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UNTRANSLATED REGIONS – INSIGHT INTO FUNCTIONAL PROSPECTIVE

SHWETA PANDEY[a1] AND BHAWANA PANDEY[b]

[a]A.P.G.M.N.S. Govt. P.G. College, Kawardha, Kabirdham, Chhattisgarh, India
[b]Bhilai Mahila Mahavidyalaya, Durg, Chhattisgarh, India

ABSTRACT

The untranslated regions, earlier considered as "junk DNA" has come into focus largely due to insufficiency of genetic information to understand basic biological processes. They play indispensible regulatory role in the genome. The 5' & 3'UTRs of m RNA contain motifs capable of regulating many aspects of m RNA functions & can thereby influence gene function. UTRs can affect m RNA nuclear export, cytoplasmic localization, translational efficiency& stability. The regulatory motifs contained within UTRs are highly conserved among mammals suggesting their regulatory functions. The review tries to touch most aspects of untranslated region to have an insight into the UTRs – their regulatory function on genome, interacting proteins & finally perturbance of the cellular metabolism due to their regulatory machine breakdown.

KEYWORDS: UTR, Intron, Translational regulation, PABP.

ABBREVIATIONS:

UTR- untranslated region,

PABP-Poly A binding protein.

ORF- Open reading frame.

IRES- Internal ribosome entry site.

IRP-Iron response protein.

PRAN-Poly A specific ribonuclease

ACE- Adenylate control element.

CPE-Cytoplasmic polyadenylaiton element

In the last decade, human genome sequencing has opened a new scenario that provides insight into the genome. There are approximately 20,000 protein coding genes, occupying approximately 1.5-2.0% of the genome(Venter JC et al.2001, Lender et al.2001).The knowledge of the entire genetic content of an organism, though necessary, is not sufficient to understand basic biological processes such as embryogenesis, development, differentiation and ageing or several pathologies such as cancer. Therefore, it is crucial to decipher the control mechanisms. Genetic information for the regulation of gene expression is stored mainly in the non-coding regions of the genome that are larger than the coding parts.The regulation can be exerted both at transcriptional (efficiency of transcription) &/or post transcriptional stage (mRNA stability, efficiency of translation, subcellular localization) (Velden AW,et al 1999; Jensen R P et al.2001). Promoters and enhancers are among the non-coding regions that play very important role in regulation of gene expression at the level of transcription control. Genetic information for posttranscriptional control is located mainly in untranslated regions upstream and downstream of the mRNA, called 5' and 3' untranslated regions (5'UTR and 3'UTR), respectively. In this case, unlike DNA-mediated information (e.g. promoters, enhancers), which is essentially contained in the primary structure, RNA-mediated information also involves elements of the secondary structure, generally recognised by proteins binding to RNA (RNA binding proteins). Hence protein interactions with the UTR can greatly affect the regulatory role. (Sweeny et al, 1996)

STRUCTURAL CHARACTERISTICS OF UTR SEQUENCES

Assessment of various genomic sequences led to conclusion that the untranslated region, both the 5' & 3' UTRs, represent some characteristic properties which are universal in nature. These can be characterized as follows.

UTRs Length

The average length of 5' UTR is almost constant over diverse taxonomic phylum & is approximately 100-200 nucleotides while lengths of the 3' UTRs are quite flexible ranging from 200 nucleotides in plants to more than 1000 in vertebrates. Mammalian in vitro system reveals that

[1]Corresponding author

even a single nucleotide is sufficient 5'UTR for translation initiation. In humans the average length of 5' UTR is 210 & that for 3' UTR is 1028 & minimum length is 18 & 21 respectively. (Flavio Mignone 2002).The greater length of vertebrate 3'UTR mRNAs, might be attributed to the new functions acquired during evolution.

