REVIEW

Curbing the nonsense: the activation and regulation of mRNA surveillance

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Gene expression requires the coordination and integration of multiple processes, including transcription, splicing, polyadenylation, nucleocytoplasmic export, and translation of mRNAs. Such complexity inevitably results in errors, many of which ultimately lead to premature termination of translation. Additionally, nonsense mutations can be introduced during DNA replication and are the cause of 20% to 40% of human genetic diseases (Frischmeyer and Dietz 1999). The truncated proteins encoded by these mutant mRNAs are potentially toxic to the cell, and therefore, a mechanism, known as mRNA surveillance or nonsense-mediated mRNA decay (NMD), has evolved to recognize mRNAs containing premature termination codons (PTCs) and cause their degradation to be accelerated.

Identifying the right stop

The NMD pathway enables the cell to distinguish between normal and premature stop codons. In mammalian cells, translation usually terminates within the last exon of a gene. Consistent with this observation, only stop codons lying >50 nucleotides upstream of the last exon–exon junction are generally recognized as premature (Nagy and Maquat 1998). Interestingly, both Hsp70 and histone mRNAs, which lack introns, are immune to NMD, suggesting that splicing enhances recognition of the premature stop codon (Maquat and Li 2001). Recent studies have shown that during the splicing of an mRNA, at least five proteins (SRm160, DEK, RNPS1, Y14, and REF/Aly) are deposited in an exon–exon junction complex (EJC) 20 to 24 nucleotides upstream of the exon–exon junction (Fig. 1; Le Hir et al. 2000). The EJC is not required for splicing but instead is thought to enhance export of the spliced mRNA, in part by recruiting TAP/p15 (Le Hir et al. 2001). In addition, one or more of the EJC components remains associated with the mRNA following export and is thought to associate with NMD factors in the cytoplasm (Kataoka et al. 2000; Zhou et al. 2000; Kim et al. 2001b; Lykke-Andersen 2001). The

RNPS1 protein and, to a lesser extent, Y14 are able to promote NMD independent of splicing when tethered downstream of a wild-type stop codon, indicating that the presence of these factors is sufficient to mark the mRNA for degradation (Lykke-Andersen et al. 2001). It has been hypothesized that during translation, the EJC and associated factors are displaced from the transcript by ribosomes. However, if translation terminates prematurely upstream of the wild-type stop codon, then the EJC proteins remain associated with the mRNA and act as a marker to be recognized by the surveillance machinery. Recent data suggests that the first, or pioneer, round of translation may differ from subsequent rounds in that the mRNA is still associated with nuclear factors such as CBP80, CBP20, and PABP2 instead of the cytoplasmic eIF4E and PABP (Ishigaki et al. 2001). NMD factors are associated with the mRNA at this time. Therefore, NMD may actually occur before assembly of cytoplasmic translation factors on the mRNA.

Some mammalian RNAs lacking introns downstream of the nonsense codon can also be degraded by the NMD pathway (Zhang et al. 1998; Rajavel and Neufeld 2001). In this instance, a downstream sequence, termed a fail-safe sequence, can replace the exon–exon junction and trigger NMD if a stop codon is located upstream. The fail-safe sequence may be able to specifically bind a component of the EJC, perhaps RNPS1, in the absence of splicing (Lykke-Andersen et al. 2001). In the yeast *Saccharomyces cerevisiae*, in which the majority of mRNAs lack introns, NMD relies on similar fail-safe sequences termed downstream sequence elements (DSEs; Zhang et al. 1995). The DSE is thought to recruit marker protein(s) similar in function to the EJC. One such marker protein, Hrp1p, has been identified as a DSE-binding factor, and an *hrp1* mutant strain is defective in the NMD process (Gonzalez et al. 2000). The DSE is a degenerate sequence element, which must lie downstream of a stop codon to elicit NMD. DSEs are normally found within coding sequences, where, like the EJC, bound factors would be displaced by the translating ribosome.

