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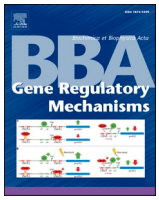

Nucleo-cytoplasmic shuttling of RNA-binding factors: mRNA buffering and beyond☆

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ABSTRACT

Gene expression is a highly regulated process that adapts RNAs and proteins content to the cellular context. Under steady-state conditions, mRNA homeostasis is robustly maintained by tight controls that act on both nuclear transcription and cytoplasmic mRNA stability. In recent years, it has been revealed that several RNA-binding proteins (RBPs) that perform functions in mRNA decay can move to the nucleus and regulate transcription. The RBPs involved in transcription can also travel to the cytoplasm and regulate mRNA degradation and/or translation. The multifaceted functions of these shuttling nucleo-cytoplasm RBPs have raised the possibility that they can act as mRNA metabolism coordinators. In addition, this indicates the existence of crosstalk mechanisms between the enzymatic machineries that drive the different mRNA life-cycle phases. The buffering of the mRNA concentration is the best known consequence of a transcription-degradation crosstalk counteraction, but alternative ways of RBP action can also imply enhanced gene regulation.

1. Introduction

In the past, gene regulation was thought to be a rather simple and straightforward process regulated by transcription factors (TFs) that bind the DNA sequences placed on gene promoters. This mechanism was first proposed by Jacob and Monod as the Operon model [1] and was then extended to *cis* (DNA)/*trans* (protein factor) for all organisms [2,3]. Next it was discovered that regulation at the mRNA stability level is also important in some cases, such as transferrin receptor mRNA in fibroblasts [4]. The importance of gene regulation at the mRNA decay level was later generalized (revised in [5]). Therefore, it is clear that gene expression is rather a complicated process that has evolved regulatory mechanisms in every possible step during the gene expression flux from genes to proteins. This makes gene expression a multifaceted and interconnected process that is driven by not only protein-DNA contacts at the promoter, but also by many other contacts among DNA, RNA and proteins after transcription initiation.

2. RNA-binding proteins (RBPs)

One of the most important players in the gene expression regulation game are mRNA-protein interactions. Proteins with mRNA-binding capacity have been known for some decades, and some of which, called heterogeneous nuclear ribonucleoproteins (hnRNPs), are associated with nascent mRNAs. Although most have been considered nucleus-specific and replaced with other cytoplasmic mRNPs [6], it was discovered that others shuttle between the nucleus and the cytoplasm, which suggests new functions for these proteins (see [6]). By the beginning of the new century, it was clear that the nuclear binding of some proteins may play the role of sending information about the fate of mRNA to the cytoplasm (see [7]). This is the case of the so-called exon-exon junction complex (EJC), which facilitates mRNA export and is also related to the detection of unspliced transcripts by the nonsense-mediated mRNA decay (NMD) pathway [7,8]. The binding of EJC to the exon-exon junction has no sequence specificity. Thus the EJC cannot return to its original binding site in spliced mRNA after being released in the cytoplasm. The persistence of the EJC bound to mRNAs is a signal of

