Research and Reviews: Drug Delivery

Mechanism of Post-Transcriptional Regulation and its Sequences

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Commentary

Received: 01-Jun-2022, Manuscript No. DD-22-56259;
Editor assigned: 02-Jun-2022, PreQC No. DD-22-56259(PQ);
Reviewed: 16-Jun-2022, QC No. DD-22-56259;
Revised: 23-Jun-2022, Manuscript No. DD-22-56259(R);
Published: 30-Jun-2022, DOI : 10.4172/resrevdrugdeliv.6.S1.003
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DESCRIPTION

Post-transcriptional regulation is the control of gene expression at the RNA level. It occurs once the RNA polymerase has been attached to the gene's promoter and is synthesizing the nucleotide sequence. Therefore, as the name indicates, it occurs between the transcription phase and the translation phase of gene expression. These controls are critical for the regulation of many genes across human tissues. It also plays a big role in cell physiology, being implicated in pathologies such as cancer and neurodegenerative diseases

After being produced, the stability and distribution of the different transcripts is regulated (post-transcriptional regulation) by means of RNA Binding protein (RBP) that control the various steps and rates controlling events such as alternative splicing, nuclear degradation (exosome), processing, nuclear export (three alternative pathways), sequestration in P-bodies for storage or degradation and ultimately translation. These proteins achieve these events thanks to an RNA recognition motif (RRM) that binds a specific sequence or secondary structure of the transcripts, typically at the 5' and 3' UTR of the transcript. In short, the dsRNA sequences, which will be broken down into siRNA inside of the organism, will match up with the RNA to inhibit the gene expression in the cell.

Modulating the capping, splicing, addition of a Poly(A) tail, the sequence-specific nuclear export rates and in several contexts sequestration of the RNA transcript occurs in eukaryotes but not in prokaryotes. This modulation is a result

of a protein or transcript which in turn is regulated and may have an affinity for certain sequences.

Capping changes the five prime end of the mRNA to a three prime end by 5'-5' linkage, which protects the mRNA from 5' exonuclease, which degrades foreign RNA. The cap also helps in ribosomal binding. In addition, it represents a unique mark for a correct gene. Therefore, it helps to select the mRNA that is going to be translated.

RNA splicing removes the introns, noncoding regions that are transcribed into RNA, in order to make the mRNA able to create proteins. Cells do this by spliceosomes binding on either side of an intron, looping the intron into a circle and then cleaving it off. The two ends of the exons are then joined.

Addition of poly(A) tail otherwise known as polyadenylation. That is, a stretch of RNA that is made solely of adenine bases is added to the 3' end, and acts as a buffer to the 3' exonuclease in order to increase the half-life of mRNA. In addition, a long poly(A) tail can increase translation. Poly(A)-Binding Protein (PABP) binds to a long poly(A) tail and mediates the interaction between EIF4E and EIF4G which encourages the initiation of translation.

RNA editing is a process which results in sequence variation in the RNA molecule, and is catalyzed by enzymes. These enzymes include the adenosine deaminase acting on RNA (ADAR) enzymes, which convert specific adenosine residues to inosine in an mRNA molecule by hydrolytic deamination. Three ADAR enzymes have been cloned, ADAR1, ADAR2 and ADAR3, although only the first two subtypes have been shown to have RNA editing activity. Many mRNAs are vulnerable to the effects of RNA editing, including the glutamate receptor subunits GluR2, GluR3, GluR4, GluR5 and GluR6 (which are components of the AMPA and kainate receptors), the serotonin2C receptor, the GABA-alpha3 receptor subunit, the tryptophan hydroxylase enzyme TPH2, the hepatitis delta virus and more than 16% of microRNAs. In addition to ADAR enzymes, CDAR enzymes exist and these convert cytosines in specific RNA molecules, to uracil. These enzymes are termed 'APOBEC' and have genetic loci at 22q13, a region close to the chromosomal deletion which occurs in velocardiofacial syndrome (22q11) and which is linked to psychosis. RNA editing is extensively studied in relation to infectious diseases, because the editing process alters viral function.

mRNA Stability can be manipulated in order to control its half-life, and the poly(A) tail has some effect on this stability, as previously stated. Stable mRNA can have a half-life of up to a day or more which allows for the production of more protein product; unstable mRNA is used in regulation that must occur quickly. mRNA stability is an important factor that is based on mRNA degradation rates.

Nuclear export only one-twentieth of the total amount of RNA leaves the nucleus to proceed with translation. The rest of the RNA molecules, usually excised introns and damaged RNAs, are kept in the nucleus where they are eventually degraded. mRNA only leaves the nucleus when it is ready to keep going, which means that nuclear export is delayed until the processing is complete. As an interesting fact, there are some mechanisms that attack this nuclear export process to regulate gene expression. An example of regulated nuclear transport of mRNA can be observed in HIV.