The surveillance complex

Several studies in yeast have focused on the link between translation termination and NMD. The transla-

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Figure 1. During mRNA splicing in the nucleus, several proteins are deposited on the mRNA 20–24 nucleotides upstream of each splice junction to form the exon–exon junction complex (EJC) and likely contain the nonsense-mediated mRNA decay (NMD) factor hUPF3. The EJC promotes export of the mRNA to the cytoplasm, where some factors dissociate and the hUPF2 protein associates. On recognition of a stop codon, the release factors and hUPF1 assemble on the ribosome. Subsequently, the hUPF1 protein searches downstream for the EJC. If the stop codon is premature, the EJC is encountered and interaction occurs. At this point, it is possible that hUPF1 is phosphorylated by the SMG-1 kinase, and this event could lead to rapid decapping of the mRNA.

tion termination process is a key event in triggering NMD and is mediated by two interacting release factors, eRF1 and eRF3. eRF1 mimics the structure of a tRNA by inserting into the A site of the ribosome at a stop codon and catalyzing release of the polypeptide chain. eRF3 is a GTPase that stimulates the activity of eRF1. The eRF3 protein has been shown to interact with a complex of three factors (Upf1p, Upf2p, and Upf3p; Fig. 1). Indeed, all three of the Upf proteins play a role in modulating translation termination as deletion of any one of them can result in a nonsense suppression phenotype, whereby premature stop codons are recognized inefficiently and translation read-through occurs (Wang et al. 2001). Although the precise function of each of the Upf proteins remains to be elucidated, the Upf1 protein has been shown to exhibit an RNA-dependent ATPase/helicase activity and belongs to the Group I superfamily of helicases (Czapinski et al. 1995). The Upf complex is also required for NMD and has been termed the surveillance complex. Following termination, it is thought to search downstream for marker proteins bound to the mRNA. In yeast, Upf1p has been shown to interact with the Hrp1p marker protein (Gonzalez et al. 2000), and this interaction eventually triggers rapid decapping of the mRNA followed by 5' to 3' exonucleolytic degradation (Muhlrad and Parker 1994; Hagan et al. 1995).

As described above, in yeast the Upf proteins play a role both in modulating suppression of a nonsense codon

and in triggering NMD. It is therefore not surprising that the UPF genes are conserved, both structurally and functionally, in higher eukaryotes. In *Caenorhabditis elegans*, NMD requires the function of seven *smg* genes (Pulak and Anderson 1993; Cali et al. 1999). Mutations in the *smg* genes were originally isolated based on their ability to allow normally recessive nonsense-containing alleles of the *unc-54* gene to act dominantly. This is achieved by allowing stabilization of the mutant *unc-54* mRNA and expression of a truncated cytotoxic *unc-54* protein. Three of these genes—*smg-2*, *smg-3*, and *smg-4*—encode homologs of UPF1, UPF2, and UPF3, respectively (Page et al. 1999; Aronoff et al. 2001; Serin et al. 2001). The *C. elegans* homolog of Upf1p, *smg-2*, is a phosphoprotein, and its phosphorylation status appears to be dependent on the function of the six other *smg* genes (Page et al. 1999). The *smg-1*, *smg-3* (UPF2), and *smg-4* (UPF3) proteins are required for the phosphorylation of *smg-2*, whereas *smg-5*, *smg-6*, and *smg-7* are necessary for dephosphorylation. Mutation of any of the *smg* genes debilitates the NMD pathway, suggesting that this phosphorylation event is integral to its function.

Human homologs of all three of the UPF genes have been identified, including two homologs of UPF3, and several experiments have shown their function in the NMD pathway (Sun et al. 1998; Mendell et al. 2000; Serin et al. 2001). A dominant-negative hUPF1/RENT1 can inhibit NMD when expressed in human cell lines

(Sun et al. 1998). Intriguingly, any one of the human UPF proteins (hUPF1, hUPF2, hUPF3A, or hUPF3B) can mark a wild-type mRNA for NMD when tethered to the 3'-UTR (Lykke-Andersen et al. 2000). The two UPF3 homologs, hUPF3A and hUPF3B, have so far proved functionally indistinguishable despite being only 42% identical (Serin et al. 2001). The hUPF3 proteins are part of the EJC as they associate specifically with spliced mRNAs upstream of exon-exon junctions, interact with both RNPS1 and Y14, and can shuttle from the nucleus to cytoplasm (Lykke-Andersen et al. 2000; Kim et al. 2001a; Le Hir et al. 2001). In fact, RNPS1, a known shuttling component of the EJC, is able to interact with all three hUPF proteins by immunoprecipitation (Lykke-Andersen et al. 2001). The hUPF2 seems to associate with the EJC following export from the nucleus, whereas hUPF1 may only bind the EJC transiently through hUPF2 and function in triggering mRNA decapping (see Fig. 1; Le Hir et al. 2001).

