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mRNP quality control goes regulatory

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The accuracy of eukaryotic gene expression relies on efficient quality control (QC). Most steps in the gene expression pathway en route from transcription to translation are error-prone and QC systems have evolved to utilise many of these biochemical processes as checkpoints to monitor the production or function of mRNA-protein particles (mRNPs). Mechanistically, such evaluation of mRNP fitness is based on competition between the opposing activities of mRNP biogenesis and/or function and mRNP turnover. In fact, quite subtle alteration of any parameter can tip the balance between mRNP persistence and degradation and, therefore, QC checkpoints also comprise perfect opportunities for controlling cellular levels of individual or even entire families of transcripts. From this perspective, QC and gene regulation represent two outcomes of the same molecular process.

Omnipresent mRNP QC

The life of a eukaryotic mRNA is astonishingly complex: from its birth in the nucleus to its cytoplasmic demise, it undergoes a series of interconnected biochemical reactions, starting with its synthesis by RNA polymerase II (RNAPII), followed by the transcription-coupled addition of a 7-methyl-guanylate cap to its 5′ end, removal of its introns and cleavage and polyadenylation of its 3′ end [1–3]. In addition to these covalent chemical changes, each mRNA has to interact correctly with a specific ensemble of RNA-binding proteins to form the mRNP that constitutes the functional entity of the message. Some of these proteins accompany the mRNA all the way until it is translated or degraded, whereas others associate in a location-specific or temporal manner to convey properties to the mRNP of only transient utility. Regardless of their exact nature, steps in the biogenesis and remodelling of mRNPs are susceptible to mistakes. To reduce the error frequency of the steady-state mRNP population, cells have evolved QC systems at several levels in both the nucleus and the cytoplasm [4–7] (Figure 1). These often take advantage of the normal reactions of mRNP biogenesis or utility where the welfare of the concerned mRNP is directly revealed. Indeed, most QC systems described so far intervene if the efficiency by which the mRNP is produced and transported is inadequate or if it performs poorly in translation. Current examples of QC checkpoints include the processes of mRNA capping [8,9], splicing [10], 3′-end formation [11–15], mRNP nuclear exit [16–18] and interaction with ribosomes [19–25].

For an in-depth discussion of the constituent factors of QC systems and their mechanisms of action, we refer the reader to recent reviews on nuclear [5–7] and cytoplasmic QC [26–30]. Here, we emphasise that QC systems are not dedicated entities evolved only to survey mRNP performance. Instead, QC is often based on the somewhat surprising intimate connection between common cellular RNA degradation activities and factors involved in productive mRNP transactions. In fact, degradation factors, or the proteins recruiting them, often participate themselves in mRNP production or remodelling. The term ‘QC’ therefore often describes a competition between the opposing processes of biogenesis and/or function, and turnover, which permits the elimination of molecules or complexes that do not meet certain standards. Interestingly, however, although QC processes normally serve to remove aberrant material, they can be readily exploited by the cell to also serve gene regulatory purposes and, because most mRNP biogenic and metabolic activities are functionally intertwined [2,3], there is ample opportunity for such regulation. Here, we illustrate this concept with recently published examples.

Balancing biogenesis and function with decay

Whenever an mRNP fails to pass QC, its progression is restricted, with the typical result that its mRNA component is degraded by ribonucleases. Recycling of particles retained by QC systems back into the functional pool is a formal possibility, but published examples are lacking. Likewise, repair of defective RNA can occur in special cases as part of stress response pathways [31], but instances of aberrant mRNA repair by QC systems have so far not been reported. Instead, and as mentioned above, the kinetic competition between steps in normal mRNP biogenesis or function and RNA turnover represents a unifying principle in many QC processes (reviewed in [4,6,32]). The outcome of this competition between normal maturation and/or function and commitment to mRNA degradation can be viewed as a double pan balance, in which one pan contains mRNPs that passed QC and the other contains complexes whose mRNAs are destined for degradation (Figure 2).

For any individual mRNP species, the fraction ending up in either pan of the balance ultimately depends on the competing rate constants, which we refer to as k_{normal} (rate constant for the normal maturation step or function) and k_{aberrant} (rate constant for commitment to mRNA decay).