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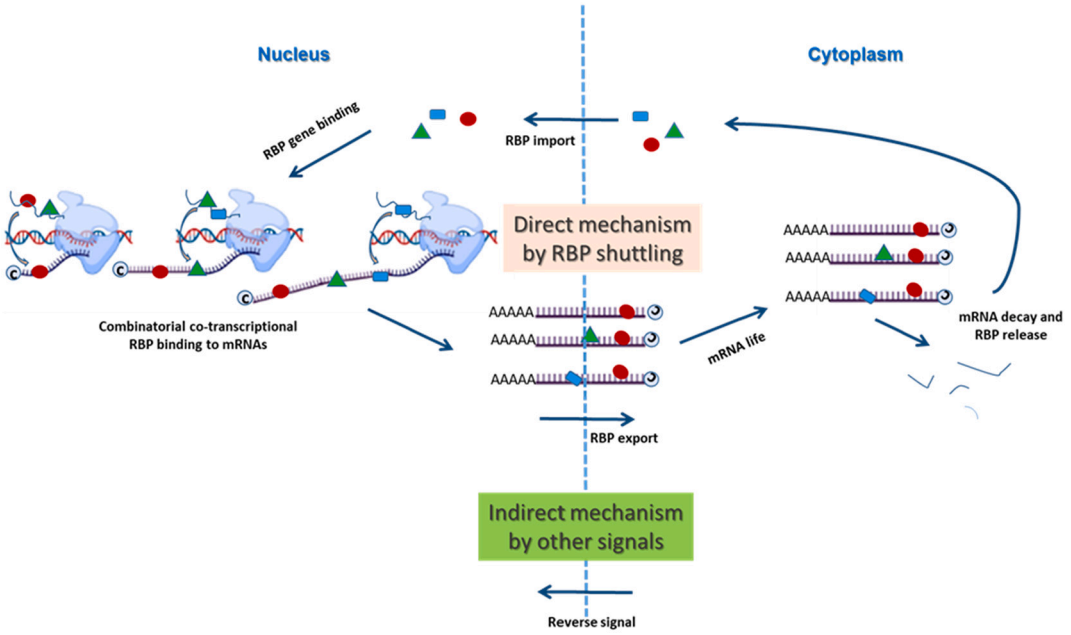
defective mRNAs that will be subjected to NMD [7,8]. This leads to the proposal that mRNA does not only carry information on its sequence, but also in the set of the RBPs that it transports to the cytoplasm [7]. More recently however, some results, mostly in the yeast *Saccharomyces cerevisiae* model, have pointed out that other kinds of proteins not previously suspected to bind mRNA in the nucleus, such as transcription factors [9], RNA pol II subunits [10] and mRNA decay factors [11–14], can also bind groups of mRNAs and affect their fate in the cytoplasm. The existence of proteins that bind DNA by acting first as transcription factors and binding mRNA later, and by playing additional roles in mRNA metabolism, is a frequent finding in many eukaryotes [15,16].

Therefore, an epitranscriptomic layer of information is added to genetic information. This idea was later extended with the discovery of many post-transcriptional modifications, such as 6-methyl (m^6A) and 1-methyl-adenine (m^1A) in mRNAs. These RNA modifications are co-transcriptionally inserted and affect mRNA stability and translation [17,18]. These results lead to the mRNA imprinting hypothesis [19]. Imprinting mRNAs during their transcription by either base modification or RBP binding can be a way to send information about the current physiological state of the cell from the nucleus to the cytoplasm, where

A)



B)

Different outcomes of RBP shuttling

RBP Transcriptional effect	RBP mRNA decay effect	[mRNA] outcome	Purpose
positive	positive	Compensatory	Buffering (global)
negative	negative	Compensatory	Buffering (global)
positive	negative	Additive	Regulation (specific)
negative	positive	Additive	Regulation (specific)

Fig. 1. A model for RBP shuttling effects on gene expression.
A. Some RNA binding proteins (RBPs) that are synthesized in the cytoplasm are imported to the nucleus where they play roles in gene transcription by binding to transcription initiation and/or elongation complexes. Then they can jump to nascent mRNA (with or without sequence specificity) and be exported to the cytoplasm bound to it. The release of these factors in the cytoplasm allows them to shuttle back to the nucleus. The presence of RBPs bound to cytoplasmic mature mRNA constitutes epitranscriptomic information that affects all mRNA life, especially its translation and stability. The crosstalk between transcription and mRNA decay uses mRNA imprinting with RBPs to send information from the nucleus to the cytoplasm. The information from the cytoplasm to the nucleus can be used as either a direct mechanism based on the return of RBPs or an indirect mechanism based on other signals (see the main text for details).
B. An RBP can have either an activating or repressing effect on transcription and, independently, can also stimulate or inhibit mRNA decay. The consequence of each combination would be a compensatory effect on the mRNA levels causing buffering or, alternatively, an additive effect used for gene expression regulation. We postulate that the compensatory effect is used mainly for global mRNA ($[mRNA]_t$) buffering and an additive effect is employed for specific gene or regulon regulation.

mRNA is translated into proteins and then degraded to nucleotides (Fig. 1A).