Intron Frequency

The frequency of introns in the gene region corresponding to 5'UTR is higher than 3'UTR (in the range 1-11% depending on the taxon). In humans, about 30% of all genes have introns in 5' UTR. The introns present in UTRs vary from those present in the coding region. Overall intron occupancy is low but intron density is higher in UTRs. Introns in 5' UTRs are 2 X as large as the introns in the coding regions. In 3' UTRs they are less abundant than in 5'UTRs. Their presence correlates with level of expression across cells & tissue types. Earlier reports suggested them to be product of random deletion & insertion to avoid upstream ORFs, now it is stated that many evolve under complex selective forces as genes with regulatory roles are enriched in 5' UTR introns. (Xin Hong et al., 2006)

Base Composition

The base composition of 5' and 3' UTR sequences also differs; the G+C content of 5' UTR sequences is greater than that of 3' UTR sequences. In mRNAs from warm-blooded vertebrates, G+C content is about 60% for 5' UTRs and 45% for 3'UTRs (Pesole et al., 1997). A significant inverse correlation exists between the G+C content of 5' and 3' UTRs and their lengths. (Duret L et al., 1995)

Repeats Distribution

Eukaryotic mRNAs contain diverse kinds of repeats in the untranslated regions which comprise SINEs, LINEs, Alu elements, various mini & microsatellites. These repetitive sequences form approximately 12% of 5' UTRs & 36% of 3' UTRs. The occurrence of repeats is lower in plants and fungi and significant differences also occur within mammals. The greater number of repeats in 3'UTRs is due to the fact that these sequences have average length considerably greater than 5'UTRs.

FUNCTIONS OF UTR

UTRs perform eminently important regulatory functions in regulation of genomes. Their functions can be categorized in following sections.

Translational Regulation

Translational efficiency is contributed by many features of an mRNA, most control elements are located within the *untranslated regions*. The 5' m7GpppG cap and the 3' poly(A) tail are main determinants of translational efficiency. Other factors affecting translation rates include 5' UTR, including length and start-site consensus sequences as well as the presence of secondary structure, upstream AUGs, upstream open reading frames (uORFs) and internal ribosome entry sites (IRES). Besides, 5' UTRs also consist of sequences that function as binding sites for regulatory proteins. Similarly, 3' UTRs contain numerous binding sites for regulatory factors usually proteins but in some cases trans-acting RNAs. Most of these elements affect translation at the level of initiation. Translation initiation of most eukaryotic cellular mRNAs can be divided into following steps (Maitra et al. 1982):

- Under normal conditions, the mRNA is transported out in the cytoplasm from nucleus after processing.
- Following transport, the formation of preinitiation complex occurs. It incorporates 40s subunit, a ternary complex of eIF2, tRNA-Met & GTP; three initiation factors eIF1, e IF1A, eIF3.
- The initiator tRNA recognizes internal AUG & is different from normal tRNA but not methylated as in case of prokaryotes.
- This preinitiation complex associates with 5' end, which is bound to cap binding protein. The cap binding complex involves eIF4A, eIF4E, eIF4G. eIF4E makes contact with cap, eIF4G acts as a bridge between eIF4E, eIF3 of preinitiation complex.
- The preinitiation complex scans along mRNA in an energy dependent manner till it reaches the Kozak consensus sequence (ACCAUGG) with the help of eIF4A & eIF4B having helicase activity.

A few RNAs need to be translated at specific location to spatially restrict gene expression within the cytoplasm, achieving high temporal resolution, providing economy (i.e. localized mRNAs can be translated multiple times to generate many copies of a protein, which is much more efficient than translating mRNAs elsewhere in the cell, then transporting each protein individually to a distinct site) and protection of the cell from proteins that might be toxic or deleterious in other cellular compartments e.g. MBP mRNA in oligodendrocytes. (Kelsey & Martin,2009).

