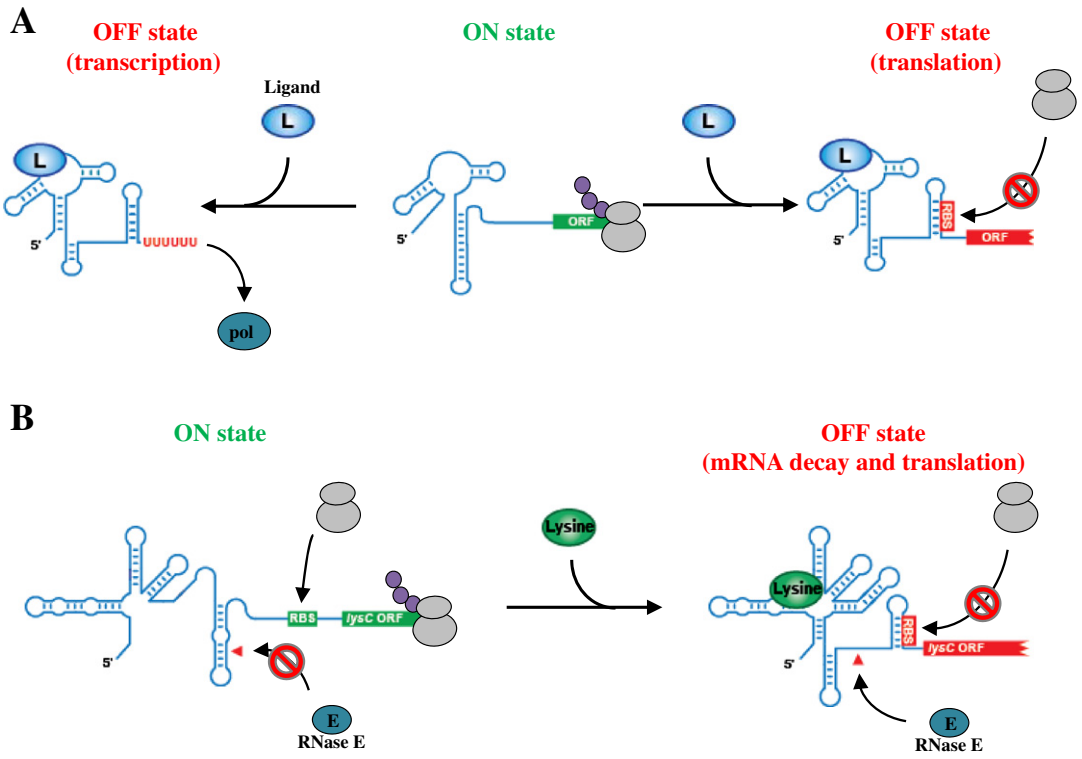

Fig. 3. Riboswitches, new targets for mRNA decay.

recruitment mechanism whereby the OFF structure is recognized by RNase E, consistent with an active nucleolytic repression. Because of the unique mechanism of *lysC* riboswitch, it is possible that the riboswitch structure is recognized by RNase E. In contrast to sRNA-mediated mRNA degradation, the nucleolytic cleavage in *lysC* riboswitch does not require the RNA chaperone Hfq [75]. However, the observed regulation of *lysC* is so rapid that it suggests the existence of a highly sophisticated mechanism [75]. Altogether, these studies revealed interesting features of riboswitch-controlled mRNA turnover. A key feature that remains to be elucidated is whether a riboswitch can control gene expression strictly by relying on the modulation of an RNase cleavage site. If this were the case, it would bring additional evidence that a RNA-based world may have evolved to protein-based life.

11. Conclusions

An increasing body of evidence supports the interpretation that, in many organisms including humans, mice, yeasts, and bacteria, transcription does not always map to genes [76–78]. In fact, it has become clearer that transcripts originate throughout the whole genome, including regions previously thought to be silent. This “pervasive” transcription also implies extensive post-transcriptional RNA regulation and processing, as suggested recently in bacteria [77]. Therefore, it is very likely that sRNAs play an even larger role than previously acknowledged in the regulation of gene expression. We believe that this new level of regulation may explain the observed lack of correlation between mRNA and protein levels [79].

