Post-transcriptional control by global regulators of gene expression in bacteria

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Several authentic or potential global regulators have recently been shown to act at the post-trancriptional level. This is the case for Hfq (HF-1), which is involved in the regulation of an increasing number of genes in *Escherichia coli*, and CsrA (RsmA) responsible for controlling the expression of genes for extracellular enzymes and secondary metabolism in Gram-negative bacteria. The cold-shock proteins of the CspA family are able to destabilise mRNA secondary structures at low temperature and, therefore, also seem to act post-transcriptionally. These findings illustrate a more general aspect of post-transcriptional control which, in the past, was generally restricted to regulators acting at a single target. The expression of several global transcriptional regulators, such as the stationary phase and heat-shock sigma factors and H-NS, have also recently been shown to be themselves under post-transcriptional control. These examples underline the importance of this type of control in bacterial gene regulation.

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Abbreviations

RBS	ribosomal-binding site
SD	Shine-Dalgarno
UTR	untranslated region

Introduction

Not so long ago, control of gene expression at the level of translation and mRNA stability in bacteria was thought to be restricted to a limited number of genes, many of which encode proteins of the translational machinery, in particular ribosomal proteins [1,2]. Recently, the number of bacterial genes whose expression is now known to be directly or indirectly dependent on post-transcriptional regulation has increased significantly for two main reasons.

The first of these is the discovery of global post-transcriptional regulators. In the past, most examples of protein-mediated translational control were specific in nature (i.e. a single ribosomal protein controlling the expression of one operon by acting at a unique target). Recently, post-transcriptional regulators have been characterised that have more global effects and seem to act at many targets.

The second reason for the large increase in the number of post-transcriptionally controlled genes is the discovery that several global transcriptional regulators are themselves controlled at a post-transcriptional level. Therefore, the targets of each of these transcriptional regulators are under indirect post-transcriptional control.

In this review, we give a few examples for each of the two cases cited above restricting ourselves to post-transcriptional controls acting at the level of either translation or mRNA stability. Another fascinating new aspect of translational control is the recent discovery of several RNA regulators or riboregulators [3]. These small RNAs can modulate the translation of an increasing number of cellular mRNAs. Since anti-sense related phenomena are the subject of another review in this same issue (see Franch and Gerdes pp 159–164), we only describe riboregulators that do not act in this capacity and those that act in conjunction with a global protein regulator.

Global regulators

Hfq – a general post-transcriptional regulator

Hfq, also called HF-1 (Host Factor I), was discovered as an *Escherichia coli* protein required for the *in vitro* synthesis of bacteriophage Qβ RNA [4]. At a step prior to the initiation of minus strand synthesis, Hfq binds to the Qβ plus-strand RNA [5] and melts the structure at the 3′ end of the wild-type plus strand RNA [6].

The disruption of the *hfq* gene causes pronounced pleiotropic phenotypes such as decreased growth rate, increased cell length, osmosensitivity, and sensitivity to UV light [7]. Because some of these phenotypes resemble those of an *rpoS* mutant, Hengge-Aronis and co-workers [8] suspected some relationship between Hfq and σ^S, the stationary phase sigma factor, a global regulator in bacteria encoded by *rpoS*. They showed that Hfq positively regulates the expression of *rpoS* at a post-transcriptional level [8] probably by altering the structure of the mRNA allowing enhanced translation (see below). Two dimensional gel analysis showed changes in the level of more than 30 proteins in an *hfq* disrupted strain. In about half of these cases, the alterations occur independently of σ^S [9]. In addition, Hfq has been shown to negatively control the expression of *mutS* and of its own gene at the post-transcriptional level by causing a decrease in mRNA stability [10].

Hfq has also been isolated as a protein that binds to the 5′ UTR (untranslated region) of the *ompA* mRNA, an exceptionally stable mRNA encoding the major outer membrane protein of *E. coli* [11]. In *hfq*⁻ strains, the half-life of *ompA* mRNA is further increased and the growth-rate regulation of its stability is lost, indicating that Hfq somehow facilitates *ompA* mRNA degradation. Also in *hfq*⁻ strains, a weak stabilisation has been observed for the *rpsO* mRNA, encoding ribosomal protein S15 (E Hajnsdorf

and P Régnier, personal communication). Also, a decrease of polyA-tail length of *rpsO* mRNA was noticed in *hfq*⁻ strains. Unfortunately, the levels of neither OmpA protein nor S15 have been measured in a *hfq*⁻ background, leaving unsettled the question of whether Hfq really controls the level of both proteins or is just involved in mRNA degradation without effect on expression.