UTRs exert their regulatory functions on translation at two levels involving 5' UTR and 3' UTR:

Regulation by 5' UTR Binding Factors

(a) **Upstream ORFs:** 15-50% of 5'UTRs contain upstream AUGs. 40S ribosomes sometime bypass upstream AUGs (uAUG). These normally down-regulate translation at the main ORF by providing alternative start sites. uAUGs must be in a different frame to the main ORF. By this, enormous number of proteins can be obtained from same mRNA. Presence of upstream AUG correlate with long 5' UTR & weak start codon (Lukkonen B G et al, 1995).However, upstream AUGs may have a role in keeping the basal translational level of a gene low.

(b) **ORF length:** Generally, mRNA translational efficiency is affected negatively by the presence of stable secondary structures ($\Delta G < -30$ kcal/mole) mainly when these are localised close to the cap site,of 5'UTR open reading frames (called upstream ORFs or uORFs) and by the presence of an unsuitable context for AUG initiation. Inefficient translation of a mRNA, owing for instance to the presence of uORFs, can decrease its stability e.g.,in yeasts, GCN4 & YAP1contain upstream ORFs which maintain their mRNA at low level. (Vilela C et al.,1999).

(c) **IRES elements:** Iron regulatory elements which are hairpin structural motifs are controlled by IRP (iron response proteins) to monitor intracellular iron concentration. It can be present on two sites – 5'cap proximal or 5'cap distal in case of 5'UTR or in 3' UTR. If present above the cap, affects the 40S recruitment but if present downstream to cap, then it hinders the scanning process. IRP-IRES also provide a platform for other proteins to interact & then control the process. (Connee et al., 2000).

(d) **PABP:** PABP binds to a cap-distal poly(A) tract in its own 5' UTR and represses translation. PABP inhibits scanning of the 40S ribosomal subunit.

(e) **5' terminal oligopyrimidine tract:** Most vertebrate mRNAs encoding ribosomal proteins and translation elongation factors contain a 5' terminal oligopyrimidine tract (TOP) consisting of 5-15 pyrimidines immediately adjacent to the m7G cap. This tract is required for coordinated translational repression in conjugation with translation cis regulatory element (TLRE) and sequences immediately downstream to 5' TOP during growth arrest, differentiation, development and certain drug treatments. (Meyuhas O et al,2000).

Regulation by 3' UTR binding factors

Most regulation occur through 3' UTR

(a) **Via PABP:** Changes in the translation of mRNAs are frequently correlated with cytoplasmic changes in poly(A)-tail length; increases in length generally correlate with translational activation.The affect of the poly(A) tail is thought to be mediated by poly(A)-binding protein (PABP)- multifunctional protein with roles in mRNA processing, stability and translation. (Jacobson et al.,1996) PABP physically interacts with eukaryotic initiation factor eIF4G (4G), Paip-1 and eIF4B(4B). The PABP–eIF4G interaction is proposed to circularize the mRNA via PABP–eIF4G–eIF4E–cap interactions (Grosset et al.,2000). Paip-1 has similarities to eIF4G and interacts with eIF4A, but not eIF4E, suggesting that it might stimulate translation by a different end-to-end mechanism. The PABP–eIF4B interaction has been suggested to enhance PABP binding to poly(A), and to stimulate the activity of the eIF4A helicase. PABP is also known to associate with eRF3, so, may have function in recycling of terminating ribosome. All of these interactions are predicted to affect the recruitment of the small (40S) ribosomal subunit to the mRNA.(Tarun SZ,1997 & Wakiyama M,2000)