Acknowledgements

Work in our respective laboratories was funded by an operating grant (MOP69005) to E.M. and (MOP82877) to D.A.L. from the Canadian Institute for Health Research (CIHR). E.M. is a Senior Scholar from the *Fonds de la Recherche en Santé du Québec* (FRSQ). DAL is a CIHR New Investigator scholar.

References

[1] Z. Li, T.M. Rana, Molecular mechanisms of RNA-triggered gene silencing machineries, Acc. Chem. Res. 45 (2012) 1122–1131.
[2] X. Chen, Small RNAs in development — insights from plants, Curr. Opin. Genet. Dev. 22 (2012) 361–367.
[3] G. Storz, J. Vogel, K.M. Wassarman, Regulation by small RNAs in bacteria: expanding frontiers, Mol. Cell 43 (2011) 880–891.
[4] I. Moll, T. Afonyushkin, O. Vytvytska, V.R. Kaberdin, U. Blasi, Coincident Hfq binding and RNase E cleavage sites on mRNA and small regulatory RNAs, RNA 9 (2003) 1308–1314.
[5] R. Raghavan, A. Sage, H. Ochman, Genome-wide identification of transcription start sites yields a novel thermosensing RNA and new cyclic AMP receptor protein-regulated genes in *Escherichia coli*, J. Bacteriol. 193 (2011) 2871–2874.
[6] D.P. Bartel, MicroRNAs: target recognition and regulatory functions, Cell 136 (2009) 215–233.
[7] A. Toledo-Arana, F. Repoila, P. Cossart, Small noncoding RNAs controlling pathogenesis, Curr. Opin. Microbiol. 10 (2007) 182–188.
[8] J.A. Opdyke, J.G. Kang, G. Storz, GadY, a small-RNA regulator of acid response genes in *Escherichia coli*, J. Bacteriol. 186 (2004) 6698–6705.
[9] E. Masse, F.E. Escorcia, S. Gottesman, Coupled degradation of a small regulatory RNA and its mRNA targets in *Escherichia coli*, Genes Dev. 17 (2003) 2374–2383.
[10] C.A. McCullen, J.N. Benhammou, N. Majdalani, S. Gottesman, Mechanism of positive regulation by DsrA and RprA small noncoding RNAs: pairing increases translation and protects rpoS mRNA from degradation, J. Bacteriol. 192 (2010) 5559–5571.
[11] H. Salvail, P. Lanthier-Bourbonnais, J.M. Sobota, M. Caza, J.A. Benjamin, M.E. Mendieta, F. Lepine, C.M. Dozois, J. Imlay, E. Masse, A small RNA promotes siderophore production through transcriptional and metabolic remodeling, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 15223–15228.
[12] K. Prevost, H. Salvail, G. Desnoyers, J.F. Jacques, E. Phaneuf, E. Masse, The small RNA RyhB activates the translation of shiA mRNA encoding a permease of shikimate, a compound involved in siderophore synthesis, Mol. Microbiol. 64 (2007) 1260–1273.
[13] A. Zhang, K.M. Wassarman, J. Ortega, A.C. Steven, G. Storz, The Sm-like Hfq protein increases OxyS RNA interaction with target mRNAs, Mol. Cell 9 (2002) 11–22.
[14] J. Vogel, B.F. Luisi, Hfq and its constellation of RNA, Nat. Rev. Microbiol. 9 (2011) 578–589.
[15] T. Moller, T. Franch, P. Hojrup, D.R. Keene, H.P. Bachinger, R.G. Brennan, P. Valentin-Hansen, Hfq: a bacterial Sm-like protein that mediates RNA-RNA interaction, Mol. Cell 9 (2002) 23–30.
[16] M.A. Schumacher, R.F. Pearson, T. Moller, P. Valentin-Hansen, R.G. Brennan, Structures of the pleiotropic translational regulator Hfq and an Hfq-RNA complex: a bacterial Sm-like protein, EMBO J. 21 (2002) 3546–3556.
