ELSEVIER

Controlling mRNA stability and translation with small, noncoding RNAs

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Recent studies have lead to the identification of more than 50 small regulatory RNAs in *Escherichia coli*. Only a subset of these RNAs has been characterized. However, it is clear that many of the RNAs, such as the MicF, OxyS, DsrA, Spot42 and RyhB RNAs, act by basepairing to activate or repress translation or to destabilize mRNAs. Basepairing between these regulatory RNAs and their target mRNAs requires the Sm-like Hfq protein which most likely functions as an RNA chaperone to increase RNA unfolding or local target RNA concentration. Here we summarize the physiological roles of the basepairing RNAs, examine their prevalence in bacteria and discuss unresolved questions regarding their mechanisms of action.

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Abbreviations

sRNA	small RNA
ncRNA	noncoding RNA
miRNA	microRNA

Introduction

A number of 40–400 nucleotide RNAs, that do not encode proteins or function as tRNAs or rRNAs have been characterized in *E. coli*. Because of their small sizes, these RNAs generally have been referred to as small RNAs (sRNAs) in bacteria, a term that will be used in this review. More generally, these RNAs are denoted noncoding RNAs (ncRNAs). Initially, only a dozen sRNAs were known in *E. coli*; some were identified on the basis of high abundance and others were discovered by serendipity (reviewed in [1]). In the past two years however, more systematic computational, microarray and cloning-based screens have lead to the identification of >40 additional sRNAs in *E. coli* [2–6,7•].

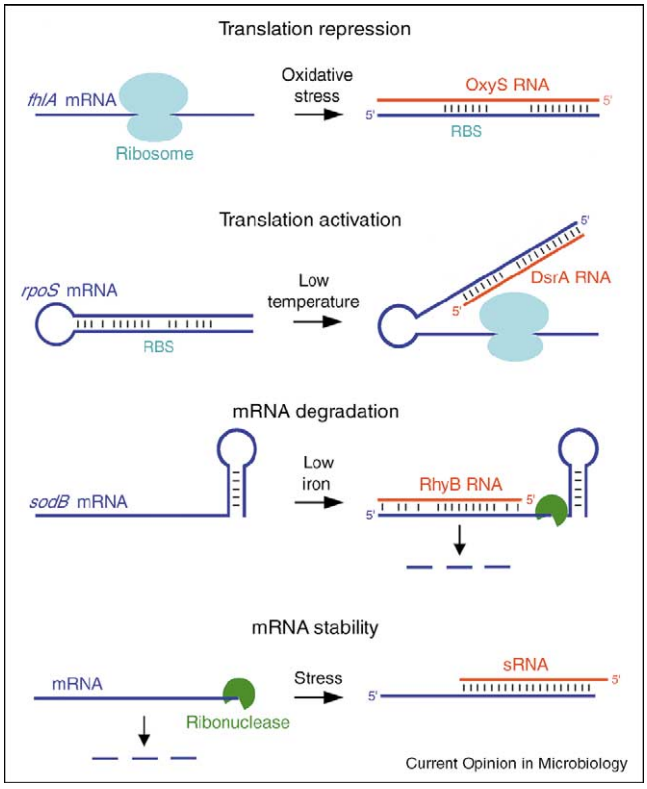
The functions of many of the sRNAs remain to be elucidated, although studies of a subset of the sRNAs indicate that they act by three general mechanisms. A few are integral parts of RNA–protein complexes, such as the 4.5S RNA component of the signal recognition particle and the RNase P RNA, which even possesses enzymatic activity *in vitro*. Some sRNAs mimic the structures of other nucleic acids. Examples of this class include the 6S RNA which binds to the σ^{70}-RNA polymerase holoenzyme possibly by resembling an open promoter, and the CsrB and CsrC RNAs which each contain multiple repeats of the CsrA protein-binding sequence found in several mRNAs. The sRNAs in the third class act by basepairing with other RNAs. These sRNAs, which are the best-characterized and most prevalent, are the focus of this review.