These effects on mRNA stability raise the question of the level at which Hfq primarily acts. This could be at the level of translation initiation by changing the number of ribosomes (which are generally thought to protect the mRNA from nuclease attack), and therefore, the stability of the mRNA. This could also be directly at the level of mRNA stability which, if affected, causes a change in translation. Resolution of this issue awaits *in vitro* experiments where inhibition at the level of translation initiation can be tested in the absence of mRNA degradation.

CsrA/CsrB – a novel regulatory duo

Romeo and co-workers [12] have characterised a gene, *csrA* (for *carbon storage regulator*), that controls the expression of the *glgCAY* and *glgBX* operons, which encode enzymes involved in glycogen metabolism. Post-transcriptional regulation of *glgC* by *csrA* was indicated by an increase in the half-life of *glgC* mRNA in a *csrA*⁻ strain [13]. A deletion analysis with the *glgCAY* operon indicates that regions near the ribosomal-binding site (RBS) are probably important for CsrA-dependent regulation. CsrA exists in a complex consisting of about 18 CsrA subunits and a single 350 nucleotide RNA called CsrB [14]. The complex is capable of repressing expression of the *glgC*, *glgA* and *glgB* genes in a coupled transcription–translation system. The effect is apparently post-transcriptional, since when transcription is uncoupled from translation, inhibition was still observed [15]. Mobility shift experiments indicate that the CsrA protein binds directly to *glgC* mRNA. Overproduction of CsrB *in vivo* enhances glycogen accumulation, indicating that CsrB is an activator of the *glgCAY* and *glgBX* operons. Importantly, the effect of CsrB is seen only in a *csrA*⁺ strain, indicating that *csrB* works through *csrA*.

Romeo has proposed a nice model to explain most of these data [16•]. On the one hand, CsrA binds the *glgC* RBS directly (and presumably that of *glgB*) and inhibits translation either by affecting ribosome binding or by causing an endonucleolytic attack of the mRNA. On the other hand, high levels of expression of CsrB titrate CsrA and cause *glg* gene derepression. The CsrB RNA carries 18 repeats of the sequence 5′-CAGGA(U,C,A)G-3′ primarily in loops or single stranded regions. Since the CsrA/B complex contains 18 CsrA proteins, it was tempting to propose that each of these repeats binds one CsrA molecule. The repeats clearly resemble the Shine-Dalgarno (SD) sequence, explaining how the *glgC* SD and the SD-like sequences of CsrB could compete for CsrA binding. Some other unknown specificity element must be required to prevent CsrA from binding to the SD of all cellular mRNAs.

In addition to its effect on glycogen metabolism, CsrA has been shown to affect glycolysis, acetate metabolism, motility, adherence, cell morphology and some other functions in *E. coli* [16•]. An ortholog (cross-species homolog) of CsrA in *Erwinia carotovora*, called RsmA, has been shown to negatively control a variety of genes involved in secondary metabolism, phytopathogenesis, and quorum-sensing [17•]. RsmA binds RsmB, an RNA that exists in two forms: a minor full-length (459 bases) species and a shorter major (259 bases) species that is processed from the full-length molecule. The shorter RNA was shown to be the positive regulator of the genes repressed by RsmA. It has been proposed that RsmA binds to the full-length RsmB form and processes and liberates the shorter RsmB form that is then free to act as a positive regulator either by blocking *rsmA* transcription and/or translation, or by decreasing RsmA stability. This model differs from that proposed for *E. coli* CsrA/B.

Many orthologs of *csrA* or *rsmA* have been found, indicating that these fascinating systems might be very general. *E. coli* has a notoriously poor secondary metabolism; the existence *csrA*/*rsmA* orthologs in species such as *Pseudomonas*, with a very rich secondary metabolism, could mean that the *csrA*/*rsmA* system is responsible for the control of a large number of genes in the eubacterial domain.

Cold-shock proteins

After temperature downshift, proteins such as CspA, B, G, CsdA, RbfA, NusA, and PNPase are strongly induced. CspA, B, G belong to a class of nine paralogs (intra-species homologs) in *E. coli*, CsdA and RbfA are ribosome-associated proteins, NusA is a transcription termination factor and PNPase is an exonuclease involved in mRNA degradation [18•]. CspA, the major and best characterised cold-shock protein, has been shown to destabilise RNA secondary structures, which may be crucial for efficient mRNA translation at low temperature [19]. Orthologs of *cspA* have been found in many bacterial species. The current model [18•] proposes that upon temperature downshift, CspA is expressed at high rate, despite the fact that the translation machinery is not yet adapted to the cold. During the acclimation phase, ribosomes adapt to the cold by binding specific factors such as RbfA and CsdA. Once the translational apparatus is adapted to low temperature, the synthesis of CspA and other transiently induced cold-shock proteins ceases.