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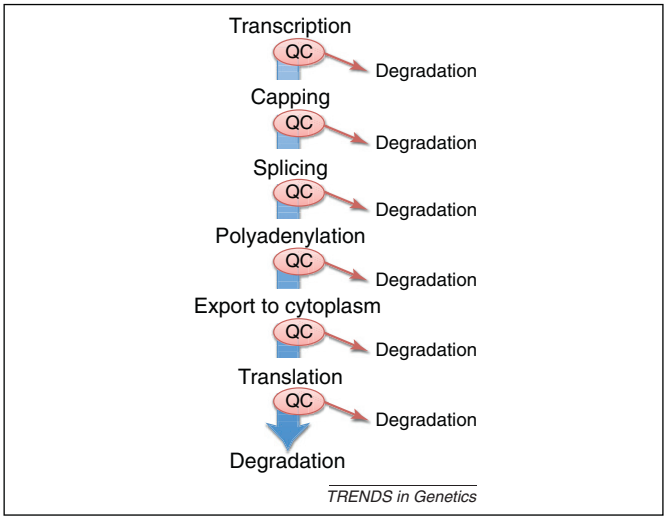

Figure 1. Quality control (QC) of mRNA-protein particles (mRNPs) occurs at several checkpoints along the gene expression pathway. Errors during RNA transcription, capping, splicing, polyadenylation, nuclear export and translation can all lead to faulty transcripts that are retained and/or removed by degradation activities (dark pink arrows). The fittest fraction of cellular mRNAs avoid QC to be processed and assembled correctly into functional mRNPs, which engage as templates for protein synthesis before they finally are also degraded (blue arrow).

Although QC systems are not yet understood in sufficient detail to allow a precise determination of these rate constants and make quantitative statements, they are still useful as tools for discussion. Owing to the inherent error rate of every step of mRNA production and mRNP assembly, any population of a specific mRNP species will harbour a fraction of particles that are defective or have reduced functionality. These mRNPs have a lower $k_{\mathrm{normal}}/k_{\mathrm{aberrant}}$ ratio compared with their flawless mRNP cousins, resulting in their differential distribution between the two pans and, hence, in efficient QC (Figure 2a). For example, aberrant mRNPs may be less efficient substrates for the processing reaction or functional activity in question (i.e. a reduced k_{normal}) or they may have acquired degradation-promoting features (i.e. an increased k_{aberrant}). Notably, when the overall capacity of a particular decay pathway is exceeded because of suboptimal mRNP production and/or function, and/or because a key degradation factor is inactivated, aberrant mRNAs will accumulate in the cell. Indeed, it is under such conditions that most QC pathways have been revealed experimentally.

If we apply the double pan balance concept to the entire cellular population of particles, each mRNP species will have its own intrinsic average $k_{\mathrm{normal}}/k_{\mathrm{aberrant}}$ ratio that determines which fraction will survive a given QC checkpoint. Thus, extrinsically induced changes affecting the overall assembly, processing or degradation rates, for example by modification of the activity of an enzyme required for mRNP production, function, or decay, will alter the species-specific $k_{\mathrm{normal}}/k_{\mathrm{aberrant}}$ ratio and, hence, the proportion of surviving mRNPs (Figure 2b). This is because