SMG-1 and the regulation of mRNA surveillance

As described above, association of the EJC during splicing, its subsequent remodeling, assembly of the surveillance complex, and the recognition of a premature stop codon require multiple protein-protein and protein-RNA interactions. Assembly and dissociation of these complexes is likely to be highly regulated, and it is becoming clear that some of this regulation occurs at the level of phosphorylation of UPF1.

Recent results have shown that human UPF1, like the *C. elegans smg-2*, is a phosphoprotein and that the phosphorylation occurs on serine and threonine residues (Pal et al. 2001). The phosphorylated form of hUPF1 appears to be associated with polysomes, whereas the unmodified protein is ribosome-free. This result suggests that the phosphorylation event may modulate association of hUPF1 with the translation machinery. An increase in hUPF1 phosphorylation is observed when starved cells are treated with serum, and addition of wortmannin, an inhibitor of PI-3 kinases, can inhibit this phosphorylation, showing that the phosphorylation status of UPF1 can be modulated in response to external signals.

Two recent papers report the cloning and characterization of the human homolog of *smg-1* (Denning et al. 2001; Yamashita et al. 2001). This large protein is a novel serine/threonine kinase related to phosphatidylinositol-3 kinases (PIK), and its significance lies in its ability to phosphorylate the human UPF1 protein. The hSMG-1 protein is expressed in many tissues and cell lines and shows auto-phosphorylation and the ability to phosphorylate hUPF1 and another PIKK substrate, PHAS-1 (Denning et al. 2001; Yamashita et al. 2001). Four serine residues were identified in the C-terminal region of hUPF1 that can be phosphorylated by hSMG-1 in vitro (Yamashita et al. 2001). Phosphospecific antibodies showed that at least two of these, S1078 and S1096, were also phosphorylated in vivo in an hSMG-1-dependent manner. The phosphorylated serines are within the usual SQ motifs known to be substrates of PIK kinases.

Significantly, the C terminus of the *C. elegans smg-2* protein also has several SQ motifs, although the positions are not conserved (Page et al. 1999). However, the yeast Upf1p, which has not been shown to be a phosphoprotein, has only one SQ motif in this region. Interestingly, there is no homolog of SMG-1 in the yeast genome. This observation, along with the fact that homologs of *smg-1*, *smg-5*, and *smg-7* are also not found in the yeast genome, suggests that the regulation of UPF1 activity and/or interactions may differ between yeast and higher eukaryotes (P. Anderson, pers. comm.).

Phosphorylation of proteins can have two possible consequences. It can modulate the catalytic activity of a protein or its association with other factors. The role of phosphorylation in modulating the ATPase/helicase activity of hUPF1 has not been studied. However, in both yeast and human cells, UPF1 can exist in a complex with UPF2 and UPF3. The UPF proteins play an integral role in both translation termination and mRNA surveillance in yeast, and it has been suggested that UPF1 must interact sequentially first with the release factors and then with marker proteins bound to the mRNA (Wang et al. 2001). Each interaction must form and dissociate in a regulated manner, and it is likely that phosphorylation plays an important role in regulating the organization of components in the surveillance complex. Human SMG-1 could coimmunoprecipitate hUPF1, hUPF2, and hUPF3A, showing that these factors are able to form a complex (Yamashita et al. 2001). Significantly, only the phosphorylated form of hUPF1 was coimmunoprecipitated with hUPF3A, suggesting that hUPF3 may play a positive role in the phosphorylation of hUPF1. Alternatively, the full surveillance complex may only assemble once hUPF1 is phosphorylated. This is consistent with the fact that the worm homolog of hUPF3, *smg-4*, is required for phosphorylation of *smg-2* (Page et al. 1999).

A kinase-deficient mutant of hSMG-1 expressed in HeLa cells was unable to phosphorylate hUPF1 in vitro and is therefore predicted to have a negative effect on NMD. In support of this idea, over-expression of a kinase-deficient mutant of SMG-1 in HeLa cells resulted in specific stabilization of a nonsense-containing reporter mRNA, whereas the wild-type protein actually enhanced decay of the same mRNA. Neither protein had any effect on decay of the wild-type β -globin mRNA (Yamashita et al. 2001).