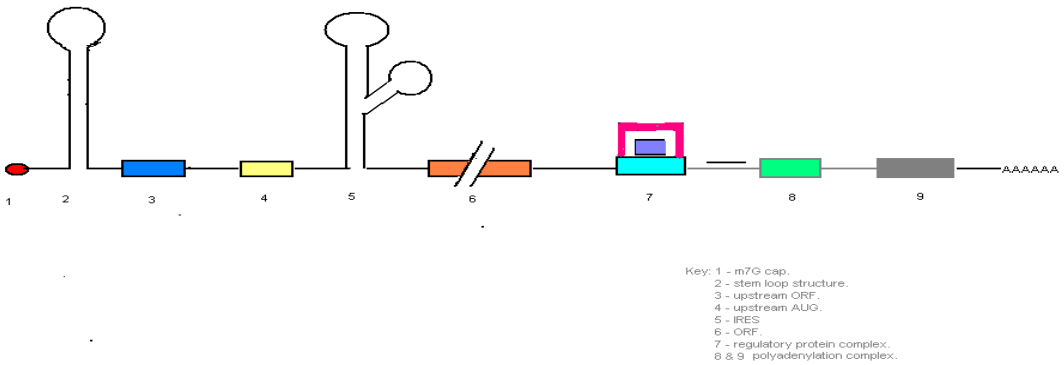
(b) **Repression via cytoplasmic polyadenylation element binding proteins:** Cytoplasmic poly(A)-tail length can be regulated by elements within the 3' UTR. The poly(A) tail appears to act through PABP. However, short poly (A) tails are often long enough to bind PABP, even then messages remain translationally silent sometimes suggesting that some mRNAs are specifically maintained in an inactive state, potentially via binding of repressor proteins. 3'-UTR-binding protein, cytoplasmic polyadenylation-element-binding protein (CPEB), provides information about relation between polyadenylation and translational repression. Cytoplasmic polyadenylation requires two 3'-UTR elements: a uridine-rich sequence known as a cytoplasmic polyadenylation element (CPE) or adenylate control element (ACE) and the hexanucleotide AAUAAA. Three of the most important proteins that control this process are CPE-binding protein (CPEB); poly(A)-specific ribonuclease (PARN), which deadenylates mRNAs; and Gld2, a poly(A) polymerase. Kim and Richter,2006). However, a short poly(A) tail in and of itself does not necessarily repress translation; for this to occur, another factor, Maskin, is involved. (Kim and Richter, 2007). Maskin not only binds to CPEB but also binds to the cap binding factor eIF4E. This configuration of factors precludes the interaction of eIF4G with eIF4E and thereby inhibits translation by indirectly interfering with the positioning of the 40S ribosomal subunit at the end of the mRNA. Before directing adenylation some CPEs are suggested to repress translation, e.g., CPEB mediates repressive effects in Xenopus laevis oocytes.(*Grey NK et al,2000).* In Xenopus laevis- maskin protein that interacts with CPEB & eIF4E is required for repression of certain CPE containing mRNA. Their interaction results in sequestration of eIF4E, so, repress translation. A member of Pumilio/ Fem 3 bp (PUF) family also plays a role in repression in Drosophila & Cenorhabditis elegans.

(c) **By microRNAs:** They can be regarded as regulators of endogenous genes. They exhibit double stranded structure & are transcribed by RNA polymerase II and hence capped & polyadenylated in nature. The binding sites for mi RNA are present in 3' UTR of mRNA, with a few exceptions. Mostly miRNA binding is not perfectly matched & comprises mismatches & bulges in animals, while in plant the same are almost perfectly complementary. This complementarity is the prime determinant of the regulatory mechanism. Perfect matching catalyse the cleavage of mRNA strand via Ago protein, whereas mismatches present in central position repress the translation. The translational repression of gene by miRNA is widespread & in addition to it perfect complementarity between miRNA & mRNA may engage it in m RNA cleavage.

There are three hypotheses for miRNA regulation:

- ✓ First mi RISC binds mRNA & repress initiation during cap recognisation stage by competing with eIF4E to bind the cap.
- ✓ Second it may induce deadenylation & therefore prevent the circularization of mRNA.
- ✓ Third mi RISC may hinder the association of 60S ribosome with preinitiation complex.