[17] A. Zhang, K.M. Wassarman, C. Rosenow, B.C. Tjaden, G. Storz, S. Gottesman, Global analysis of small RNA and mRNA targets of Hfq, Mol. Microbiol. 50 (2003) 1111–1124.
[18] C. Lorenz, T. Gesell, B. Zimmermann, U. Schoeberl, I. Bilusic, L. Rajkowitsch, C. Waldsich, A. von Haeseler, R. Schroeder, Genomic SELEX for Hfq-binding RNAs identifies genomic aptamers predominantly in antisense transcripts, Nucleic Acids Res. 38 (2010) 3794–3808.
[19] Y. Chao, K. Papenfort, R. Reinhardt, C.M. Sharma, J. Vogel, An atlas of Hfq-bound transcripts reveals 3′ UTRs as a genomic reservoir of regulatory small RNAs, EMBO J. 31 (2012) 4005–4019.
[20] A. Sittka, S. Lucchini, K. Papenfort, C.M. Sharma, K. Rolle, T.T. Binnewies, J.C.D. Hinton, J. Vogel, Deep sequencing analysis of small noncoding RNA and mRNA targets of the global post-transcriptional regulator, Hfq, PloS Genet. 4 (2008) 20.
[21] A. Sittka, C.M. Sharma, K. Rolle, J. Vogel, Deep sequencing of Salmonella RNA associated with heterologous Hfq proteins in vivo reveals small RNAs as a major target class and identifies RNA processing phenotypes, RNA Biol. 6 (2009) 266–275.
[22] T.A. Geissmann, D. Touati, Hfq, a new chaperoning role: binding to messenger RNA determines access for small RNA regulator, EMBO J. 23 (2004) 396–405.
[23] G. Desnoyers, E. Masse, Noncanonical repression of translation initiation through small RNA recruitment of the RNA chaperone Hfq, Genes Dev. 26 (2012) 726–739.
[24] G. Desnoyers, A. Morissette, K. Prevost, E. Masse, Small RNA-induced differential degradation of the polycistronic mRNA iscRSUA, EMBO J. 28 (2009) 1551–1561.
[25] M.W. Gorna, A.J. Carpousis, B.F. Luisi, From conformational chaos to robust regulation: the structure and function of the multi-enzyme RNA degradosome, Q. Rev. Biophys. 45 (2012) 105–145.
[26] I.J. Silva, M. Saramago, C. Dressaire, S. Domingues, S.C. Viegas, C.M. Arraiano, Importance and key events of prokaryotic RNA decay: the ultimate fate of an RNA molecule, Wiley Interdiscip. Rev. RNA 2 (2011) 818–836.
[27] Y. Ikeda, M. Yagi, T. Morita, H. Aiba, Hfq binding at RhlB-recognition region of RNase E is crucial for the rapid degradation of target mRNAs mediated by sRNAs in *Escherichia coli*, Mol. Microbiol. 79 (2011) 419–432.
[28] T. Morita, H. Aiba, RNase E action at a distance: degradation of target mRNAs mediated by an Hfq-binding small RNA in bacteria, Genes Dev. 25 (2005) 294–298.
[29] J.F. Jacques, S. Jang, K. Prevost, G. Desnoyers, M. Desmarais, J. Imlay, E. Masse, RyhB small RNA modulates the free intracellular iron pool and is essential for normal growth during iron limitation in *Escherichia coli*, Mol. Microbiol. 62 (2006) 1181–1190.
[30] E. Masse, M. Arguin, Ironing out the problem: new mechanisms of iron homeostasis, Trends Biochem. Sci. 30 (2005) 462–468.
[31] E. Masse, S. Gottesman, A small RNA regulates the expression of genes involved in iron metabolism in *Escherichia coli*, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 4620–4625.
[32] E. Masse, C.K. Vanderpool, S. Gottesman, Effect of RyhB small RNA on global iron use in *Escherichia coli*, J. Bacteriol. 187 (2005) 6962–6971.
