Nonsense Mediated Decay (NMD)

Nonsense-mediated decay (NMD) is a mechanism that detects and degrades mRNA transcripts containing premature termination codons (PTCs). PTCs can occur due to germline or somatic mutations in DNA, transcription errors, or errors in mRNA processing. If these faulty mRNAs are not degraded, they can produce truncated proteins that may be harmful. NMD helps protect cells from these harmful proteins by targeting and degrading the defective mRNAs. PTCs are found in about 30% of inherited diseases, making NMD crucial for the organism's survival and fitness. A surveillance complex of proteins (eRF1, eRF3, Upf1, Upf2, and Upf3) assembles in response to premature translation termination and scans the mRNA for PTCs. If a PTC is found, the mRNA is marked for degradation. In organisms like yeast (*Saccharomyces cerevisiae*) and worms (*Caenorhabditis elegans*), seven smg genes (smg1-7) and three UPF genes (Upf1-3) are essential for NMD. These genes are also conserved in fruit flies (*Drosophila melanogaster*) and mammals, indicating their critical role in NMD across eukaryotes. The main components conserved in NMD are the Upf1/SMG-2, Upf2/SMG-3, and Upf3/SMG-4 complexes. Upf1/SMG-2 is a phosphoprotein and its phosphorylation is believed to play a role in NMD, though the exact interactions and roles of these proteins are still being studied.

Non-Stop Decay (NSD)

Nonstop mediated decay (NSD) targets mRNA transcripts that lack a stop codon. These faulty mRNAs can be produced by mechanisms like premature 3′ adenylation or hidden polyadenylation signals within the gene. Without a stop codon, ribosomes translate into the mRNA's 3′ poly-A tail and get stuck, unable to release the mRNA. This sequesters the ribosomes, making them unavailable for translating other mRNAs. NSD fixes this by freeing the ribosomes and marking the nonstop mRNA for degradation by nucleases. NSD operates through two main pathways, Ski7 and Non-Ski7. When the Ski7 protein is present, it binds to the empty A site of the ribosome and called **ski-7 pathway**. This binding helps eject the stuck mRNA, freeing the ribosome to translate other mRNAs. The Ski7 protein then associates with the nonstop mRNA, targeting it for recognition by the cytosolic exosome. The Ski7-exosome complex quickly removes the mRNA's poly-A tail, allowing the exosome to degrade the mRNA from the 3′ to 5′ end. In yeast, another **NSD pathway operates without Ski7**. Here, the ribosome's action causes the loss of poly-A binding proteins (PABP) from the mRNA's poly-A tail. This leads to the removal of the protective 5′ m7G cap. Without this cap, the mRNA is rapidly degraded by a 5′ to 3′ exonuclease, such as XrnI. NSD targets mRNAs that lack a proper stop codon. These defective mRNAs can arise from mutations, incomplete transcription, or errors in mRNA processing, leading to transcripts that are translated into overly long polypeptides without termination. When a ribosome translates through the polyadenylated tail of such an mRNA, indicating the absence of a stop codon, it stalls. The stalled ribosome is recognized by proteins like Dom34 (Pelota in mammals) and Hbs1, which promote ribosome recycling and the release of the incomplete polypeptide. The exosome, a multi-protein complex with exonuclease activity, then degrades the defective mRNA from the 3′ end, often facilitated by the protein Ski7.

No-Go Decay (NGD)

No-Go Decay (NGD) is a surveillance mechanism that degrades mRNAs with stalled ribosomes, ensuring cellular health. Stalling can happen due to stable RNA structures, enzymatic cuts, chemical damage, or rare codons. These errors can result from stable secondary structures, rare codons, or damaged RNA impeding the ribosome's progression. NGD relies on translation and involves an endoribonuclease that cleaves the mRNA just before the stall site. Sometimes, mRNAs without a stop codon are initially handled by the Nonstop Decay (NSD) pathway, but if the ribosomes stall at the new 3′ end, NGD steps in. The Dom34/Hbs1 complex plays a crucial role in rescuing these stalled ribosomes by dissociating them into subunits, which are then managed by the Ribosome Quality Control (RQC) pathway, leading to the rapid degradation of the nascent peptide. However, the exact details of where NGD cleavage happens and how the resulting RNA fragments are fully degraded remain unclear. After the ribosome dissociates, the mRNA fragments are quickly degraded by 5′–3′ and 3′–5′ exoribonucleases. Research shows that in cells lacking Dom34, stalled ribosomes at the 3′ ends of truncated mRNAs prevent exosome degradation, helping map where endonucleolytic cleavages occur. Interestingly, mutations in dom34 and xrn1 (which blocks the main 5′–3′ degradation pathway) are not lethal, indicating that NGD cleavages can still happen without Dom34. Creating truncated mRNAs in vivo has helped study NGD-targeted mRNAs.