The expression of the *cspA* gene is regulated at multiple levels. Upon cold-shift, the stability of *cspA* mRNA increases 150-fold, causing a corresponding increase in translation. Thus, it appears that induction upon cold-shift relies on *cspA* mRNA stabilisation by a yet unknown mechanism. However, induction also relies on translational effects independent of mRNA stability, as indicated by the role of the long and highly structured 5′ UTR of the *cspA* mRNA. Deletion mapping indicates that portions of the 5′ UTR are responsible for the low level of expression at

high temperature and induction upon down-shift [20]. However, these deletions, which have a drastic effect on expression, have only a minor effect on *cspA* mRNA steady-state levels, indicating that an effect on the level of translation might also explain the induction, independently of effects on *cspA* mRNA stability. It is possible that the secondary structure of the *cspA* leader mRNA is directly responsible for induction at low temperature and acts as a thermosensor, as has been demonstrated for the heat-shock sigma factor (see below).

The shut-down of *cspA* synthesis occurs by negative autoregulation at a transcription terminator located between the promoter and the structural gene. Upon temperature down-shift, transcription bypasses this termination site, whereas after acclimation, CspA binds to its own mRNA and causes pausing or termination of transcription.

Although CspA and the other cold-shock proteins have the potential to be global post-transcriptional regulators by destabilising mRNA secondary structure at low temperature and thereby allowing efficient mRNA translation, the nature of their primary targets has still to be characterised before any definitive conclusion can be drawn about their biological function.

Translational control of transcriptional regulators

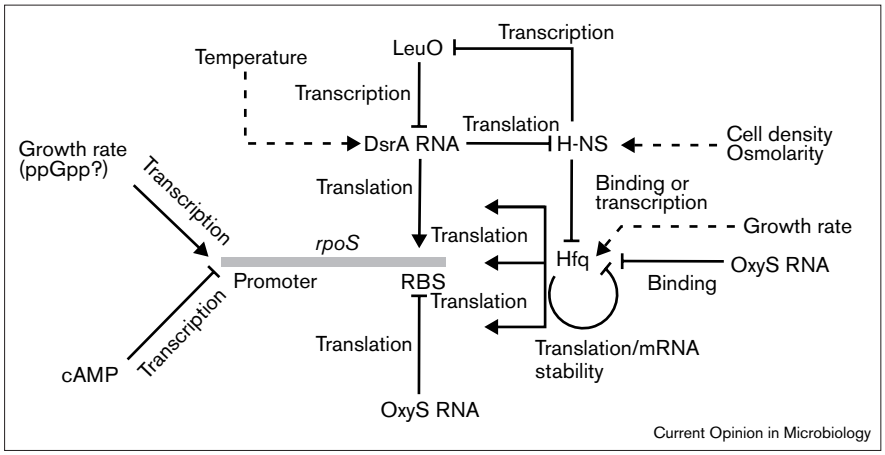
The stationary phase sigma factor and H-NS

The sigma factor σ^S controls the expression of probably more than 50 genes and is responsible for the cellular response to very different stresses such as entry into stationary phase, starvation, osmotic shock, and acid shock [21]. The expression of its gene, *rpoS*, is controlled at the level of translation and protein stability [22]. Figure 1 illustrates the different control loops involved in *rpoS* expression. As mentioned above, Hfq acts as a positive regulator of *rpoS* translation. The importance of the role of Hfq is underlined by the fact that an interruption of its gene is epistatic to mutations affecting all the other factors that modulate *rpoS* mRNA translation (i.e. in an *hfq* mutant, *hns*, *dsrA*, and *oxyS* mutations are without effect). This indicates that Hfq acts downstream of all other effectors, probably directly on *rpoS* mRNA translation itself. *Cis*-acting mutations that either decrease or eliminate the effect of Hfq were selected in the *rpoS* gene of *Salmonella typhimurium* [23]. Most of the mutations occurred in the leader mRNA of *rpoS* and destabilise secondary structures that trap the *rpoS* mRNA in a conformation that does not permit translation initiation. These mutations either directly affect the way Hfq acts on *rpoS* or are simply bypass mutations (i. e. mutations that open the structure of the *rpoS* mRNA which thus does not need to be destabilised by Hfq) [23].

A second factor involved in *rpoS* translation is H-NS, which is also a modulator of the expression of a large number of genes at the transcriptional level [24]. H-NS has a negative effect on Hfq-mediated stimulation of *rpoS* translation either by inhibiting *hfq* gene transcription [8,25] or by binding to Hfq itself [26]. Interestingly, the increase of *rpoS* mRNA translation upon entry into stationary phase or to osmotic upshift is lost in *hns* mutants, indicating that these environmental signals act on H-NS levels and/or on the putative H-NS/Hfq association.