Known inhibitors of PIK kinases—wortmannin and caffeine—can inhibit both phosphorylation of hUPF1 and rapid decay of the nonsense-containing β -globin reporter mRNA in vivo (Pal et al. 2001; Yamashita et al. 2001). The inhibitors are also able to block decay of an endogenous nonsense-containing p53 mRNA in two cancer cell lines (Yamashita et al. 2001). Notably, the inhibition of NMD resulted in accumulation of truncated p53 protein product. This experiment suggests that inhibition of the NMD pathway allows accumulation of truncated proteins in vivo. In some cases, such shortened proteins may be partially functional, and their expression could alleviate disease phenotypes associated with PTC-containing genes. It remains to be seen whether the

SMG-1 kinase also plays a role in translation termination. If this were the case, then inhibitors of SMG-1 may also allow nonsense suppression and expression of full-length proteins from genes containing PTCs. These experiments strongly suggest that hSMG-1 is an integral component of the NMD machinery in mammalian cells and point to a vital role for the SMG-1 kinase in controlling the activity of the NMD pathway. However, phosphorylation is not a constitutive state, and both phosphorylation and dephosphorylation of Upf1p may be involved in regulating the association and dissociation of the complexes involved in the translation termination and NMD processes. The phosphatase encoded by the *SAL6* gene in yeast was isolated as a factor that improves translation termination efficiency (Vincent et al. 1994). It is therefore possible that *SAL6* may play a role in modulating NMD. It will be interesting to determine which phosphatase(s) is involved in reversing the phosphorylation of hUPF1. As mentioned above, *smg-5* is required for dephosphorylation of *smg-2* in *C. elegans*. The *smg-5* gene encodes a protein that has been shown to interact with a subunit of protein phosphatase 2A (P. Anderson, pers. comm.). Consistent with this, a PP2A inhibitor, okadaic acid, increases accumulation of phosphorylated hUPF1 in vivo (Yamashita et al. 2001). Therefore, PP2A may be an antagonist of hSMG-1. It is also interesting to note that the catalytic subunit of PP2A has been found to associate with the translation termination factor, eRF1, in mammalian cells (Andjelkovic et al. 1996). Thus, both the kinase and a potential phosphatase of hUPF1 can be linked to the translating ribosome. These observations implicate a cycle of phosphorylation and dephosphorylation in regulating the association and dissociation of the complexes involved in the translation termination and NMD processes.

Kinases are generally thought of as signaling proteins, transducing either extracellular or intracellular signals. The PIK-related kinase family is somewhat unique in that these kinases generally respond to signals occurring within the cell and are peculiarly involved in monitoring the fidelity of cellular processes. For example, ATM (ataxia telangiectasia mutated) is activated in response to detection of double-stranded DNA breaks within the nucleus and modulates cell-cycle checkpoints and DNA repair (Durocher and Jackson 2001). FRAP/mTOR responds to changes in amino acid levels and regulates translation accordingly; however, it also modulates the p70^{S6K} signal transduction pathway, which is activated by extracellular mitogens (Gingras et al. 2001). It seems likely therefore that SMG-1 acts intracellularly and is activated in response to recognition of a PTC. We hypothesize that activation of SMG-1 leads to phosphorylation of hUPF1, and this event ultimately results in the rapid decapping of the offending mRNA (Fig. 1). It is also possible that SMG-1 can be regulated by external stimuli to modulate the activity of the NMD pathway. A subset of cell types may use the NMD pathway to regulate expression of specific genes.

These recent studies of the factors involved in NMD give us a hint of the complexity of this surveillance path-

way. In the model depicted in Figure 1, mRNA surveillance commences during the splicing process when the EJC is deposited on the mRNA. The EJC promotes export of the mRNA to the cytoplasm and then remodels into a marker for NMD through association with UPF2 and dissociation of REF/Aly. In the majority of cases, the EJC would simply be displaced during the first round of translation. However, if translation terminates prematurely upstream, the UPF1 protein is predicted to encounter the EJC and trigger rapid decay of the mRNA. It will be important to determine at which step(s) of the pathway the SMG-1 protein is activated and by what mechanism. If it acts at the time of EJC recognition (Fig. 1), then SMG-1 may affect only mRNA decay and not the translation termination process. The fact that only phosphorylated UPF1 is found associated with hUPF3 favors this model (Yamashita et al. 2001). It may be that the phosphorylation event is critical in the next step of the pathway, activation of decapping.

