7.4 mRNA STABILITY (5)

The stability of mRNA molecules is an important factor that can regulate the gene expression. The steady-state level of any given mRNA is determined by the balance between its synthesis and degradation rates. This balance allows cells to adjust gene expression in response to various environmental cues, such as changes in nutrient availability, stress conditions, or developmental signals. mRNA stability can be modulated through several pathways, including deadenylation-dependent decapping, which involves shortening the poly(A) tail, removing the 5′ cap, and subsequent degradation by exonucleases. Another pathway degrades mRNAs from the 3′ to 5′ end after deadenylation, primarily involving the exosome complex. Specialised decay pathways include deadenylation-independent decapping, which targets aberrant mRNAs like those with premature stop codons, and endonucleolytic cleavage, which is sequence-specific and regulated by various factors. These pathways ensure the removal of faulty mRNAs and enable rapid adjustments in gene expression, which are essential for maintaining cellular function and growth. Effective mRNA turnover is thus integral to cellular homeostasis, allowing for the dynamic regulation of protein synthesis in response to changing physiological conditions. There are four possible pathways though which turnover of mRNA can be regulated by directing or preventing it from the degradation.

Deadenylation-Dependent Decapping: This major pathway starts with shortening the poly(A) tail (deadenylation), followed by removing the 5′ cap (decapping). The decapped mRNA is then degraded from the 5′ end by the exonuclease Xrn1p.

3′ to 5′ Exonucleolytic Degradation: After deadenylation, mRNAs are degraded from the 3′ end by the exosome complex. This pathway is crucial for complete mRNA degradation and is important across different eukaryotic organisms.

Deadenylation-Independent Decapping and mRNA Surveillance: This pathway targets faulty mRNAs, such as those with premature stop codons or unspliced introns. It involves direct decapping without prior deadenylation, followed by 5′ to 3′ degradation to ensure only functional mRNAs are translated.

Endonucleolytic Cleavage-Initiated Decay: Specific endonucleases cleave mRNAs internally at certain sequences, and the resulting fragments are degraded from both ends. This pathway allows precise control over mRNA stability based on the presence of specific sequences.