Some proteins & structural features of UTRs that can regulate translational process is shown in figure given below.



mRNA STABILITY

Post transcriptional regulation of gene expression is an important aspect affected by UTRs. Several mechanisms are proposed to explain the mRNA decay. Degradation can be preceded by shortening of poly A tail or removal of 5' cap. mRNA is basically affected by the following means:

By ARE Elements

Many labile RNAs are known to contain adenylate/uridylate rich elements, these including mRNAs of protooncogene, growth factors and their receptors cytokines etc. Size of AU rich elements that primarily functions to target mRNA for selective degradation ranges from 50-150 nucleotides & consists of AUUUA or UUAUUUA(U/A)(U/A) repeats or single sequence. They are bound by various factors: AUF1, hnRNPA1 & hnRNPC etc. Best characterized example of ARE binding proteins influencing mRNA stability is the effect of AUF1 & HuR.

Both act in contradictory manner. AUF1 is ubiquitous in nature, involved in decay of mRNA encoding- c-myc, c-fos, β adrenergic receptors, luteinizing hormone, GM-CSF, histones etc.AUF1 related proteins interact with PABP, eIF4G& other initiation proteins & 5'UTR initiation factors. HU proteins stabilize mRNA encoding cytokines, lymphokines & proto-oncogene by binding to AU rich elements in 3'UTR. This increases the stability of mRNA by displacing the inhibitory factors which deadenylates or cleave mRNA, e.g., ribonuclease E cleavage motif (AUUUA) is recognized by the protein, get bound & become inaccessible to the endonucleolytic cleavage or Hu protein may compete with destabilizing factors as AUF1. It may bind mRNA in the nucleus & protect it both in nucleus & during transport in cytoplasm. In cytoplasm it may act as positive signal for translation or dissociate from mRNA or shuttle back to nucleus leading to mRNA decay.

Binding of Proteins to Specific Sites

The proteins binding to 3'UTR can be enhanced by formation of special structural elements in mRNA or by sequence specific binding. mRNA of glucose transporter (GLUT1) is protected from endonucleolytic cleavage. 106 nucleotide GC rich regions present in mRNA of GLUT1 is responsible for degradation of mRNA as well as its stabilization in response to presence of TNF. Under normal circumstances endonucleolytic cleavage causes mRNA turnovers. There is no protein bound to the destabilizing region the GU rich element. Two proteins bind to the same region on exposure to TNF this cause stabilization of protein.

Length of 3' UTR

Length of 3' UTR is inversely proportional to protein expression levels i.e. the longer 3'UTR is associated with lower protein expression levels and vice versa. Expression of mRNAs with shorter 3'UTRs was also increased in T-lymphocytes on activation of the T-cell antigen receptor, an event that correlates with cellular proliferation. Shorter 3'UTRs do not contain the miRNA target sites that are located in transcripts for which expression is increased on cellular activation, indicating that in T-lymphocytes the long 3'UTR modulates translation efficiency through association with RNA-binding proteins and miRNAs.

SUBCELLULAR LOCALIZATION

Spatial control of gene expression too is affected by UTR. Localization results in asymmetric distribution of cellular protein. Most mRNA are localized as ribonucleoprotein complex in association with proteins involved in translation process. There are mainly three mechanisms responsible for spatial difference in various mRNA:

- active directed transport- this require mRNA interacting specific motor proteins & functional cytoskeleton;
- local stabilization of mRNA transcript;
- local entrapment of m RNA preceded by its diffusion.

The targeting of mRNAs to specific subcellular sites involves multiple steps.

- These cis-acting elements, called ''localization elements'' or ''zipcodes" encode the cellular "address" & are mostly found in the 3' untranslated region (UTR), however, in some cases they are present in the 5'UTR or in the coding sequence.

- Specific RNA-binding proteins that recognise localisation elements, can function both in transcript localization and translational regulation. (Kelsey C. Martin1, and Anne Ephrussi, 2009).

The following diagram shows the mode of transportation, in nucleus the UTR get bound to proteins may transport it to cytoplasm. In cytoplasm they get incorporated to RNA granules & localised with help of motor proteins.