[33] C.K. Vanderpool, S. Gottesman, Involvement of a novel transcriptional activator and small RNA in post-transcriptional regulation of the glucose phosphoenolpyruvate phosphotransferase system, Mol. Microbiol. 54 (2004) 1076–1089.
[34] V. Pfeiffer, K. Papenfort, S. Lucchini, J.C. Hinton, J. Vogel, Coding sequence targeting by MicC RNA reveals bacterial mRNA silencing downstream of translational initiation, Nat. Struct. Mol. Biol. 16 (2009) 840–846.
[35] C.M. Sharma, K. Papenfort, S.R. Pernitzsch, H.J. Mollenkopf, J.C. Hinton, J. Vogel, Pervasive post-transcriptional control of genes involved in amino acid metabolism by the Hfq-dependent GcvB small RNA, Mol. Microbiol. 81 (2011) 1144–1165.
[36] E. Holmqvist, J. Reimegard, M. Sterk, N. Grantcharova, U. Romling, E.G. Wagner, Two antisense RNAs target the transcriptional regulator CsgD to inhibit curli synthesis, EMBO J. 29 (2010) 1840–1850.
[37] M. Guillier, S. Gottesman, The 5′ end of two redundant sRNAs is involved in the regulation of multiple targets, including their own regulator, Nucleic Acids Res. 36 (2008) 6781–6794.
[38] M. Guillier, S. Gottesman, G. Storz, Modulating the outer membrane with small RNAs, Genes Dev. 20 (2006) 2338–2348.
[39] K. Papenfort, M. Bouvier, F. Mika, C.M. Sharma, J. Vogel, Evidence for an autonomous 5′ target recognition domain in an Hfq-associated small RNA, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 20435–20440.
[40] T. Morita, Y. Mochizuki, H. Aiba, Translational repression is sufficient for gene silencing by bacterial small noncoding RNAs in the absence of mRNA destruction, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 4858–4863.
[41] M. Overgaard, J. Johansen, J. Moller-Jensen, P. Valentin-Hansen, Switching off small RNA regulation with trap-mRNA, Mol. Microbiol. 73 (2009) 790–800.
[42] K.J. Bandyra, N. Said, V. Pfeiffer, M.W. Gorna, J. Vogel, B.F. Luisi, The seed region of a small RNA drives the controlled destruction of the target mRNA by the endoribonuclease RNase E, Mol. Cell 47 (2012) 943–953.
[43] E.G. Wagner, Kill the messenger: bacterial antisense RNA promotes mRNA decay, Nat. Struct. Mol. Biol. 16 (2009) 804–806.

[44] S. Chen, A. Zhang, L.B. Blyn, G. Storz, MicC, a second small-RNA regulator of Omp protein expression in *Escherichia coli*, J. Bacteriol. 186 (2004) 6689–6697.
[45] C.P. Corcoran, D. Podkaminski, K. Papenfort, J.H. Urban, J.C. Hinton, J. Vogel, Superfolder GFP reporters validate diverse new mRNA targets of the classic porin regulator, MicF RNA, Mol. Microbiol. 84 (2012) 428–445.
[46] K. Prevost, G. Desnoyers, J.F. Jacques, F. Lavoie, E. Masse, Small RNA-induced mRNA degradation achieved through both translation block and activated cleavage, Genes Dev. 25 (2011) 385–396.
[47] J.G. Belasco, All things must pass: contrasts and commonalities in eukaryotic and bacterial mRNA decay, Nat. Rev. Mol. Cell Biol. 11 (2010) 467–478.
[48] A.J. Callaghan, M.J. Marcaida, J.A. Stead, K.J. McDowall, W.G. Scott, B.F. Luisi, Structure of *Escherichia coli* RNase E catalytic domain and implications for RNA turnover, Nature 437 (2005) 1187–1191.