Translation of *rpoS* is also controlled by two riboregulators, OxyS and DsrA (see Franch and Gerdes, this issue, pp 159–164). DsrA is an 87 nucleotide RNA that positively

Figure 1



Regulation of the expression of the gene for the stationary phase sigma factor, *rpoS*. The different controls are indicated by arrows (for positive controls) or by a line with a bar (for negative controls). The dashed arrows designate the genes that sense the environment. The level at which the control is exerted is indicated (e.g. transcription, translation, binding). The controls acting at the *rpoS* promoter (i.e. growth rate and cAMP) are shown on the left. Those acting at the level of the RBS are shown on the right. The triple arrow pointing from Hfq to the RBS of *rpoS* indicates that Hfq could act directly on the RBS, or act on the association between the *rpoS* mRNA and the OxyS or DsrA riboregulators. Translation of *rpoS* is also under indirect negative control of a LysR-like regulator, LeuO, which negatively regulates the transcription of DsrA and, therefore, the translation of *rpoS* at low temperature [34]. The DsrA riboregulator also controls *rpoS* translation by inhibiting H-NS, which inhibits Hfq.

regulates the expression of *rpoS* by two different pathways. The first is indirect: DsrA negatively regulates the translation of the *hns* mRNA [27•] by pairing with a region immediately downstream of the ATG of the *hns* mRNA to block translation initiation. The second pathway leading to *rpoS* activation is direct: at low temperature, *rpoS* mRNA translation is blocked because a part of the 5′-UTR folds back onto the RBS [28•]. DsrA binds to this negatively acting upstream region, freeing the RBS for translation initiation.

The second riboregulator OxyS is a 109 nucleotide RNA that negatively regulates the translation of the *rpoS* [29••] and other mRNAs [30]. The negative effect on *rpoS* is explained by titration of Hfq, to which OxyS specifically binds, and/or by the simultaneous binding of Hfq and OxyS to the *rpoS* mRNA to block translation initiation (both possibilities are shown in Figure 1) .

The heat-shock sigma factor

In *E. coli*, expression of the heat-shock regulon is under positive control of another sigma factor, σ^H [31•]. As in the case of σ^S, σ^H is regulated at the level of translation and protein stability. A 200 nucleotide region downstream of the translation initiation site has been shown to be responsible for the induction of *rpoH* expression at high temperature. This region folds into several stem-loop structures, one of them trapping the RBS in a conformation that inhibits translation [32]. Recent experiments indicate this region can change conformation and permit translation of the *rpoH* mRNA at high temperature independently of *trans*-acting factors [33••]. Although a few other similar cases have been reported, one is tempted to speculate, that because of RNA's capacity to change its conformation easily, many other examples will be described in the future.

Conclusions

A true regulator should be able to activate or repress gene expression in either a direct or an indirect response to the environment or the physiological state of the cell. Because Hfq senses cell density and osmolarity through H-NS (Figure 1), it may be considered as a true regulator, although the mechanism by which Hfq acts and the way H-NS affects Hfq are not yet precisely understood. In the case of *csrA/B* (or *rsmA/B*), the situation is different. We know that the negatively acting protein and the positively acting RNA have the ability to modulate the expression of many genes, but they can only be designated as potential regulators for now. Future experiments will tell us whether *csrA/B* can sense the environment or the physiological state of the cell, like *bona fide* regulators. As regards the major cold shock protein CspA, the situation is again different in the sense that it is clearly able to sense the environmental change (temperature downshift) but its regulatory targets are yet uncharacterised.

The discovery of true or potential global regulators such as Hfq, CsrA, and the cold-shock proteins that act at the post-transcriptional level has significantly increased the number of genes regulated in this way in *E. coli*. Since all of these regulators have orthologs in other bacteria, there is a very good chance that their role is very general. The fact that global transcriptional regulators such as the heat-shock and stationary phase sigma factors and H-NS are also controlled at the post-transcriptional level, further increases the number of genes under this type of control, even if indirectly.

One is struck by the lack of knowledge about how these global post-transcriptional regulators work on the molecular level. The relationship between translation and mRNA degradation has to be clarified in each case. Several of the controls described here have been characterised on the basis of alteration of mRNA stability. As mentioned in the case of Hfq, alterations in mRNA stability can be either a consequence of effects at the translational level or directly responsible for the regulation, by affecting translational yields. We have a tendency to believe that the first scenario occurs more often than accredited. In this case, it will be interesting to determine whether classic translational regulation models, such as those proposed for specific ribosomal protein operons, will apply. Independently of the precise mechanisms, there is a good chance that mRNA secondary structure will play a major role either as a target for interaction with specific protein or RNA factors, or as a direct sensor of the physiological state of the cell, as is the case of *rpoH*.

Note added in proof

The paper referred to in the text as (E Hajnsdorf and P Régnier, personal communication) has now been accepted for publication [35].

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