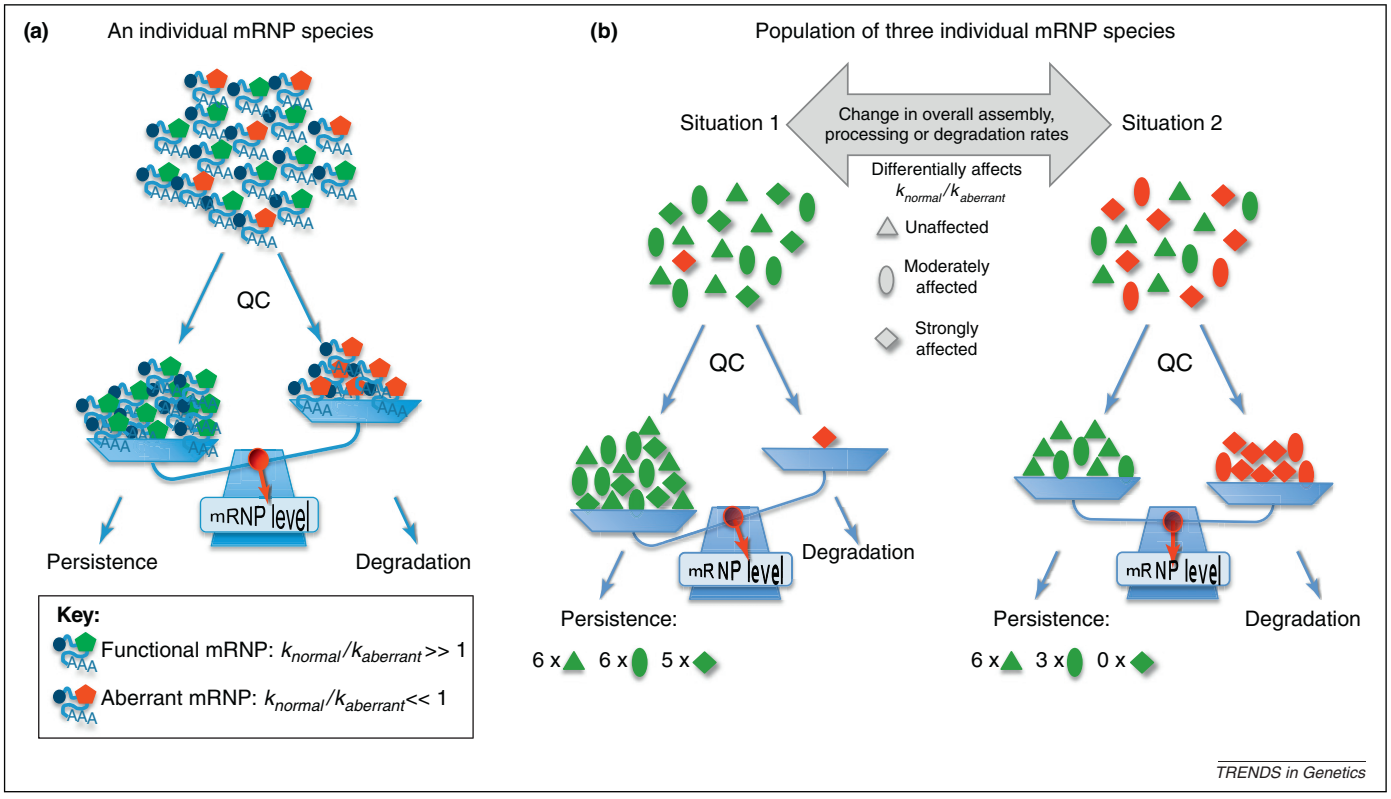

Figure 2. Schematic illustration of the balance between mRNA-protein particle (mRNPs) function and decay. The amount of mRNPs persisting after a given step in its biogenesis or after a functional task is determined by the net outcome between two competing rate constants: the rate of mRNP production/function (k_{normal}) and the rate of commitment to decay ($k_{aberrant}$). Modulating this balance alters mRNP abundance and, depending on the perspective, this can be perceived as removal of faulty mRNPs **(a)** or as changing the relative mRNP distribution in the cell **(b)**. **(a)** When applied to the population of a single mRNP species (individual mRNPs denoted by a hexagon) that contains a majority of functional particles (green) and a smaller number of defective, or less functional, particles (red), the competition between k_{normal} and $k_{aberrant}$ identifies and removes aberrant mRNPs. Thus, the system performs quality control (QC). **(b)** When applied to a population of different mRNP species (here three depicted as triangles, squares and ovals) that rely on the same assembly, processing and degradation activities, extrinsically induced changes of one of these parameters will affect $k_{normal}/k_{aberrant}$ differently for each individual mRNP species. This will result in an altered relative abundance of the different mRNP species. Thus, the same molecular process as in **(a)** is now performing gene regulation.

mRNA-inherent features influencing k_{normal} or $k_{aberrant}$ are diverse and of different strengths, hereby providing a wide and gradual spectrum of possible responses to, for example, stress or changed growth conditions. The concentration of a single mRNP species may also be specifically regulated via alteration of one or several of its constituents, changing the k_{normal} and/or $k_{aberrant}$ of that species only. In such considerations, the system controls gene expression and the distinction between mRNP QC and gene regulation becomes arbitrary.

Nuclear QC systems at work

As a general nuclear surveillance measure, QC systems in this locale efficiently remove mRNAs undergoing slow or aberrant 5′ capping, splicing or 3′-end formation (reviewed in [6,33]). Moreover, QC deals with malformed mRNPs, presumably via their inability to mature in a timely manner [14]. Although it is not known how much 'QC activity' is invested in these tasks during normal cellular growth, studies from several eukaryotic model systems have shown that nuclear QC machineries are constantly kept busy by the ubiquitous activity of RNAPII outside protein-coding genes. This is because large portions of eukaryotic genomes are transcribed, often on both strands and in a rather promiscuous manner [34–36]. As many of these transcripts are not destined for cytoplasmic translation or immediate nuclear usage [37–41], under physiological conditions the majority are rapidly removed and accumulate only when QC components (e.g. the 3′-5′ exo- and endoribonucleolytic RNA exosome or its cofactors) are artificially inhibited [37,41]. Hence, cryptic unstable transcripts (CUTs) from *Saccharomyces cerevisiae* [37] or promoter upstream transcripts (PROMPTs) from human cells [41,42] constitute examples where the balance between maturation and decay is tilted almost all the way towards complete degradation. In *S. cerevisiae*, transcription termination of CUTs by the Nrd1p/Nab3p/Sen1p complex is aided by Nrd1p/Nab3p-binding sites in the affected RNA and is directly coupled to their degradation by the RNA exosome aided by its coactivator TRAMP [39]. Although human exosome cofactors involved in PROMPT turnover have recently been identified, it is not yet clear how tightly the degradation of these transcripts is linked to the transcription termination event [43]. Finally, whether situations exist that tip the balance towards preferential stabilisation of CUTs or PROMPTs to yield potentially functional RNAs remains to be seen.