Regulation by basepairing

Early studies revealed that several plasmid, bacteriophage and transposon functions are regulated by sRNAs that are encoded in *cis* on the opposite strands of the target RNAs and that basepair with and inhibit the complementary mRNAs (reviewed in [8]). The first chromosomally-encoded sRNA to be characterized from *E. coli* was the MicF RNA [9]. Expression of this sRNA is induced by a variety of environmental stress conditions including elevated temperature and exposure to toxic agents such as paraquat [10,11]. Unlike the plasmid, bacteriophage and transposon sRNAs however, the MicF RNA is encoded in *trans*; the sRNA blocks translation of the OmpF porin by basepairing with the *ompF* mRNA which is encoded at a separate locus on the *E. coli* chromosome [9,12,13]. The OxyS and DsrA RNAs are two other basepairing sRNAs that are encoded in *trans* to their target mRNAs (Figure 1). Expression of the OxyS RNA is strongly induced by hydrogen peroxide [14], and DsrA RNA levels increase at low temperature [15]. The OxyS RNA basepairs with and represses translation of the *fhlA* mRNA which encodes a transcriptional activator [16,17]. In contrast, DsrA basepairing with the *rpoS* mRNA, which encodes the stationary phase sigma factor σ^S, leads to increased translation [18,19]. The DsrA RNA promotes translation by preventing the formation of an inhibitory secondary structure that normally occludes the ribosome binding site of the long *rpoS* transcript. The MicF, OxyS and DsrA RNAs are all induced under stress conditions, a property that is also true for many of the sRNAs identified and studied more recently.

The characterization of other sRNAs in the past two years has revealed additional modes of sRNA action and has led to the solution of a number of regulatory mysteries (summarized in Table 1). One example is the Spot42

Figure 1



Different known and potential regulatory outcomes brought about by sRNA basepairing with mRNAs. sRNAs (red) can repress or activate translation by blocking or promoting ribosome binding to mRNAs (blue). sRNAs also can destabilize or possibly stabilize mRNAs by increasing or decreasing accessibility to ribonucleases.

RNA, the expression of which is repressed by cAMP-Crp when cells are grown on carbon sources other than glucose. This sRNA was found to basepair with sequences internal to the *galETKM* mRNA and thus provided an explanation for the differential expression of the UDP-galactose-4-epimerase encoded by *galE* and galactokinase encoded by *galK*. When glucose levels are high, Spot42 expression is elevated and the sRNA base-pairs with sequences overlapping and blocking the *galK* ribosome binding site resulting in an increased GalE-to-GalK ratio [20•]. Another sRNA, the RyhB RNA, is subject to repression by Fur, and is thus only expressed upon iron starvation. The discovery of the RyhB RNA explains how some genes show positive regulation by the Fur repressor. Under conditions of limiting iron, RyhB is expressed and promotes the degradation of target transcripts such as the *sodB* mRNA which encodes an iron superoxide dismutase [21•]. Under conditions of high iron, Fur represses RyhB expression and thus prevents degradation of the RyhB target mRNAs, resulting in elevated levels of these transcripts.

As illustrated by the examples cited above and shown in Figure 1, sRNA basepairing with a target mRNA can have multiple regulatory outcomes in *E. coli*. Basepairing between the MicF, OxyS and Spot42 RNAs and their targets prevents translation, while basepairing between the DsrA RNA and *rpoS* mRNA facilitates translation. RyhB RNA basepairing with its targets is associated with degradation of the mRNAs. It is also conceivable that sRNA basepairing with a target could block access of a ribonuclease and thus stabilize the mRNA. Interestingly, the 21–25 nucleotide microRNAs (miRNAs) that have recently been discovered in worms, flies, fish, plants and mammals, similarly basepair with mRNAs and impact mRNA stability and translation (reviewed in [22]).

What is not yet clear is whether some sRNAs predominantly affect mRNA stability and others predominantly affect translation or whether these processes are coupled. For example, does a block in translation lead to rapid degradation of the mRNA? While elevated RyhB levels are associated with decreased levels of the target mRNAs *in vivo*, RyhB also has been shown to block translation of

Table 1

Basepairing sRNAs of known function in *E. coli*.

sRNA (alternative name)	5′ nucleotide (strand)	Length (in nucleotides)	Target(s)	Effect(s)	Refs
MicC (IS063)	1435145 (+)	109	ompC[a]	Translation repression	[b]
DicF	1647406 (+)	53	*ftsZ*	Translation repression	[41]
RprA	1768396 (+)	105	*rpoS*[a]	Translation activation	[42,43]
DsrA	2023335 (–)	85	*rpoS*[a]	Translation activation	[18,19,27]
			hns, *rbsD*[a]	Translation repression	
MicF	2311104 (+)	93	*ompF*[a]	Translation repression	[9,12,13]
GcvB	2940718 (+)	204	*oppA*, *dppA*	Translation repression	[44]
RyhB (SraI)	3578647 (–)	90	*sodB*[a]	mRNA degradation, translation repression	[21•,23,24,32]
			sdhCDAB	mRNA degradation	
Spot42 (*spf*)	4047479 (+)	109	*galETKM*	Translation repression	[20•]
OxyS	4155973 (–)	109	*fhlA*, *rpoS*[a]	Translation repression	[14,16,17,45]

[a]Mutational studies have demonstrated direct basepairing interactions between these mRNAs and corresponding sRNAs. Basepairing is assumed for the other sRNAs and their mRNA targets. [b]S Chen, A Zhang, LB Blyn and G Storz, unpublished.