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References

- Andjelkovic, N., Zolnierowicz, S., Van Hoof, C., Goris, J., and Hemmings, B.A. 1996. The catalytic subunit of protein phosphatase 2A associates with the translation termination factor eRF1. *EMBO J.* **15**: 7156–7167.
- Aronoff, R., Baran, R., and Hodgkin, J. 2001. Molecular identification of *smg-4*, required for mRNA surveillance in *C. elegans*. *Gene* **268**: 153–164.
- Cali, B.M., Kuchma, S.L., Latham, J., and Anderson, P. 1999. *smg-7* is required for mRNA surveillance in *Caenorhabditis elegans*. *Genetics* **151**: 605–616.
- Czapinski, K., Weng, Y., Hagan, K.W., and Peltz, S.W. 1995. Purification and characterization of the Upf1 protein: A factor involved in translation and mRNA degradation. *RNA* **1**: 610–623.
- Denning, G., Jamieson, L., Maquat, L.E., Thompson, E.A., and Fields, A.P. 2001. Cloning of a novel phosphatidylinositol kinase-related kinase: Characterization of the human SMG-1 RNA surveillance protein. *J. Biol. Chem.* **276**: 22709–22714.
- Durocher, D. and Jackson, S.P. 2001. DNA-PK, ATM and ATR as sensors of DNA damage: Variations on a theme? *Curr. Opin. Cell Biol.* **13**: 225–231.
- Frischmeyer, P.A. and Dietz, H.C. 1999. Nonsense-mediated mRNA decay in health and disease. *Hum. Mol. Genet.* **8**: 1893–1900.
- Gingras, A.C., Raught, B., and Sonenberg, N. 2001. Regulation of translation initiation by FRAP/mTOR. *Genes & Dev.* **15**: 807–826.
- Gonzalez, C.I., Ruiz-Echevarria, M.J., Vasudevan, S., Henry, M.F., and Peltz, S.W. 2000. The yeast hnRNP-like protein Hrp1/Nab4 marks a transcript for nonsense-mediated mRNA decay. *Mol. Cell* **5**: 489–499.