Shifting the balance: selective recruitment of QC activity

CUT transcription can provide regulatory function by impacting the activity of a closely positioned downstream gene [44–47]. This regulation is imposed by the CUT transcription event itself and, therefore, probably leaves the resulting CUT RNA as a disposable byproduct for exosomal degradation. In related instances, the Nrd1p/Nab3p/Sen1p complex is also involved in the premature transcription termination of genes, hereby hindering their production of full-length gene transcripts. The *NRD1* gene itself is a particularly interesting case as it is subjected to autoregulation by Nrd1p-dependent termination and exosomal degradation in approximately 80% of all transcription events [48] (Figure 3a). Such dramatic dampening of *NRD1* mRNA synthesis is guided by the presence of Nrd1p/Nab3p-binding sites in the 5′ untranslated region (UTR) and coding region of the *NRD1* mRNA. Thus, gene expression can be selectively downregulated by directed recruitment of QC factors. An intriguing glimpse of potentially complex interactions impacting this regulation was recently provided by the demonstration that the *S. cerevisiae* mitogen-activated protein (MAP) kinase Mpk1p can prevent Nrd1p/Nab3p/Sen1p-dependent transcription termination of the FK560 hypersensitive *2* (*FKS2*) gene by blocking the recruitment of the complex to RNAPII [49].

Exploitation of QC factors for gene regulatory purposes also occurs at the post-transcriptional level. In one example, the autoregulated expression of the nuclear polyadenylated RNA-binding protein (*NAB2*) gene, encoding the *S. cerevisiae* nuclear RNA poly(A) binding protein (PABP), relies on a stretch of 26 adenosine residues in the *NAB2* 3′UTR [50] (Figure 3b). Proper 3′-end formation of *NAB2* mRNA appears to occur by the non-conventional 3′ trimming of extended *NAB2* mRNA species by the nuclear exosome component Rrp6p, and the TRAMP factor Trf4p, eventually resulting in polyadenylation near or within the A_{26} stretch [51]. Presumably via binding to the A_{26} sequence, increasing levels of Nab2p prevents polyadenylation at this site and instead shifts the balance towards Rrp6p-dependent degradation of *NAB2* mRNA. The mechanism by which Nab2p sensitises the transcript to exosomal decay is not known, but may depend on the ability of Nab2p to recruit Rrp6p (THJ, unpublished observation). Moreover, this involvement of QC factors in the 'normal' 3′-end formation process appears to be of a broader nature, as a related phenomenon has been reported for the *S. cerevisiae* cysteine-three-histidine protein 2 (*CTH2*) mRNA [52].

It is also a strategy utilised in a second, conceptually related example from *Schizosaccharomyces pombe*. Here, vegetative cells are maintained by the direct recruitment of nuclear RNA exosome activity for the selective elimination of an estimated >20 meiotic mRNAs, whose protein products would otherwise adversely affect growth [53–56] (Figure 3c). Again, PABP is involved in the process: the nuclear *S. pombe* Pab2p protein, the homolog of mammalian PABPN1, physically associates with Rrp6p [57]. Remarkably, poly(A) tail addition by the conventional *S. pombe* poly(A) polymerase, Pla1p, appears to be underlying Pab2p and/or exosome recruitment to RNA, demonstrating that destabilisation through polyadenylation, which is a hallmark for TRAMP-associated enzymes, can also be achieved by a regular poly(A) polymerase [56]. Pab2p and/or exosome specificity towards meiosis-specific RNAs is achieved with the help of the RNA-binding protein Mmi1p, which belongs to the YTH family and interacts with 'determinant of selective removal' (DRS) regions residing in the 3′ ends of these transcripts. From this position, Mmi1p is thought to aid Pab2p/Rrp6p recruitment and simultaneously interfere with 3′-end processing of these pre-mRNAs, which as a consequence become easy preys for the exosome [54]. During meiosis, continuous degradation is inhibited, presumably by sequestration of

