Nonsense-mediated mRNA decay in mammals

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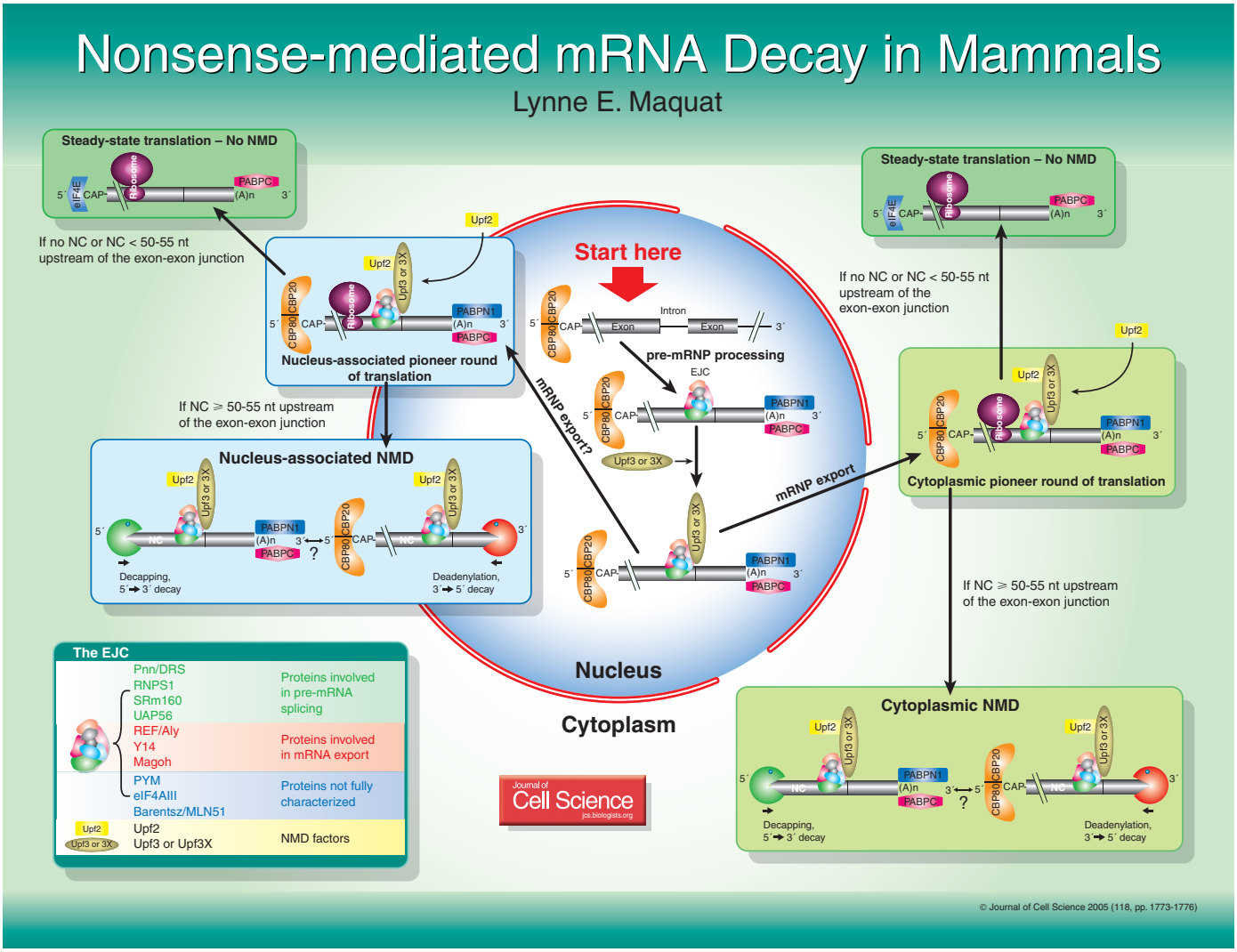
Nonsense-mediated mRNA decay (NMD) in mammalian cells generally degrades mRNAs that terminate translation more than 50-55 nucleotides upstream of a splicing-generated exon-exon junction (reviewed in Maquat, 2004a; Nagy and Maquat, 1998). Notably, dependence on exon-exon junctions distinguishes NMD in mammalian cells from NMD in all other organisms that have been examined, including *Saccharomyces cerevisiae* and *Drosophila melanogaster* (reviewed in Maquat, 2004b). NMD downregulates spliced mRNAs that prematurely terminate translation so