[49] D.J. Koslover, A.J. Callaghan, M.J. Marcaida, E.F. Garman, M. Martick, W.G. Scott, B.F. Luisi, The crystal structure of the *Escherichia coli* RNase E apoprotein and a mechanism for RNA degradation, Structure 16 (2008) 1238–1244.
[50] S.S. Jourdan, L. Kime, K.J. McDowall, The sequence of sites recognised by a member of the RNase E/G family can control the maximal rate of cleavage, while a 5′-monophosphorylated end appears to function cooperatively in mediating RNA binding, Biochem. Biophys. Res. Commun. 391 (2010) 879–883.
[51] S.S. Jourdan, K.J. McDowall, Sensing of 5′ monophosphate by *Escherichia coli* RNase G can significantly enhance association with RNA and stimulate the decay of functional mRNA transcripts in vivo, Mol. Microbiol. 67 (2008) 102–115.
[52] C.M. Arraiano, J.M. Andrade, S. Domingues, I.B. Guinote, M. Malecki, R.G. Matos, R.N. Moreira, V. Pobre, F.P. Reis, M. Saramago, I.J. Silva, S.C. Viegas, The critical role of RNA processing and degradation in the control of gene expression, FEMS Microbiol. Rev. 34 (2010) 883–923.
[53] S. Boisset, T. Geissmann, E. Huntzinger, P. Fechter, N. Bendridi, M. Possedko, C. Chevalier, A.C. Helfer, Y. Benito, A. Jacquier, C. Gaspin, F. Vandenesch, P. Romby, Staphylococcus aureus RNAIII coordinately represses the synthesis of virulence factors and the transcription regulator Rot by an antisense mechanism, Genes Dev. 21 (2007) 1353–1366.
[54] E. Huntzinger, S. Boisset, C. Saveanu, Y. Benito, T. Geissmann, A. Namane, G. Lina, J. Etienne, B. Ehresmann, C. Ehresmann, A. Jacquier, F. Vandenesch, P. Romby, Staphylococcus aureus RNAIII and the endoribonuclease III coordinately regulate spa gene expression, EMBO J. 24 (2005) 824–835.
[55] F. Darfeuille, C. Unoson, J. Vogel, E.G. Wagner, An antisense RNA inhibits translation by competing with standby ribosomes, Mol. Cell 26 (2007) 381–392.
[56] S.C. Viegas, I.J. Silva, M. Saramago, S. Domingues, C.M. Arraiano, Regulation of the small regulatory RNA MicA by ribonuclease III: a target-dependent pathway, Nucleic Acids Res. 39 (2011) 2918–2930.
[57] K.S. Frohlich, J. Vogel, Activation of gene expression by small RNA, Curr. Opin. Microbiol. 12 (2009) 674–682.
[58] J. Georg, W.R. Hess, cis-Antisense RNA, another level of gene regulation in bacteria, Microbiol. Mol. Biol. Rev. 75 (2011) 286–300.
[59] J.A. Opdyke, E.M. Fozo, M.R. Hemm, G. Storz, RNase III participates in GadY-dependent cleavage of the gadX-gadW mRNA, J. Mol. Biol. 406 (2011) 29–43.
[60] A. Tramonti, M. De Canio, D. De Biase, GadX/GadW-dependent regulation of the *Escherichia coli* acid fitness island: transcriptional control at the gadY-gadW divergent promoters and identification of four novel 42 bp GadX/GadW-specific binding sites, Mol. Microbiol. 70 (2008) 965–982.
[61] T. Romeo, Global regulation by the small RNA-binding protein CsrA and the non-coding RNA molecule CsrB, Mol. Microbiol. 29 (1998) 1321–1330.
[62] T. Weilbacher, K. Suzuki, A.K. Dubey, X. Wang, S. Gudapaty, I. Morozov, C.S. Baker, D. Georgellis, P. Babitzke, T. Romeo, A novel sRNA component of the carbon storage regulatory system of *Escherichia coli*, Mol. Microbiol. 48 (2003) 657–670.