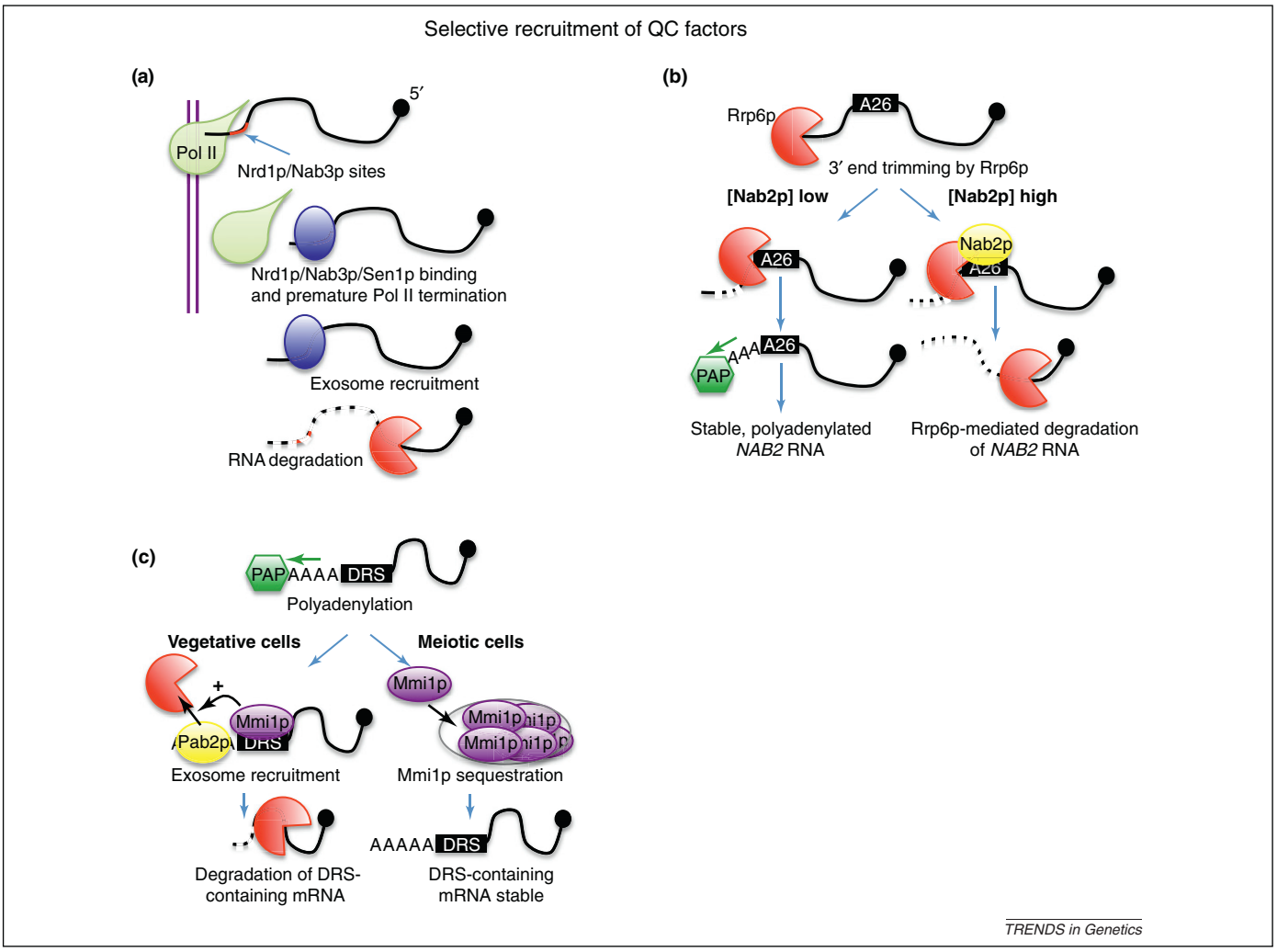

Figure 3. Gene regulation accomplished by the selective recruitment of nuclear quality control (QC) factors. **(a)** Autoregulation of Nrd1p levels in *Saccharomyces cerevisiae* is achieved by the premature transcription termination of the *NRD1* gene directed by the binding of the Nrd1p/Nab3p/Sen1p complex (blue oval) to the nascent *NRD1* RNA. Subsequent exosome (red pacman) recruitment results in the elimination of the prematurely terminated transcripts. **(b)** Nab2p, the nuclear poly(A) binding protein (PABP) of *S. cerevisiae,* negatively regulates its own expression by binding to a stretch of 26 genomically encoded adenosines (A26) in the 3′ untranslated region (UTR) of the nuclear polyadenylated RNA-binding protein (*NAB2*) RNA. In the absence of Nab2p at this site (low intracellular Nab2p concentrations), Rrp6p of the nuclear exosome trims the 3′ end of the transcript down to the A26 sequence, where after poly(A) polymerase (Pap1p) produces a poly(A) tail, leading to stable *NAB2* RNA. At high intracellular Nab2p levels, the factor binds to the A26 sequence and directs complete target degradation by Rrp6p, reducing *NAB2* RNA levels. **(c)** A set of mRNAs encoding meiosis-specific proteins is rapidly degraded in vegetative *Schizosaccharomyces pombe* cells owing to the direct recruitment of Rrp6p and the exosome by the nuclear PABP Pab2p. Exosome/Pab2p presence is furthered and, hence, specified by the RNA-binding protein Mmi1p, which targets the determinant of selective removal (DRS) regions in the 3′ UTRs of these mRNAs. During meiosis, Mmi1p is sequestered away from DRS-containing mRNAs into meiosis-specific foci, so-called 'Mei2 dots', thereby allowing for the cytoplasmic accumulation of DRS-containing transcripts. Abbreviation: Pol II, RNA polymerase II.