production of the potentially toxic truncated proteins that they encode. NMD also downregulates naturally occurring mRNAs, such as an estimated one-third of alternatively spliced mRNAs, certain selenoprotein mRNAs, some mRNAs that have upstream open reading frames, and some mRNAs that contain an intron within the 3′ untranslated region (Hillman et al., 2004; Mendell et al., 2004; Moriarty et al., 1998). In fact, it is thought that NMD has been maintained throughout evolution not only because it degrades transcripts that are the consequence of routine abnormalities in gene expression but also because it is widely used to achieve proper levels of gene expression. Although disease-associated mutations that result in the premature termination of translation led to the discovery of NMD, it is not likely that this type of mutation ever drove significant evolutionary selection. Nevertheless, some of these mutations nicely illustrate the importance of NMD. For example, nonsense mutations within the last exon of the human β-globin gene do not elicit NMD because there is no downstream exon-exon junction. As a consequence, the resulting truncated β-globin has near-normal abundance, fails to properly associate with α-globin and causes a dominantly inherited form of what is otherwise (e.g. for nonsense codons



(See poster insert)

located within exons other than the last exon) a recessively inherited thalassemia (Thein, 2004).

The importance of NMD is exemplified by the findings that mouse embryos that cannot perform NMD because they lack a key NMD protein, Upf1, resorb shortly after implantation (Medghalchi et al., 2001). Furthermore, blastocysts that have the same defect, isolated 3.5 days post-coitum, undergo apoptosis in culture after a brief growth period (Medghalchi et al., 2001). The inviability of NMD-deficient embryos and cells probably reflects the combined failure to regulate natural substrates properly and eliminate transcripts that were generated in error. Note that, Upf1 has been shown to function in other pathways, as well as NMD (see below), which may also contribute to the observed inviability.

NMD in mammalian cells is a consequence of a pioneer round of translation (Chiu et al., 2004; Ishigaki et al., 2001; Lejeune et al., 2004). As illustrated in the poster, precursor (pre)-mRNA in the nucleus is bound to by the major nuclear cap-binding protein (CBP) CBP80-CBP20 heterodimer and, after 3′-end formation, the major nuclear poly(A)-binding protein (PABP) PABPN1 (Chiu et al., 2004; Ishigaki et al., 2001). Pre-mRNA splicing generates spliced mRNA that is bound by CBP80, CBP20, PABPN1 and the major cytoplasmic PABPC (Chiu et al., 2004; Ishigaki et al., 2001; Lejeune et al., 2004) as well as an exon junction complex (EJC) of proteins that is deposited, as a consequence of splicing, ~20-24 nucleotides upstream of each exon-exon junction (Le Hir et al., 2000a; Le Hir et al., 2000b). Constituents of EJCs include Y14, RNPS1, SRm160, REF/Aly, UAP56, Magoh, Pnn/DRS, eIF4AIII, PYM and Barentsz/MLN51 (Bono et al., 2004; Chan et al., 2004; Custodio et al., 2004; Degot et al., 2004; Ferraiuolo et al., 2004; Kataoka et al., 2000; Kim et al., 2001; Le Hir et al., 2001; Le Hir et al., 2000a; Le Hir et al., 2000b; Lejeune et al., 2002; Li et al., 2003; Luo et al., 2001; Palacios et al., 2004; Shibuya et al., 2004). The EJC also contains additional proteins, including the NMD factors Upf3 (also called Upf3a) or Upf3X (also called Upf3b), Upf2 and, presumably transiently, Upf1 (Kim et al., 2004; Lykke-Andersen et al., 2000; Lykke-Andersen et al., 2001; Mendell et al., 2000; Ohnishi et al., 2003; Serin et al., 2001). Either Upf3 or Upf3X, each of which is mostly nuclear but shuttles to the cytoplasm and interacts with Upf2, is thought to recruit Upf2, which concentrates along the cytoplasmic side of the nuclear envelope (Kadlec et al., 2004; Lykke-Andersen et al., 2000; Serin et al., 2001).