These RNA surveillance mechanisms ensure that mRNAs causing translation errors are quickly removed, preventing ribosomes from becoming sequestered on defective mRNAs. This process maintains the efficiency and fidelity of translation, ensuring that only properly

terminated and functional mRNAs are translated into proteins. NSD and NGD play vital roles in cellular health by preventing the production of faulty proteins and supporting overall protein homeostasis. In eukaryotic cells, RNA surveillance mechanisms operate in both the nucleus and cytoplasm, assessing mRNA transcripts for fidelity and ensuring that only correctly processed and error-free mRNAs are translated, thus upholding the integrity of gene expression and protein synthesis.

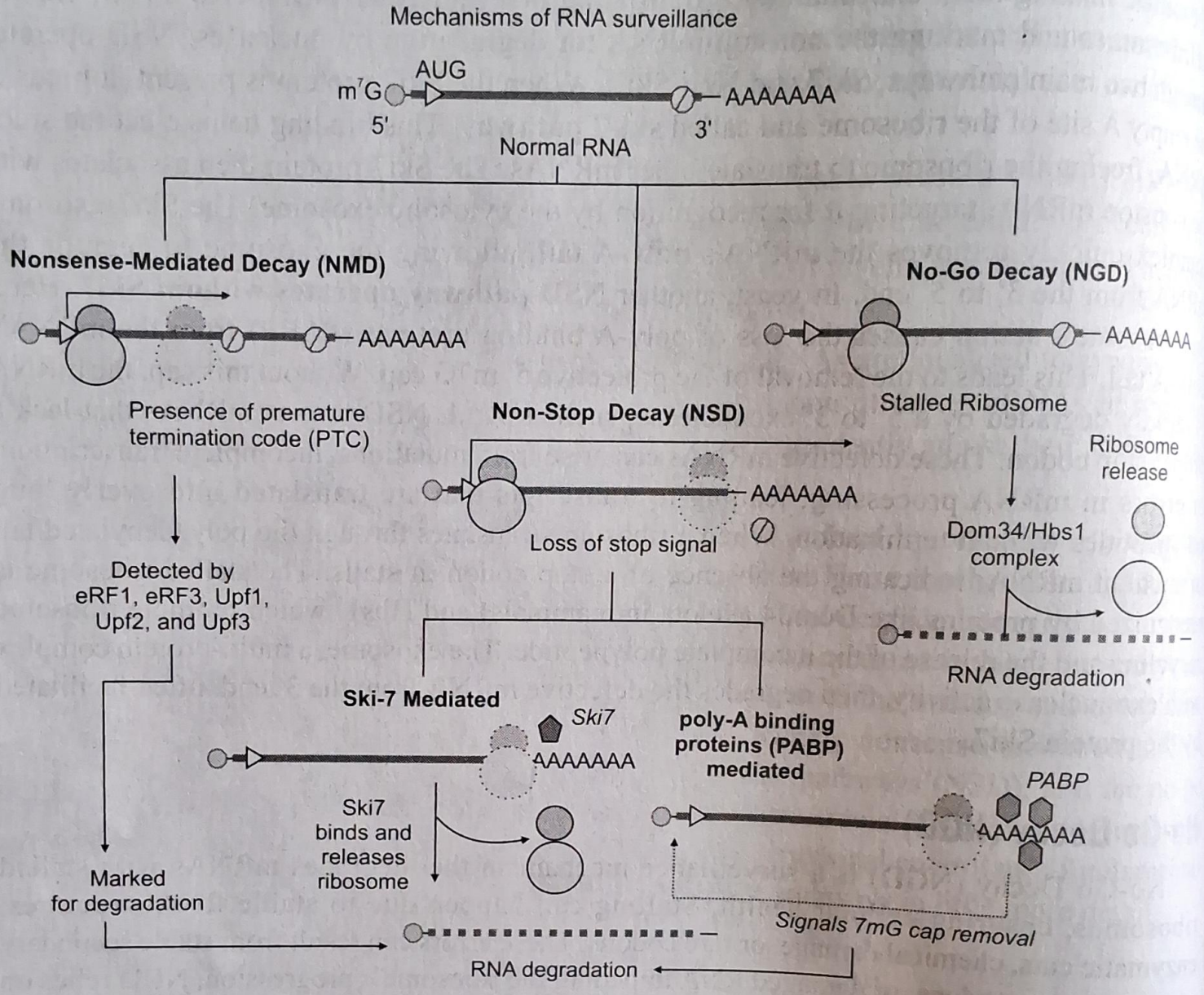

Fig. 7.8. *RNA surveillance mechanism.*