Mmi1p away from meiosis-specific mRNAs and into nuclear 'Mei2 dots', microscopically detectable foci consisting of the meiosis-specific Mei2p protein and additional components [53].

Collectively, these examples of QC factor-mediated post-transcriptional gene regulation challenge the traditional view that nuclear PABPs solely function in poly(A) tail biogenesis of regular mRNA: they may in addition facilitate the recruitment of QC factors, resulting in mRNA decay unless the targeted mRNP has evolved other means to deflect this nuclear ribonucleolytic challenge (e.g. preventive *cis*-elements or *trans*-factors, or a rapid expedition into the cytoplasm) [58].

Shifting the balance: modification of QC activity

Gene expression control by altering nuclear QC activity has been well documented in *S. cerevisiae* and *S. pombe*. It is based on the widespread antisense (as) transcription of these genomes and the ability of RNA degradation activities to alter rapidly cellular levels of such molecules [59–64]. A prime example is the as-transcription through the *S. cerevisiae* inorganic phosphate transporter *PHO84* gene [59,60] (Figure 4). Because *PHO84* antisense (as)RNA negatively regulates gene sense transcription through chromatin modification and histone deacetylation of the *PHO84* promoter, and because it is a target of the nuclear exosome, QC activity dictates cellular levels of both antisense and sense RNAs. Along these lines, *PHO84* gene silencing is observed in ageing cells, where less Rrp6p is recruited to the *PHO84* locus than in young cells [60]. Notably, Rrp6p abundance remains unchanged during ageing, which argues for a post-translational regulation of the Rrp6p activity, but the exact mechanism still needs to be determined.

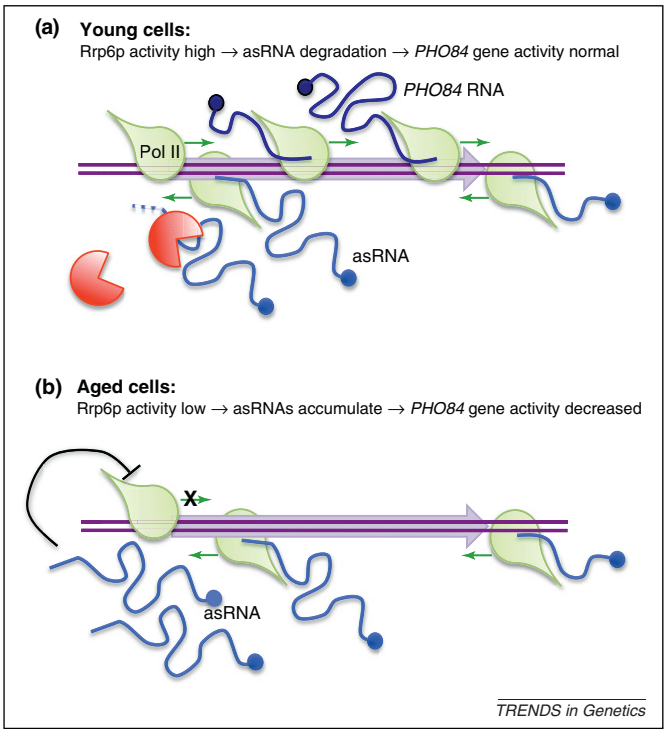

Figure 4. Gene regulation accomplished by modulating the activity of nuclear quality control (QC) factors. *PHO84* gene activity in *Saccharomyces cerevisiae* is controlled by the overlapping production of antisense (as)RNA. **(a)** In young cells, Rrp6p is targeted to *PHO84* asRNA, resulting in unperturbed transcription of *PHO84* RNA. **(b)** In aged cells, however, Rrp6p recruitment to the *PHO84* locus is diminished, allowing asRNA to accumulate with the consequent dampening of *PHO84* RNA transcription.

Changing intracellular Rrp6p levels represents an alternative way to modulate Rrp6p activity, as exemplified by the switch from mitosis to meiosis in *S. cerevisiae*: at the onset of meiosis, Rrp6p is degraded, leading to the stabilisation of multiple so-called 'meiotic unannotated transcripts' (MUTs) [65]. As diploid cells lacking Rrp6p cannot undergo efficient meiotic development, this sudden switch in the nuclear repertoire of ncRNA may have important consequences for the meiotic gene expression program.