[63] K. Suzuki, P. Babitzke, S.R. Kushner, T. Romeo, Identification of a novel regulatory protein (CsrD) that targets the global regulatory RNAs CsrB and CsrC for degradation by RNase E, Genes Dev. 20 (2006) 2605–2617.
[64] P. Babitzke, T. Romeo, CsrB sRNA family: sequestration of RNA-binding regulatory proteins, Curr. Opin. Microbiol. 10 (2007) 156–163.
[65] K. Lapouge, M. Schubert, F.H.T. Allain, D. Haas, Gac/Rsm signal transduction pathway of gamma-proteobacteria: from RNA recognition to regulation of social behaviour, Mol. Microbiol. 67 (2008) 241–253.
[66] E. Sonnleitner, M. Schuster, T. Sorger-Domenigg, E.P. Greenberg, U. Blasi, Hfq-dependent alterations of the transcriptome profile and effects on quorum sensing in *Pseudomonas aeruginosa*, Mol. Microbiol. 59 (2006) 1542–1558.
[67] T. Sorger-Domenigg, E. Sonnleitner, V.R. Kaberdin, U. Blasi, Distinct and overlapping binding sites of *Pseudomonas aeruginosa* Hfq and RsmA proteins on the non-coding RNA RsmY, Biochem. Biophys. Res. Commun. 352 (2007) 769–773.
[68] L. Bossi, A. Schwartz, B. Guillemardet, M. Boudvillain, N. Figueroa-Bossi, A role for Rho-dependent polarity in gene regulation by a noncoding small RNA, Genes Dev. 26 (2012) 1864–1873.
[69] M. Naville, D. Gautheret, Transcription attenuation in bacteria: theme and variations, Brief. funct. Genom. Proteomic. 8 (2009) 482–492.
[70] M. Boudvillain, M. Nollmann, E. Margeat, Keeping up to speed with the transcription termination factor Rho motor, Transcription 1 (2010) 70–75.
[71] M. Rabhi, O. Espeli, A. Schwartz, B. Cayrol, A.R. Rahmouni, V. Arluison, M. Boudvillain, The Sm-like RNA chaperone Hfq mediates transcription antitermination at Rho-dependent terminators, EMBO J. 30 (2011) 2805–2816.
[72] L. Bastet, A. Dube, E. Masse, D.A. Lafontaine, New insights into riboswitch regulation mechanisms, Mol. Microbiol. 80 (2011) 1148–1154.
[73] R.R. Breaker, Prospects for riboswitch discovery and analysis, Mol. Cell 43 (2011) 867–879.
[74] E. Loh, O. Dussurget, J. Gripenland, K. Vaitkevicius, T. Tiensuu, P. Mandin, F. Repoila, C. Buchrieser, P. Cossart, J. Johansson, A trans-acting riboswitch controls expression of the virulence regulator PrfA in *Listeria monocytogenes*, Cell 139 (2009) 770–779.
[75] M.P. Caron, L. Bastet, A. Lussier, M. Simoneau-Roy, E. Massé, D.A. Lafontaine, Dual-acting riboswitch control of translation initiation and mRNA decay, Proc Natl Acad Sci U S A.
[76] A. Jacquier, The complex eukaryotic transcriptome: unexpected pervasive transcription and novel small RNAs, Nat. Rev. Genet. 10 (2009) 833–844.
[77] I. Lasa, A. Toledo-Arana, A. Dobin, M. Villanueva, I.R. de los Mozos, M. Vergara-Irigaray, V. Segura, D. Fagegaltier, J.R. Penades, J. Valle, C. Solano, T.R. Gingeras, Genome-wide antisense transcription drives mRNA processing in bacteria, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 20172–20177.
[78] J.E. Dornenburg, A.M. Devita, M.J. Palumbo, J.T. Wade, Widespread antisense transcription in *Escherichia coli*, MBio 1 (2010).
[79] Y. Taniguchi, P.J. Choi, G.W. Li, H. Chen, M. Babu, J. Hearn, A. Emili, X.S. Xie, Quantifying *E. coli* proteome and transcriptome with single-molecule sensitivity in single cells, Science 329 (2010) 533–538.