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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

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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

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

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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].

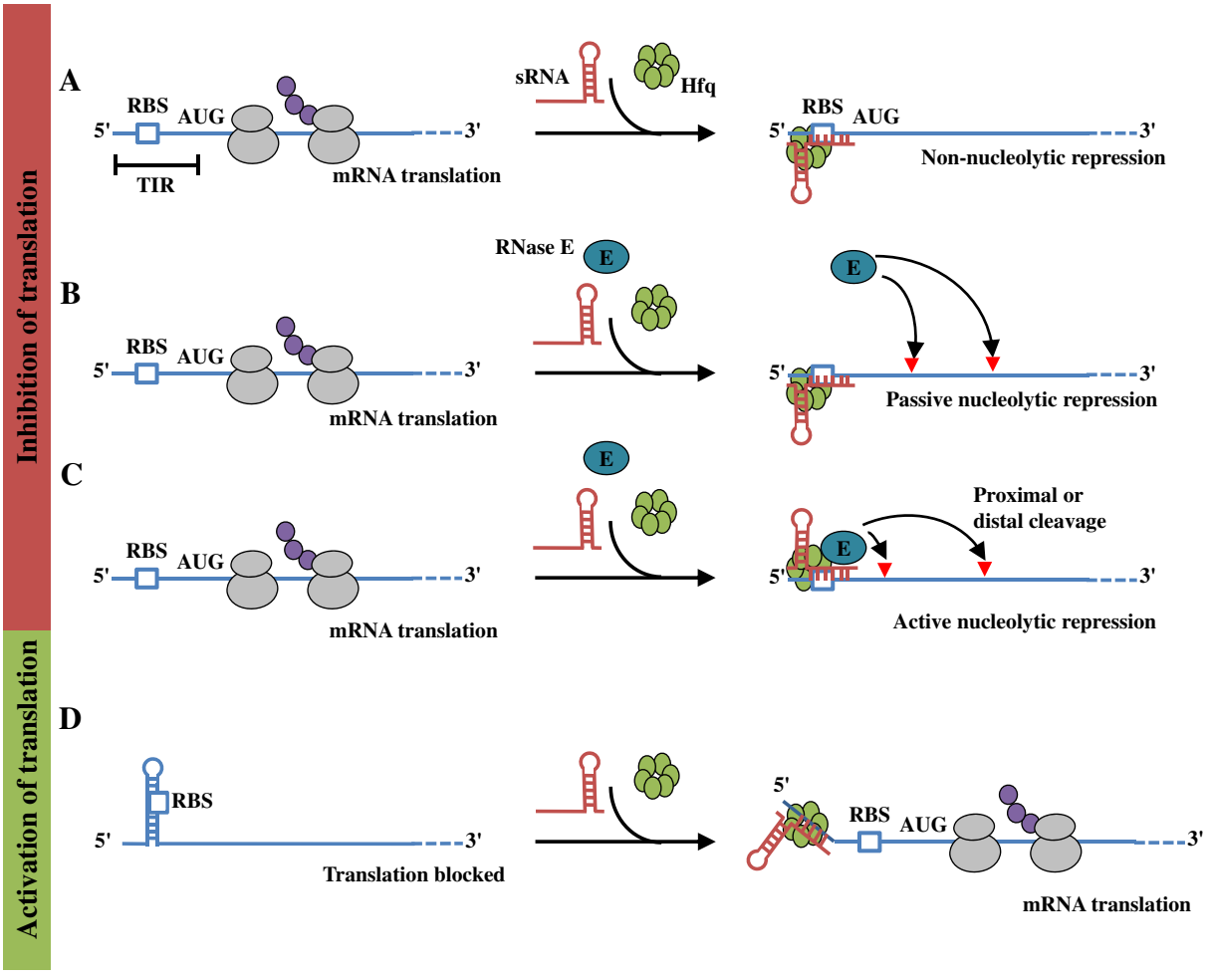

Fig. 1. Small RNA-based regulatory mechanisms of mRNA expression.