A related example is provided by the asRNA-mediated regulation of *S. cerevisiae GAL* genes required for galactose metabolism [61]. Under conditions of *GAL* gene repression, asRNA expression through the *GAL1-10* cluster leads to recruitment of the Rpd3 histone deacetylation complex and suppression of the *GAL1-10* promoter. The asRNA is also targeted here by TRAMP/exosome and, because exosome activity is affected by carbon source supply [10], it is tempting to speculate that this constitutes at least part of the *GAL* gene regulatory circuit. As ncRNAs are thought to participate in the regulation of numerous catabolic genes, modulation of TRAMP/exosome activity is likely to contribute broadly to changes in gene expression programs upon changes in nutrient availability. Moreover, the potential for gene expression regulation via control of asRNA levels by the regulation of QC factor activity is enormous, as turnover of asRNAs is not confined to the exosome. For example, of 1658 Xrn1p-sensitive unstable transcripts (XUTs; ncRNAs destabilised by the major cytoplasmic 5′-3′ exonuclease Xrn1p) identified in a recent genome-wide survey, 66% were antisense to open reading frames (ORFs) [62]. Given the increasing realisation that sense-antisense RNA pairs also impact biological processes in higher eukaryotic cells, which also harbour their stocks of yeast-like QC factors, this type of regulation is probably evolutionary conserved.

QC at the level of translation: NMD, NSD and NGD

Even after mRNPs engage with the translation apparatus, QC ensues. Failure of ribosomes to terminate translation properly commonly triggers the rapid destruction of the concerned mRNA [1,4,26], which under certain conditions is accompanied by degradation of the involved ribosomes [66,67]. Well-documented examples include transcripts harbouring a premature termination codon (PTC) targeted by nonsense-mediated decay (NMD) (reviewed in [27,29,30]), mRNAs that lack a termination codon targeted by nonstop mRNA decay (NSD) [19,20] and mRNAs with ribosomes stalled at stable secondary structures or at a stretch of rare codons targeted by no-go mRNA decay (NGD) [21].

Recent studies suggest that NSD and NGD are mechanistically related processes. First, translation of the poly(A) tail of a nonstop mRNA generates a poly-lysine chain that was reported to stall ribosomes by clogging their exit tunnels [68], which essentially creates a no-go situation. Second, NSD and NGD both involve the release factor eRF1 homolog Pelota (Dom34p in yeast) and the eRF3 homologous GTPase Hbs1p [21,69]. In addition to these two release factor-mimicking proteins [70–72], the yeast E3 ubiquitin ligase Ltn1p was recently found to mark the nascent peptides produced from nonstop mRNAs for proteasomal degradation [68], revealing an interesting conceptual analogy to the bacterial transfer-messenger (tm)RNA-based surveillance system. In bacteria, a unique bi-functional aminoacylated tmRNA binds to the stalled ribosome, allows it to resume translation and serves as a template for addition of a peptide tag to the nascent polypeptide chain that induces its rapid proteolysis [73]. Concerning $k_{normal}/k_{aberrant}$ ratios (Figure 2), nonstop mRNAs are presumably efficiently recognised aberrant transcripts with the balance tilted strongly towards decay, whereas the frequency and duration of ribosome stalling on NGD substrates to a large extent will depend on extrinsic factors (e.g. temperature, availability of helicases, tRNA concentration, etc.). Thus, although specific examples of gene regulation by NGD have not yet been reported, a rich potential for exploitation of QC factors exists.

NMD at the crossroad between QC and gene regulation

NMD represents the most intensively studied QC system, not the least because it has long been recognised as an important modulator of the clinical manifestations of approximately 30% of all known disease-associated mutations [74]. NMD has traditionally been portrayed as a QC process that rids cells of faulty mRNAs with prematurely truncated ORFs. However, transcriptome-wide studies from different species have revealed a significant number of functional mRNAs targeted by NMD, demonstrating that it also undertakes translation-dependent post-transcriptional gene regulation (reviewed in [27–29,75]). Physiological NMD targets are usually downregulated

moderately (2- to 5-fold [76]), whereas classical PTC-containing substrates tend to swing the balance towards decay more dramatically by reducing transcript levels 10- to 50-fold.

The precise mode of selecting mRNAs for the NMD pathway is not yet understood. However, data from both *S. cerevisiae* and human cells suggest an evolutionarily conserved core mechanism at the heart of which there is a kinetic competition between PABPC1 [the major human cytoplasmic PABP (Pab1p in yeast)] and the NMD factor regulator of nonsense transcripts 1 (UPF1) for a mutually exclusive interaction with eRF3 (Sup35p in yeast) [77,78] (Figure 5). According to this model, the eRF3–PABC1 interaction is required for proper mRNA translation termination, whereas the competing eRF3–UPF1 interaction represents the first step towards NMD (reviewed in [79,80]). A key determinant for efficient eRF3–PABPC1 interaction is the physical distance between eRF3 bound to the ribosome stalled at the termination codon and PABPC1 bound to the poly(A) tail. The larger this distance, the less efficient the eRF3–PABPC1 interaction is, increasing the likelihood of UPF1 interference and congregation of other NMD components. Consequently, any mRNP rearrangements that alter the structure of the 3′UTR are predicted to affect the mRNA half-life and comprise a possibility for gene regulation [80,81]. This mode of regulation has so far only been demonstrated with engineered reporter gene constructs [81] and physiological examples are awaiting discovery.