The resulting mRNP constitutes the pioneer translation initiation complex (Chiu et al., 2004; Ishigaki et al., 2001; Lejeune et al., 2002; Lejeune et al., 2004). This complex is thought to undergo a ‘pioneer’ round of translation either in association with nuclei, in the case of mRNAs that are subject to nucleus-associated NMD, or in the cytoplasm, in the case of mRNAs that are subject to cytoplasmic NMD. If NMD occurs, it is the consequence of nonsense codon (NC) recognition during this pioneer round of translation (Chiu et al., 2004; Ishigaki et al., 2001; Lejeune et al., 2004). Upf1 may function as a component of the translation termination complex before it functions in NMD, considering that NMD requires translation termination and Upf1 associates with eukaryotic translation release factors 1 (F. Lejeune and L.E.M., unpublished) and 3 (G. Singh and J. Lykke-Andersen, personal communication). Upf1 might associate with mRNA regardless of whether termination occurs at a position that elicits NMD. If translation terminates at an NC that resides more than 50-55 nucleotides upstream of an exon-exon junction, then Upf1 is thought to elicit NMD by interacting with EJC-associated Upf2 (Maquat, 2004a; Lykke-Andersen et al., 2000; Mendell et al., 2000; Serin et al., 2001). Consistent with a role for EJCs in NMD is the observation that NC-containing mRNAs that derive from intronless genes fail to undergo NMD (Brocke et al., 2002; Maquat and Li, 2001).

Once the mRNA is remodeled so that eukaryotic translation initiation factor (eIF)4E replaces CBP80-CBP20 at the mRNA cap, PABPC replaces PABPN1 at the poly(A) tail, and EJCs have been removed from mRNA, the mRNA becomes immune to NMD (Chiu et al., 2004; Ishigaki et al., 2001; Lejeune et al., 2002). Translation has been reported to remove Y14 (Dostie and Dreyfuss, 2002), and it may remove other mRNA-binding proteins as well. Although these conclusions derive largely from studies of mRNP structure, they are consistent with kinetic analyses indicating that NMD is restricted to newly synthesized mRNA and does not detectably target steady-state mRNA (Belgrader et al., 1994; Cheng and Maquat, 1993; Lejeune et al., 2003).

Cell fractionation studies indicate that most nonsense-containing mRNAs are subject to nucleus-associated NMD (reviewed in Maquat, 2004a). This means that mRNA decay occurs prior to the release of newly synthesized mRNAs into the cytoplasm. Nucleus-associated NMD has been proposed to occur within the nucleoplasm, but it is generally thought to take place during or after mRNA transport across the nuclear pore complex (Dahlberg et al., 2003; Maquat, 2002). A fraction of mRNAs is subject to cytoplasmic NMD (e.g. Dreumont et al., 2004; Moriarty et al., 1998). What destines some mRNAs for nucleus-associated NMD and others for cytoplasmic NMD is currently unknown.

NMD in mammalian cells occurs both 5′-to-3′ and 3′-to-5′; it thus involves decapping and 5′-to-3′ exonucleolytic activities as well as deadenylating and 3′-to-5′ exosomal activities (Lejeune et al., 2003; Chen and Shyu, 2003). It remains to be determined whether NMD occurs in association with translating ribosomes or so-called cytoplasmic foci, which appear to be ribosome-free sites of general mRNA decay (Cougot et al., 2004; Ingelfinger et al., 2002). Notably, the efficiency of NMD in mammalian cells is generally not influenced by NC position, indicating that a higher number of downstream EJCs does not lead to more efficient NMD. However, NMD can be augmented by additional mechanisms that are not well understood. For example, replacing exons 2-4 and flanking intron sequences of the triosephosphate isomerase (*TPI*) gene with the 383-bp *VDJ* exon and flanking intron sequences of the T-cell receptor β (TCR-β) gene, which generates mRNA that is more efficiently targeted for NMD than *TPI* mRNA, increases the efficiency

with which *TPI* mRNA undergoes NMD >15-fold (Gudikote and Wilkinson, 2002). The efficiency of NMD is increased only when the TCR-β sequence is located upstream of an NC.