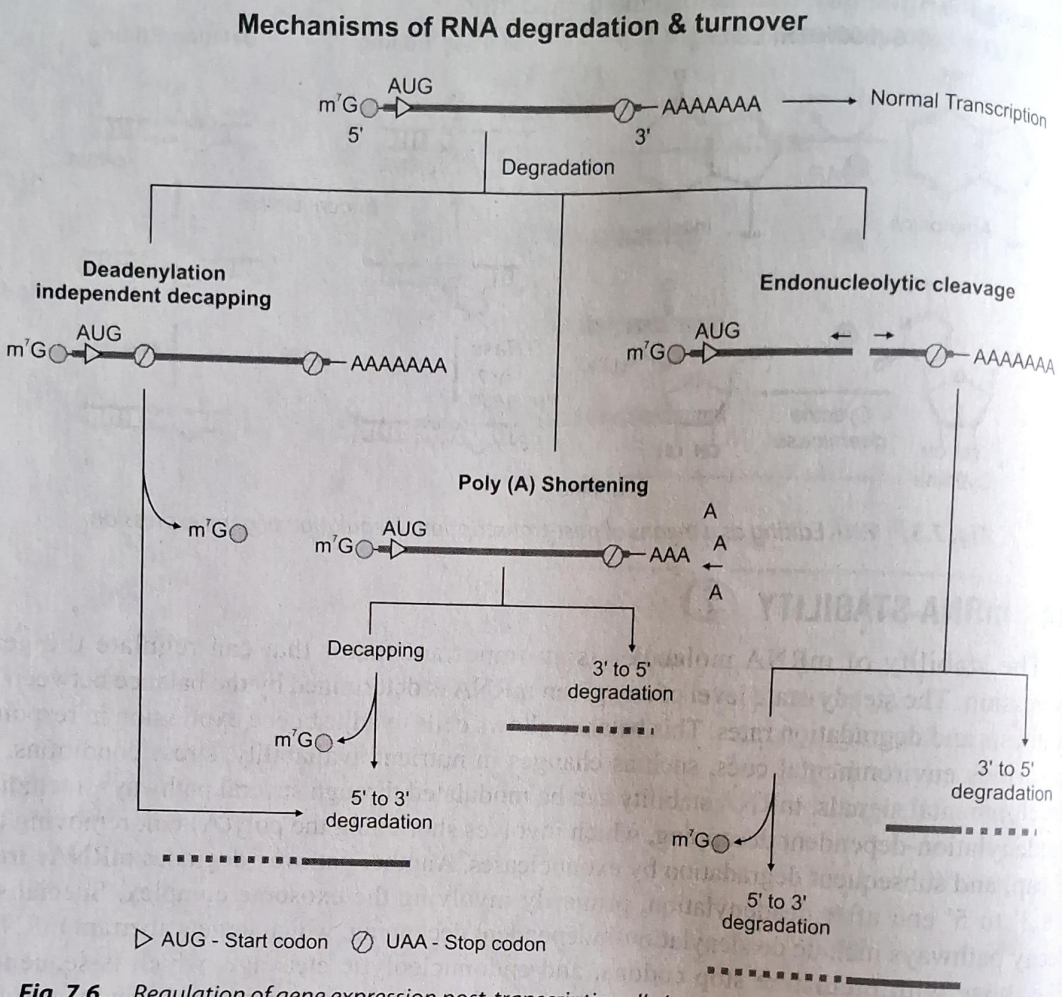

Fig. 7.6. *Regulation of gene expression post-transcriptionally by regulating the RNA turnover and degradation, four, well-understood pathways. (After, Dunckley and Parker, 2001).*

RNA Stability Regulation by Regulatory RNAs (6)

The initiation of translation is a key regulatory point. The availability and activity of translation initiation factors, as well as the secondary structure of the mRNA (such as the 5′ UTR), can influence ribosome binding and the start of translation. microRNAs (miRNAs) and Small Interfering RNAs (siRNAs): These small non-coding RNAs can bind to complementary sequences on target mRNAs, usually in the 3′ UTR, leading to translational repression or mRNA degradation. miRNAs are part of the RNA-induced silencing complex (RISC) and play critical roles in fine-tuning gene expression. We have already discussed the small non-coding RNA mediated regulation in the previous chapter and the same can be referred there.

Yet another popular post-transcriptional regulation of gene expression is through the localisation of RNA within the cell. This spatial regulation ensures that proteins are synthesized at specific locations where they are needed, rather than being distributed uniformly throughout the cell. This mechanism is particularly crucial in highly polarised and asymmetric cells such

as neurons, fibroblasts, and oocytes. The localisation of messenger RNA (mRNA) involves multiple steps, starting with the "marking" of the mRNA by specific sequences known as cis-acting elements or "localisation elements." These elements act like zip codes, directing the mRNA to particular locations within the cell. They are usually found in the 3′ untranslated region (UTR) of the mRNA but can also be located in the 5′ UTR or the coding sequence. These localisation elements are recognised by RNA-binding proteins, which play a crucial role in transporting the mRNA to its destination. Once marked, the mRNA binds to RNA-binding proteins to form a ribonucleoprotein (RNP) complex. This complex is then transported along the cytoskeleton by molecular motors such as kinesins or dyneins, which move the RNP to its target location. During transport, the mRNA is often kept in a translationally repressed state to prevent premature protein synthesis. Upon reaching its destination, additional mechanisms anchor the mRNA in place and regulate its translation in response to local signals.

Regulating gene expression by mRNA localisation offers several advantages. First, it allows for the spatial restriction of protein synthesis, meaning that proteins are produced precisely where they are needed, which is especially important in large, polarised cells. Second, it provides rapid and localised responses to environmental stimuli, as the mRNA can be quickly translated on-site without needing to go back to the nucleus for new transcription. Third, this method is economical since one mRNA molecule can be translated multiple times in the same location, reducing the need for extensive protein transport across the cell. Lastly, it helps protect the cell from potentially toxic proteins by ensuring they are synthesized only in specific locations. Several well-studied examples illustrate the importance of mRNA localisation:

- **ASH1 mRNA in Yeast:** In the budding yeast, the ASH1 mRNA localises to the bud tip of a dividing cell, ensuring that only the daughter cell receives the ASH1 protein. This localisation prevents the mother cell from switching mating types, demonstrating how mRNA localisation can control cell fate.