- Hagan, K.W., Ruiz-Echevarria, M.J., Quan, Y., and Peltz, S.W. 1995. Characterization of *cis*-acting sequences and decay intermediates involved in nonsense-mediated mRNA turnover. *Mol. Cell. Biol.* **15**: 809–823.
- Ishigaki, Y., Li, X., Serin, G., and Maquat, L.E. 2001. Evidence for a pioneer round of mRNA translation: mRNAs subject to nonsense-mediated decay in mammalian cells are bound by CBP80 and CBP20. *Cell* **106**: 607–617.
- Kataoka, N., Yong, J., Kim, V.N., Velazquez, F., Perkinson, R.A., Wang, F., and Dreyfuss, G. 2000. Pre-mRNA splicing imprints mRNA in the nucleus with a novel RNA-binding protein that persists in the cytoplasm. *Mol. Cell* **6**: 673–682.
- Kim, V.N., Kataoka, N., and Dreyfuss, G. 2001a. Role of the nonsense-mediated decay factor hUpf3 in the splicing-dependent exon–exon junction complex. *Science* **293**: 1832–1836.
- Kim, V.N., Yong, J., Kataoka, N., Abel, L., Diem, M.D., and Dreyfuss, G. 2001b. The Y14 protein communicates to the cytoplasm the position of exon–exon junctions. *EMBO J.* **20**: 2062–2068.
- Le Hir, H., Izaurralde, E., Maquat, L.E., and Moore, M.J. 2000. The spliceosome deposits multiple proteins 20–24 nucleotides upstream of mRNA exon–exon junctions. *EMBO J.* **19**: 6860–6869.
- Le Hir, H., Gatfield, D., Izaurralde, E., and Moore, M.J. 2001. The exon–exon junction complex provides a binding platform for factors involved in mRNA export and nonsense-mediated mRNA decay. *EMBO J.* **20**: 4987–4997.
- Lykke-Andersen, J., Shu, M.D., and Steitz, J.A. 2000. Human Upf proteins target an mRNA for nonsense-mediated decay when bound downstream of a termination codon. *Cell* **103**: 1121–1131.
- . 2001. The protein RNPS1 communicates the position of exon–exon junctions to the mRNA surveillance machinery. *Science* **293**: 1836–1839.
- Maquat, L.E. and Li, X. 2001. Mammalian heat shock p70 and histone H4 transcripts, which derive from naturally intronless genes, are immune to nonsense-mediated decay. *RNA* **7**: 445–456.
- Mendell, J.T., Medghalchi, S.M., Lake, R.G., Noensie, E.N., and Dietz, H.C. 2000. Novel upf2p orthologues suggest a functional link between translation initiation and nonsense surveillance complexes. *Mol. Cell. Biol.* **20**: 8944–8957.
- Muhlrad, D. and Parker, R. 1994. Premature translational termination triggers mRNA decapping. *Nature* **370**: 578–581.
- Nagy, E. and Maquat, L.E. 1998. A rule for termination-codon position within intron-containing genes: When nonsense affects RNA abundance. *Trends Biochem. Sci.* **23**: 198–199.
- Page, M.F., Carr, B., Anders, K.R., Grimson, A., and Anderson, P. 1999. SMG-2 is a phosphorylated protein required for mRNA surveillance in *Caenorhabditis elegans* and related to Upf1p of yeast. *Mol. Cell. Biol.* **19**: 5943–5951.
- Pal, M., Ishigaki, Y., Nagy, E., and Maquat, L.E. 2001. Evidence that phosphorylation of human Upf1 protein varies with intracellular location and is mediated by a wortmannin-sensitive and rapamycin-sensitive PI 3-kinase-related kinase signalling pathway. *RNA* **7**: 5–15.
- Pulak, R. and Anderson, P. 1993. mRNA surveillance by the *Caenorhabditis elegans* smg genes. *Genes & Dev.* **7**: 1885–1897.
- Rajavel, K.S. and Neufeld, E.F. 2001. Nonsense-mediated decay of human HEXA mRNA. *Mol. Cell. Biol.* **21**: 5512–5519.
- Serin, G., Gersappe, A., Black, J.D., Aronoff, R., and Maquat, L.E. 2001. Identification and characterization of human orthologues to *Saccharomyces cerevisiae* upf2 protein and upf3 protein (*Caenorhabditis elegans* SMG-4). *Mol. Cell. Biol.* **21**: 209–223.
- Sun, X., Perlick, H.A., Dietz, H.C., and Maquat, L.E. 1998. A mutated human homologue to yeast Upf1 protein has a dominant-negative effect on the decay of nonsense-containing mRNAs in mammalian cells. *Proc. Natl. Acad. Sci.* **95**: 10009–10014.
- Vincent, A., Newnam, G., and Liebman, S.W. 1994. The yeast translational allosuppressor, SAL6: A new member of the PP1-like phosphatase family with a long serine-rich N-terminal extension. *Genetics* **138**: 597–608.
- Wang, W., Czaplinski, K., Rao, Y., and Peltz, S.W. 2001. The role of Upf proteins in modulating the translation read-through of nonsense-containing transcripts. *EMBO J.* **20**: 880–890.
- Yamashita, A., Ohnishi, T., Kashima, I., Taya, Y., and Ohno, S. 2001. Human SMG-1, a novel phosphatidylinositol 3-kinase-related protein kinase, associates with components of the mRNA surveillance complex and is involved in the regulation of nonsense-mediated mRNA decay. *Genes & Dev.* **15**: 2215–2228.
- Zhang, J., Sun, X., Qian, Y., and Maquat, L.E. 1998. Intron function in the nonsense-mediated decay of β -globin mRNA: Indications that pre-mRNA splicing in the nucleus can influence mRNA translation in the cytoplasm. *RNA* **4**: 801–815.
- Zhang, S., Ruiz-Echevarria, M.J., Quan, Y., and Peltz, S.W. 1995. Identification and characterization of a sequence motif involved in nonsense-mediated mRNA decay. *Mol. Cell. Biol.* **15**: 2231–2244.
- Zhou, Z., Luo, M.J., Straesser, K., Katahira, J., Hurt, E., and Reed, R. 2000. The protein Aly links pre-messenger-RNA splicing to nuclear export in metazoans. *Nature* **407**: 401–405.

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