An understanding of how various factors function in NMD is far from complete. Upf1 is an ATP-dependent group 1 RNA helicase and phosphoprotein (Bhattacharya et al., 2000; Pal et al., 2001; Sun et al., 1998) that, as described above, presumably triggers NMD by interacting with Upf2 at an EJC that resides sufficiently far downstream of an NC. Also, as noted above, Upf2 and either Upf3 or Upf3X, which appear to have distinct but overlapping functions (Lykke-Andersen et al., 2000; Serin et al., 2001; Gehring et al., 2003), are components of the EJC. In fact, Upf3 and Upf3X consist of multiple isoforms that result from alternative pre-mRNA splicing. Whether or not Upf2, Upf3 and Upf3X are involved in Upf1 dephosphorylation, as are their orthologues in *C. elegans* (Page et al., 1999), remains to be determined. However, as in *C. elegans* (Grimson et al., 2004; Page et al., 1999), Upf1 phosphorylation is mediated by the PIK-related kinase SMG1 (Brumbaugh et al., 2004; Denning et al., 2001; Yamashita et al., 2001). Also as in *C. elegans* (Anders et al., 2003; Page et al., 1999) and, possibly, *D. melanogaster* (Gatfield et al., 2003), Upf1 dephosphorylation is mediated by SMG5 and, presumably, SMG6 and SMG7 (Chiu et al., 2003; Gatfield et al., 2003; Ohnishi et al., 2003).

Interestingly, factors that function in NMD have also been shown to function in other pathways. For example, SMG1 is an ATM-related kinase that is also involved in the recognition and/or repair of damaged DNA (Brumbaugh et al., 2004). SMG1 phosphorylates the tumor suppressor checkpoint protein p53 in response to UV and γ irradiation, and cells in which SMG1 has been downregulated accumulate spontaneous DNA damage and are sensitized to ionizing radiation (Brumbaugh et al., 2004). Providing another example, Upf1 is the δ helicase that partially co-purifies with DNA polymerase δ (Carastro et al., 2002). Upf1 (unlike Upf2, the only other NMD factor tested) also appears to function in nonsense-mediated altered splicing (NAS), a poorly understood pathway by which NCs influence the efficiency or accuracy of splicing (Mendell et al., 2002; Wang et al., 2002). In fact, Upf1 can be mutated so that it functions in NAS but not NMD (Mendell et al., 2002), indicating that the two pathways are genetically separable. Furthermore, Upf1 has recently been found to function in a new pathway called Staufen 1 (Stau1)-mediated mRNA decay (SMD) (Kim et al., 2005). In this pathway, the RNA-binding protein Stau1 interacts directly with Upf1 to elicit mRNA decay when bound sufficiently far downstream of an NC, including the normal termination codon. The results of microarray analyses indicate that there are a number of natural targets for SMD (Kim et al., 2005). Finally, Upf1 interacts with PABPC and forms distinct complexes of approximately 1.3 MDa and 400-600 kDa that appear to differ in their content (Schell et al., 2003). The functional significance of all these findings remains unknown. Multiple roles for NMD factors are also evident in the case of SMG5, SMG6 and SMG7, which are identical to the Ever Shorter Telomere (EST) proteins EST1B, EST1A and EST1C, respectively (Reichenbach et al., 2003; Snow et al., 2003). Each associates with active telomerase and is involved in telomere integrity (Reichenbach et al., 2003; Snow et al., 2003).

As is evident from this short overview, many mechanistic details of NMD still require resolution. In the future, it will also be important for us to understand the extent to which NMD regulates the level of proper mRNA production as opposed to degrading mRNAs that produce aberrant and, therefore, potentially harmful proteins. How NMD is mechanistically linked to other cellular processes, some of which can also be viewed as a type of quality control, requires further study.

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