3. RNPs shuttling functions

The nuclear location of RBPs depends on the presence of nuclear location signals (NLSs). The export of the RBPs bound to mRNA could, however, be based on nuclear export sequences (NESs) in proteins or could, alternatively, result from passive "piggy backing" on mRNA [6]. In any case, the RBPs that perform nuclear functions and are co-transcriptionally bound to mRNAs probably return back to the nucleus and repeat shuttling in several cycles. This roundtrip would close the circle of information crosstalk between transcription in the nucleus and cytoplasmic mRNA decay [13] (Fig. 1A).

Many of the factors that have been described to date to be putatively and co-transcriptionally bound to mRNAs play active roles in transcription or mRNA decay [20]. Therefore, as expected, the use of mutants in any of them provokes the global lowering of either transcription (synthesis, SR) or decay (DR) rates. Interestingly, although the reduction in these rates is assumedly affected by the factor's primary activity, it is (partially or totally) compensated by the parallel lowering of the reciprocal rate, which leads to the buffering of the global mRNA concentration ($[mRNA]_t$). Although this has been investigated mainly in yeast [13,21,22], similar cases in higher eukaryotes have been found. Slobodin et al. [18] proposed that global transcription changes impact degradation machinery (Ccr4-Not complex) to buffer mRNA levels in mammalian B-cells. Singh et al. [23] demonstrated the existence of buffering for some specific mRNAs after the perturbation of some decay factors. As their study was not genome-wide, it is not possible to know if buffering is global or not. More recently, Berry et al. [24] found that $[mRNA]_t$ homeostasis in HeLa cells is maintained across thousands of genetic perturbations in spite of alterations in the SRs of mRNAs because, assumedly, DRs compensatorily changed. One conclusion drawn from these experiments is that transcription-related factors can also have effects on mRNA stability and cytoplasmic decay factors may also play a role in transcription activation [20,25]. Whether this additional effect is direct or indirect is a complex matter.

If a buffering pathway exists, $[mRNA]_t$ it will be stable against perturbations like those caused by external injuries or stresses, or by a mutation in another factor acting in mRNA synthesis or decay. If there is only a single pathway, and it is played by a factor or complex that acts as both a nuclear transcription stimulator and a cytoplasmic decay factor, a mutation in a gene that plays a direct role in the buffering pathway is expected to lead to a drastic alteration to $[mRNA]_t$. This is the idea behind the screening of Sun et al. [21], who proposed that 5′-3′ exoribonuclease Xrn1 is the main player in yeast $[mRNA]_t$ buffering. They also proposed an indirect reverse crosstalk mechanism, in which the level of transcriptional repressor Nrg1 is induced because of the impairment in mRNA decay, and it acts by repressing global transcription. Their data have been, however, questioned due to the artefactual side effects of thiouridine in the *xrn1Δ* background [26], because these authors did not take into account the large cell size of the *xrn1* mutant [13,27,28] and also because recent experiments with an *nrg1* mutant did not observe any effect in mRNA dynamics and transcription [28].

However, an alternative view is that if the factor directly involved in buffering is lacking, and by acting as a transcription and decay activator, it will provoke a simultaneous decrease in both the SR and DR which will, in turn, bring about $[mRNA]_t$ balance in any case. Nevertheless, this balance in a buffering-less cell would be sensitive to perturbations because $[mRNA]_t$ buffering is an important process for a living cell [27]. Surprisingly, the deletion of the putative buffering factors in yeast (i.e., Xrn1 and partners, Ccr4-NOT subunits, Rpb4, etc.) grow reasonably well under favorable conditions, which suggests that several parallel and partially redundant pathways can exist for $[mRNA]_t$ buffering [29,30]. These mutants do show, however, major defects during stress responses or culture conditions changes [31], which indicate a key role of $[mRNA]_t$ buffering for cells' adaptation to situations in which the whole transcriptome should be reorganized.