the *sodB* mRNA *in vitro* [23]. Other open questions are whether specific sRNA features, such as the length and position of basepairing, favor different modes of action and whether specific sRNAs act differently at different targets. While only one target is known for the MicF RNA, multiple targets have been suggested for other sRNAs. Further studies are also needed to fully elucidate how sRNAs modulate translation and mRNA stability. sRNA basepairing across or near the Shine-Dalgarno sequence is likely to block ribosome binding and thus negatively regulate translation, while sRNA basepairing with one side of an inhibitory mRNA structure should facilitate ribosome binding and thus positively regulate translation. The mechanisms by which sRNAs might modulate mRNA stability are less obvious. RyhB basepairing with its target mRNAs has been shown to lead to increased RNase E digestion of both RyhB and the target mRNAs but it is not yet known how this occurs [24].

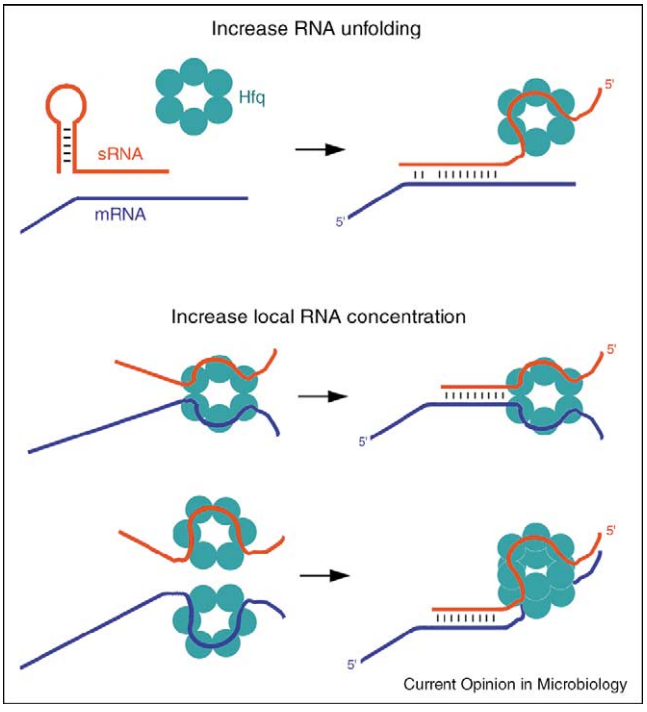
Requirement for the Sm-like Hfq protein

Basepairing between some of the sRNAs and their targets has been seen in the absence of other proteins *in vitro* [17], although genetic studies showed that the Hfq protein, initially identified as a host factor required for Qβ bacteriophage replication, is required for the functions of the sRNAs *in vivo* [25•,26•,27]. Recent characterization of Hfq revealed that the protein is a homolog of the Sm and Sm-like proteins that form the core of splicing and mRNA degradation complexes in eukaryotic and archaeal cells (reviewed in [28,29]). Like the Sm and Sm-like proteins, Hfq binds AU-rich sequences. It also forms a homohexameric ring with dimensions similar to the hexameric and heptameric rings formed by the eukaryotic and archaeal proteins [25•,26•]. The sequence of Hfq can be aligned with the sequences of the eukaryotic and archaeal proteins, but the most convincing evidence that Hfq is a homolog of Sm and Sm-like proteins comes from the recent crystal structures of the *Staphylococcus aureus* and *E. coli* Hfq proteins which are superimposeable on the structures of mammalian and archaeal Sm and Sm-like proteins [30•,31].

Several consequences of Hfq binding to sRNAs have been noted. The RNase digestion patterns observed for OxyS and Spot42 RNAs as well as the *sodB* target mRNA, are different in the presence and absence of Hfq, indicating that the protein induces changes in the structures of these RNAs [25•,26•,32]. However, no changes in secondary structure were detected upon Hfq binding to the DsrA RNA [33]. Hfq binding to the OxyS and Spot42 RNAs also was found to promote basepairing between these sRNAs and their mRNAs targets, but not to other control RNAs [25•,26•]. The sRNA-mRNA basepairing is maintained on removal of Hfq, and Hfq shows activity in RNA chaperone assays [25•,26•,34]. Thus, it has been proposed that Hfq acts as an RNA chaperone to promote basepairing interactions between all Hfq-binding sRNAs and their targets. Another observed consequence of Hfq binding to many sRNAs is protection against RNase E digestion [7•,35,36]. As Hfq binding sites and sites of RNase E cleavage share sequence similarity, it is thought that Hfq-binding blocks cleavage by occluding the RNase E cleavage sites.