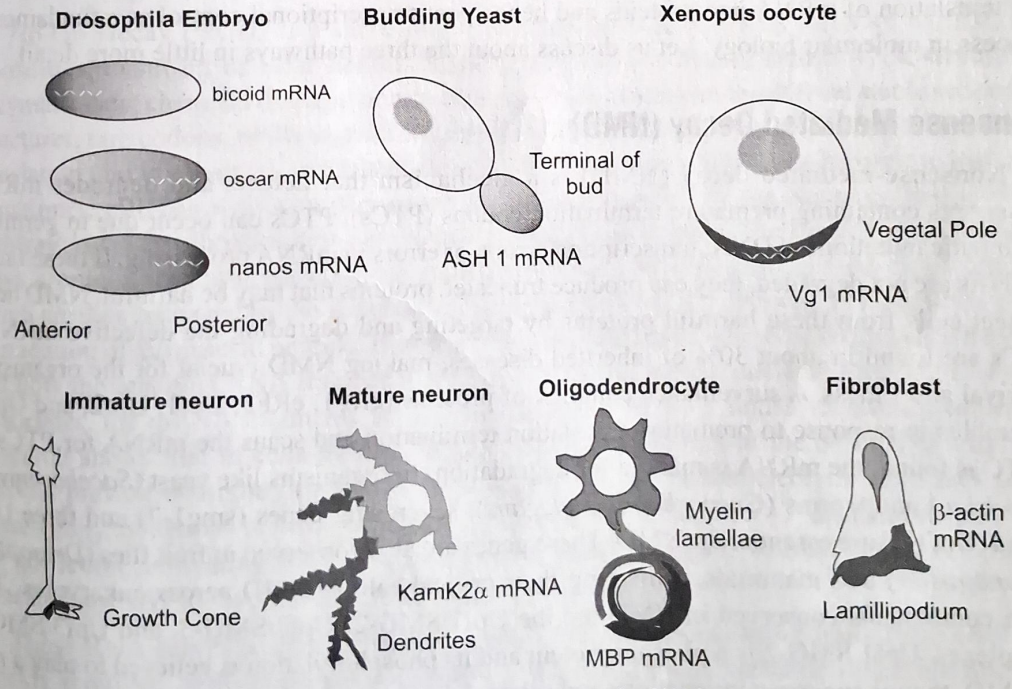

Fig. 7.7. *Regulation of Gene expression by RNA localisation.*

- **Bicoid, Oskar, and Nanos mRNAs in *Drosophila*:** In fruit fly embryos, these mRNA localize to specific poles of the oocyte, establishing gradients that are critical for prope embryonic development. These gradients ensure that different parts of the embryo develo into distinct tissues and organs.
- **β-actin mRNA in Fibroblasts:** In migrating fibroblasts, β-actin mRNA localises to the leading edge of the cell, where its translation is necessary for cell movement. This localised translation allows the cell to quickly respond to environmental cues and move in the desired direction.
- **MBP mRNA in Oligodendrocytes**: The myelin basic protein (MBP) mRNA in oligodendrocytes is transported to the distal processes where myelination occurs. This localised synthesis is crucial for the proper formation of myelin sheaths around neurons, which is essential for efficient nerve signal transmission.
- **Synaptic mRNAs in Neurons:** In neurons, many mRNAs are localised to synapses, the contact points between neurons. The localised translation of these mRNAs in response to synaptic activity allows individual synapses to independently adjust their strength and function, which is vital for learning and memory.

mRNA surveillance mechanisms are a set of pathways utilised by organisms to maintain fidelity and quality of messenger RNA (mRNA) molecules. These mechanisms function at various steps of the mRNA biogenesis pathway to detect and degrade transcripts that have not properly been processed. This phenomenon has been documented in bacteria and yeast. In eukaryotes, these mechanisms are known to function in both the nucleus and cytoplasm. There are three major pathways of RNA surveillance, namely nonsense-mediated mRNA decay pathway (NMD); the nonstop mediated mRNA decay pathways (NSD); and the no-go mediated mRNA decay pathway (NGD). These pathways are crucial for preventing errors in the translation of mRNA into proteins and hence post-transcriptional control as a fundamental process in molecular biology. Let us discuss about the three pathways in little