4. Mechanisms for transcription-mRNA decay crosstalk and its effect on mRNA buffering

Several hypotheses of crosstalk mechanisms have been proposed, which can be divided between direct and indirect. We call direct a mechanism when the crosstalk factor plays roles in both transcription and mRNA decay. This would be the case of the aforementioned yeast factors, which have been demonstrated to participate in both processes (i.e. Rpb4/7, Ccr4-NOT, Xrn1, etc.). We call a mechanism indirect when the effect of the nuclear factor on transcription and/or of the cytoplasmic factor on mRNA decay is led through an independent molecule. For $[mRNA]_t$ buffering in yeast, it has been proposed that Snf1 protein kinase may play a role in it because it phosphorylates many RBPs, some of which (e.g. Xrn1, Ccr4, Dhh1, Puf3) have been shown to be involved in both transcription and decay [27]. $[mRNA]_t$ buffering needs crosstalk in both directions: from the nucleus to the cytoplasm, and vice versa (Fig. 1A). If we assume that the message from the nucleus to the cytoplasm is driven by mRNA imprinting, the main gap to be filled in the model would be the reverse crosstalk mechanism. Several authors [20,28] propose some indirect mechanisms for this: the 5-AMP released by deadenylation or the concentration of free ribosomes. There are several indications to suggest that the total mRNA level (i.e. $[mRNA]_t$) can be the original signal sensed by reverse crosstalk [20,32]. A careful kinetic analysis of the transcriptional response performed in yeast after the degron-depletion of several decay factors has shown that the primary effect is a lower degradation rate that provokes an increase in $[mRNA]_t$. This is followed by an adaptation phase (after 45–60 min), in which the synthesis rate lowers and leads to a final $[mRNA]_t$ buffering after some hours. The differential kinetics seen in the depletion of decay factors, faster for Not1 (polyA shortening) than for Dcp2 (decapping) and Xrn1 (5–3′ exonuclease), indicates that the accumulation of intact polyA mRNAs, and not that of the intermediate decay products (deadenylated or decapped mRNAs), is the signal that triggers reverse crosstalk [28]. These authors suggest several mechanisms to sense $[mRNA]_t$. Some are based on RBPs, such as polyA-binding proteins (e.g. Pab1 or Nab2, that were previously suggested by other authors in higher eukaryotes: see [33,34]) or the Ccr4-NOT complex. A recent model has been proposed for the buffering action of polyA-binding proteins. It is called "local feedback" [26] and acts primarily at the nucleus. The nuclear total mRNA concentration ($[mRNA]_n$) is sensed by the nuclear pool of one of these proteins (i.e., Nab2, see [35]) because its binding is necessary to avoid nuclear mRNA degradation and to properly export it to the cytoplasm. According to this model, productive net transcription would be repressed by excess $[mRNA]_n$ [24,30]. Although this mechanism would well explain $[mRNA]_n$ buffering, this is not the case for $[mRNA]_t$ buffering because it is mostly cytoplasmic. It is not clear how changes in the biologically more relevant cytoplasmic [mRNA] would influence either the $[mRNA]_n$ or the mRNA synthesis rates.

It is important to stress that the logic behind mRNA buffering applies mostly to total $[mRNA]_t$, and not to the concentration of a specific mRNA of a single gene or gene group. This is because of the need to control global cytoplasmic composition [36,37] and the ratio between free and bound ribosomes [38,39]. This is at least the case of budding yeast, which has been demonstrated by us [32] and others [28]. It seems unlikely that cells have mechanisms for the buffering of a specific [mRNA]. A specific buffering mechanism would involve the regulation of the transcriptional response by a specific transcription factor in direct response to changes in the concentrations of the mRNAs of its target genes. This would be futile behavior for most growth conditions, but could be useful in some specific situations. For instance, it has been shown that specific mRNA buffering occurs in the phenomenon called genetic compensation, where the destabilization of some defective mRNAs by the non-sense-mediated decay (NMD) pathway is partially

compensated by a rise in the SRs of sequence-related genes [40,41]. This specific buffering does not occur in yeast [31]. Another case in which [mRNA] buffering can be useful is during stress responses. In this situation, some induced mRNAs can be imprinted to become less stable and to provoke a sharper peak that reduces the stress response cost [5,42].