Although much has been learned about the Hfq requirement for sRNA function, a number of questions regarding Hfq action remain. It is clear that Hfq binds to the sRNAs and also binds to some mRNA targets. However, it is not known whether Hfq binding to both the sRNA and the mRNA target is required for all cases of basepairing. It is also not known if other factors such as high transcript levels or extensive basepairing can obviate the need for Hfq. The location of RNA binding on Hfq is still under debate. The structure of the *S. aureus* Hfq protein in complex with the ribo-oligonucleotide 5'-AUUUUUG indicates that RNA binds in a circular conformation around the center of the Hfq ring [30•], but others have suggested there may be additional RNA binding sites on the Hfq hexamer [33]. Similarly, the mechanisms by which Hfq promotes interactions between sRNAs and their targets are not fully understood. Possible mechanisms are shown schematically in Figure 2. As Hfq changes the structures of some RNAs, it may promote basepairing by opening up the regions of pairing. It is also possible that Hfq facilitates basepairing by increasing the local

Figure 2



Mechanisms by which Hfq might facilitate sRNA-mRNA basepairing. Hfq (aqua ring) may promote RNA unfolding or may increase the local concentrations of the sRNA (red) and its mRNA target (blue).

concentrations of the RNAs involved in pairing. One Hfq hexamer may bind to the sRNA and target mRNA simultaneously. Alternatively, one Hfq hexamer may bind the sRNA and a second Hfq hexamer may bind the mRNA. The two Hfq hexamers could be brought together via interactions between the hydrophobic backs of the two hexamers [30•]. For some sRNAs Hfq may function to both increase RNA unfolding and the local RNA concentration. Other unresolved questions are whether Hfq binds additional proteins and whether interactions with these proteins are required for function. Hfq copurifies with ribosomes, but it is not known how this association affects Hfq activity. Finally, it is important to consider whether there is competition for Hfq binding among different sRNAs. Although the Hfq protein is abundant, strong induction of one sRNA may compete the binding of other sRNAs and thus indirectly impact the functions of the other sRNAs.

Prevalence of Hfq binding RNAs

The majority of the *E. coli* sRNAs characterized thus far act by basepairing and require Hfq for function. It will be interesting to see how many of the sRNAs ultimately fall into this class. Co-immunoprecipitation with Hfq has shown that many of the uncharacterized sRNAs also bind Hfq [7•]. An intriguing possibility is that sRNA regulators are associated with each major regulon in *E. coli* given that MicF, OxyS, Spot42 and RyhB respectively have been found to be members of the SoxRS, OxyR, Crp and Fur regulons.

Hfq is widely distributed in bacteria [37]. Approximately half of the organisms for which a complete or nearly complete genomic sequence is available contain at least one gene encoding Hfq. The presence or absence of the protein follows major bacterial clades: the *hfq* gene appears to have been lost from some clades represented by *Chlamydia*, *Actinomycetes*, *Deinococcus* and *Cyanobacteria*, but is present in ancient clades represented by *Aquifex* and *Thermotoga*. Although no Hfq-binding sRNAs have been reported for organisms other than enteric bacteria, based on what has been found for *E. coli*, it is likely that similar regulatory sRNAs will be found in all organisms that contain Hfq. The approach of characterizing the RNAs that co-immunoprecipitate with Hfq has been very successful in identifying novel Hfq-binding sRNAs in *E. coli* and should allow the identification of basepairing sRNAs in other species [7•]. It is noteworthy that *Yersinia enterocolitica*, *Brucella abortus* and *Pseudomonas aeruginosa hfq* mutant strains all have been found to be defective in virulence suggesting a critical role for sRNAs in the unique environment of the host cell [38–40].

Conclusions

The characterization of several sRNAs in *E. coli* has shown that basepairing between a regulatory RNA and an mRNA can lead to increased or decreased translation or stability of the target transcript. The RNA chaperone Hfq is required for the functions of these sRNAs and appears to facilitate the basepairing between the sRNAs and their targets. While we have made great progress in identifying sRNAs in recent years and have uncovered the cellular roles of several of the Hfq-binding sRNAs, there is still much to be learned about the basepairing sRNAs. What are the requirements for basepairing and how is specificity achieved? Given the limited, usually discontinuous basepairing between sRNAs and mRNAs, how can targets of sRNAs be identified? What are the mechanisms by which Hfq brings sRNAs and mRNAs together? Do all RNAs that act by basepairing require Hfq? Given the many tools available for the study of bacteria, answers to these questions undoubtedly are forthcoming. These studies should not only give insights into the functions of bacterial sRNAs, but also should give clues to the functions of archaeal and eukaryotic Sm and Sm-like proteins as well as the large number of recently discovered eukaryotic miRNAs.

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