After identification as an NMD substrate (i.e. after sorting to the right pan in Figure 2a), the RNA moiety of the mRNP is degraded in different ways depending on the species. In yeast, degradation of NMD substrates involves deadenylation, decapping and exonucleolytic decay [82–85]. In *Drosophila* and human cells, the metazoan-specific NMD factor and the endonuclease SMG6 cuts substrates in the vicinity of the stalled ribosome [86–88], although there is also evidence for exonucleolytic decay triggered by deadenylation and decapping in human cells [89–92].

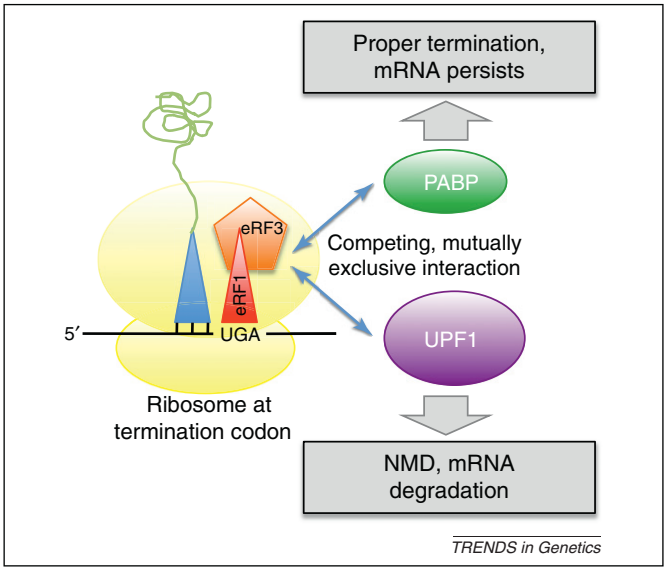

Figure 5. Model for gene regulation by nonsense-mediated mRNA decay (NMD)-mediated gene regulation. Eukaryotic poly(A) binding protein (PABP) and Upframeshift 1 (UPF1) proteins compete for a mutually exclusive interaction with the release factor complex eRF3/eRF1 at the terminating ribosome. Binding of PABP promotes proper translation termination and leaves the mRNA unaffected, whereas binding of UPF1 signals the assembly of an NMD-promoting complex that eventually recruits ribonucleases to trigger rapid mRNA decay.

Given its role as an effector of 3–10% of all cellular mRNAs [75], the activity and substrate selectivity of the NMD system is expected to be controlled by extrinsic signals. For example, during the differentiation of myoblast cells to myotubes, the overall efficiency of NMD diminishes as a consequence of the instigation of another mRNA turnover process called Staufen-mediated mRNA decay, which competes for the rate-limiting UPF1 protein. This leads to derepression of the myogenin mRNA, which encodes a protein required for myogenesis [93]. Similarly, cellular stress, such as hypoxia or amino acid deprivation, has also been found to reduce NMD potency, resulting in increased levels of numerous mRNAs encoding proteins associated with the respective stress response [94,95]. Furthermore, a recent discovery revealed that inhibition of NMD in neurons of the developing brain upregulates NMD-sensitive mRNAs encoding neural-specific factors [96]. Interestingly, the underlying mechanism conferring NMD downmodulation depends on binding of the developmentally regulated neuron-specific miRNA miR-128 to the 3′UTR of the *UPF1* mRNA, and miR-128 overexpression or *UPF1* depletion in neural stem cells individually promotes a neural differentiation phenotype [96]. Finally, two recent publications revealed autoregulation of NMD factors by demonstrating that most mRNAs encoding these factors are themselves targeted by NMD [76,97]. Although this feedback control on the one hand serves to buffer NMD activity against uncontrolled fluctuations caused by genetic and environmental perturbations, on the other hand, cell type-specific and developmental regulation of the NMD pathway have also been identified [97]. Altogether, these examples emphasise the role of NMD in physiological gene expression regulation and probably represent only the tip of a slowly surfacing iceberg.

Concluding remarks

Using examples, we have illustrated how the distinction between QC and gene regulation is often blurred. Future discoveries and more detailed dissection of the various molecular processes affecting the quality and quantity of expressed genetic information will further scrutinise this concept and reveal its validity and limitation. Irrespectively of the specific model, current data demonstrate that the life of an mRNA is a tightrope walk with decay factors lurking all around. mRNP constituents can be friend or foe and much remains to be learned about when mRNA interactors function as bodyguards or assassins. Studies of the group dynamics of mRNP components should reveal some of these secrets.

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