5. Enhanced gene regulation by transcription-mRNA decay crosstalk

$[mRNA]_t$ buffering can easily be explained by a direct mechanism if it is assumed that only an RBP is co-transcriptionally bound to its targets and released in the cytoplasm after mRNA decay when it returns to the nucleus. We mathematically modeled it and found that this simple mechanism provokes buffering when the RBP is both a transcriptional activator and a decay factor, or is a transcriptional repressor and a decay inhibitor [43]. Our modeling also considered the possibility of RBPs having synergistic effects on transcription and decay (Fig. 1B). That is to say, an RBP activates transcription, binds mRNA co-transcriptionally and stabilizes it at the cytoplasm (or the symmetric case of an RBP that acts negatively on transcription and destabilizes mRNA). In these cases, we found that transcriptional responses are stronger and faster than in the absence of the RBP [43]. By performing a meta-analysis of the yeast genomic datasets for SR, DR and mRNA levels, we identified several mutants where lack of a RBPs factor increased SR and mRNA stability. We argued that those RBPs were both transcription repressors and transcript destabilizers. We also found a case (Sfp1) in which a known positive transcription factor also acted as a transcript stabilizer. Slobodin et al. [18] observed in B-cells that transcription elongation impacts m^6A deposition in specific mRNAs, and leads to additive effects on their mRNA level: higher transcription provokes enhanced mRNA stability and vice versa. Another interesting case in higher eukaryotes was that studied by Gilbertson et al. [33]. They found that infection by gammaherpesvirus induces accelerated cytoplasmic mRNA decay. In this case, massive mRNA degradation led to a global decrease in transcription because of the sudden release of the cytoplasmic polyA-binding protein (PABPC) that is imported back to the nucleus and causes a global repression of RNA pol II promoter recruitment. The nuclear import of PABPC seems to be activated by the release from mRNA because it exposes a previously covered NLS.

The nuclear effect on transcription by the imported RBPs (either positive or negative) is not known. It has been suggested that the nuclear accumulation of PABPC impacts early PIC assembly stages [33]. When an RBP has a positive effect on transcription, some RBPs bind genes in both the promoter and coding regions [9,13]. A clear effect of some RBPs (either decay or transcription factors) on RNA pol II elongation has been reported [11–13].

6. Concluding remarks

Although most work in this field has been performed in the yeast *S. cerevisiae,* there are several published works that demonstrate the involvement of RBPs in mRNA buffering and regulatory circuits in higher eukaryotes [7,8,15,16,18,23,24,30,33,40,41]. The need for global or specific mRNA buffering could, however, be different in free living cells that should respond individually to genetic and environmental changes, and in the cells that belong to different tissues that may adopt coordinated responses. In any case, it is clear that $[mRNA]_t$ buffering exists in all kinds of eukaryotic cells [18,23,24,30], and both specific [mRNA] buffering [40,41] and the additive effects of SRs and DRs are used to regulate global and specific responses in higher eukaryote cells [7,18,33].

Crosstalk mechanisms could contribute to $[mRNA]_t$ buffering (compensatory action) and, in other cases, could favor fast regulations of specific regulons in response to regulatory signals (additive regulation) (Fig. 1B). In fact, the existence of concerted, or even synergistic, responses might be necessary in the regulons with many genes and/or high mRNA levels to compensate the effect of global $[mRNA]_t$ buffering actions. The antibuffering effect of additive regulation in large regulons can be implemented by compensatory changes in other mRNA groups. Indeed, we recently demonstrated that ribosomal proteins and mitochondrial proteins regulons are subjected to a specific concerted response mediated by factors Sfp1 and Puf3, which could make them escape from $[mRNA]_t$ buffering during the growth rate variation caused by transcription-mRNA decay crosstalk [43]. Interestingly, these two large gene groups are often regulated inversely in the yeast *S. cerevisiae* [44,45].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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