FORMATION OF MODIFIED AMINO ACIDS

Selenocysteine formation require UGA codon in the coding region immediately followed by a short sequence forming stem loop structure & selenocysteine specific translation factor, SELB, in place of EF-TU. SECIS- Selenocysteine insertion sequence is present in 3' UTR of selenoprotein. Differences between prokaryotic & eukaryotic mechanisms are present at RNA level. In bacteria there is a stem loop structure adjacent to UGA selenocysteine codon, whereas, in eukaryotes a special region is identified within 3' UTR which is highly conserved & situated approximately 1 kb downstream to UGA selenocysteine codon. (R Walczak, E Westhof, P Carbon, *et al*.,2011).

Table 1: Effector molecules binding to UTR and their functions

m RNA	Effector molecule	Region of binding	Function
Bcl2 m RNA	SATB1	MBR	Increased translation
DMPK	RNA binding protein	Expanded CUG in 3' UTR	Missplicing, nuclear retention
TNFα	FXR1 & AGO 2	ARE	Activate translation
GU rich RNA	Proteins of CELF family	GU rich elements	Polyadenylation, mRNA decay, translation
Preproinsulin	hn RNA, PTB	3' UTR	Stabilisation
c myc, ILs	HuR/ELAV	ARE	Stabilization, translational activation
Picornavirideae genome	RNA binding proteins	5' UTR	Initiate translation
FMR1	Methylating proteins	CGG expansion in 5' UTR	Hypermethylation & gene silencing
BACE1	AP1,CREB, MEF	5' UTR	
α globin	Erythroid enrich endoribonuclease	3' UTR	Increase mRNA turnover
α globin	PABP & α complex	3' UTR	Prevent ErEN mediated decay
ARE containing m RNA	HuD protein	3' UTR	Stabilization
Transferrin receptor	IRP1 & 2	5' or 3' UTR	Stabilization
Ceruloplasmin	GAIT	3' UTR	Translation inhibition
Histones	Hairpin binding proteins	3' UTR	Translation & stability
Parathyroid harmone	Various trans factors	3' UTR	Stabilization
Hypothalamic corticotrophin releasing harmone	Cytosolic proteins & minicistron	5' UTR	Translation
CTGF	TGFβ	Promoter	Induction
Haeme oxygenase	Translation factors	5' UTR with AP1& metal responsive element	Increase translation
Vasopressin receptor	IRP	IRES	Activates translation
HIV genome	NFκB, AP1	5' UTR	Increase transcription
mRNA & noncoding RNA	Cis acting RNA elements	Mostly 3' UTR	Localization

Table 2: UTR regulatory elements and associated diseases

Regulatory element involved	Diseases
5'UTR	
Mutations affecting length & secondary structure	Breast cancer.
Upstream ORF	Hereditary thrombocythemia Alzheimer's disease Bipolar affective disorder(BPAD) Arrhythmogenic right ventricular cardiomyopathy(AVRC) Melanoma
IRES	X linked Charcot – Marie-tooth(CMTX) Multiple myloma Fragile X syndrome(FXS)
Stem loop structure & RNA Binding Protein	Hereditary hyperferritinemia catract syndrome
3'UTR	
Termination codon	Aniridia Epidermolysis bullosa simplex
Polyadenylation signal	Haemoglobin H disease Immune dysfunction polyendocrinopathy enteropathy X linked(IPEX)
Secondary structure	Congenital heart disease Arrhythmogenic right ventricular cardimyopathy (AVRC)

CONCLUSION

The lingering perception about the coding regions of the genome to be only important regions of the genome has been challenged recently. The reason lies in the fact there are increasing reports for the role of untranslated regions (5' UTR and 3'UTR) in the genome to be essential in the regulation of the gene expression by affecting the mRNA stability and translational efficiency. They consist of regulatory motifs that show conservation and play important role in their activity. They provide binding sites for a large number of proteins thus resulting in the stabilization or destabilization of the transcripts. They also affect physiological response of the cells thus resulting in diseased state. Thus, it is evident that the untranslated regions are as important as the coding regions and acts as players in providing additional regulatory possibilities.

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