Review Article

Non-protein coding RNAs: making their own path losing translation

Chinmoy Mishra*, Lipismita Samal

Indian Veterinary Research Institute, Izatnagar- 243 122, India

Abstract

Ribonucleic acid (RNA) can serve genetic, catalytic, structural, and regulatory roles. Non-coding RNA (ncRNA) genes make transcripts that function directly as RNA, rather than encoding proteins. Transfer RNA and ribosomal RNA are well known examples of non-coding RNA. Around 98% of all transcriptional output in humans is non-coding RNA. RNA-mediated gene regulation is widespread in higher eukaryotes and complex genetic phenomena like RNA interference, co-suppression, transgene silencing, imprinting, methylation, and possibly position-effect variegation and transvection, all involve intersecting pathways based on or connected to RNA signaling. Due to its high abundance, non-coding RNAs have several important biological roles in living organisms.

Keywords: RNA; Non-coding; Transcription; RNA interference; Imprinting

Introduction

Over the past decade there has been an explosion of large-scale genome sequencing, which leads to a dramatic change in our understanding of genome organization. Genome which was earlier considered as a linear arrangement of protein coding regions with a small set of non-coding regions is now being believed to contain chiefly two distinct classes of RNAs: messenger RNAs (mRNAs), which are translated into proteins, and the nonprotein-coding RNAs (ncRNAs), which function at the RNA level. Earlier there were only a few ncRNAs (e.g. transfer RNAs (tRNAs), ribosomal RNAs (rRNAs)and spliceosomal RNAs) were identified. However, advancement of technology reveals a much more complex genomic picture through understanding the function of small ncRNAs. Around 98% of all transcriptional output in humans is non-coding RNA (Carninci *et al.*, 2008) and only 2% are coding part. Given the importance and ubiquity of ncRNAs and RNA-based mechanisms in all extant life forms, it is surprising that we still know relatively little about the most of RNA classes.

Non-coding RNAs consist of a growing class of transcripts that contain a high density of stop codons and lack any extensive "Open Reading Frame" (ORF). A more conventional definition for ncRNAs is an RNA that is biologically functional rather than simply being an intermediate messenger between DNA and proteins. The first eukaryotic ncRNA (excluding the already known snoRNAs, tRNAs and rRNAs) described in the literature was a large RNA named H19, and it was identified as a maternally expressed gene in mice (Bartolomei *et al.*, 1991). Since then, there has been an explosion of new examples of ncRNAs implicated in normal and pathological conditions in eukaryotic cells. The list of ncRNA examples is growing fast in the literature indicating that our understanding of the cellular mechanisms in eukaryotic cells is far from complete.

The diversity of ncRNAs discovered is so great that it is difficult to categorize them except broadly based on their occurrence and function but not on the primary or secondary structure (Erdmann *et al.*, 2001). The non-coding RNA can be grouped into classical 'housekeeping' ncRNAs, small ncRNAs, repetitive element associated ncRNAs, and long ncRNAs (lncRNAs). The 'housekeeping' ncRNAs, such as tRNAs, rRNAs, and small nuclear RNAs (snRNAs) are critical components of many cellular processes. The small/short ncRNAs, such as mi-

*Corresponding author: Chinmoy Mishra
Address:.Indian Veterinary Research Institute, Izatnagar- 243 122, India
*E-mail address:*drchinmoymishra@gmail.com

croRNAs (miRNAs) and piwi-interacting RNAs (piRNAs), have important roles as regulators for a number of biological processes. Some lncRNAs (>200 nt) have only recently emerged as a major class of eukaryotic transcripts (Bertone *et al*., 2004, Birney *et al*., 2007, Kapranov *et al*., 2007). Although lncRNAs have frequently been disregarded as artifacts of chromatin remodeling or transcriptional 'noise' (Brosius, 2005), there is substantial evidence to suggest that they mirror protein coding genes. While the majority of the identified lncR-NAs are polyadenylated, an increasing number of non-polyadenylated transcripts have also been identified in recent years. In addition, many lncR-NAs encompass repetitive elements, such as telomeric RNAs, satellite RNAs, long terminal repeat retrotransposon elements (LINEs) and short interspersed nuclear elements (SINEs).

Transfer RNA

Transfer RNA (tRNA) molecules function as carriers for the amino acids and transfer them to the machinery site of protein synthesis in the cell (Ribosome). Transfer RNA constitutes 15% of all RNA in the cell. There is, at least, a specific tRNA for each amino acid, which means that there are, at least, 20 different tRNA molecules in every cell. Each tRNA is specialized to carry one of the 20 different amino acids required for the process of protein synthesis. Transfer RNA molecule has a clover-leaf structure presenting three loops and having 2 free ends, the 3`and 5`ends (Fig. 1). The CCA end acts as an amino acid acceptor site.
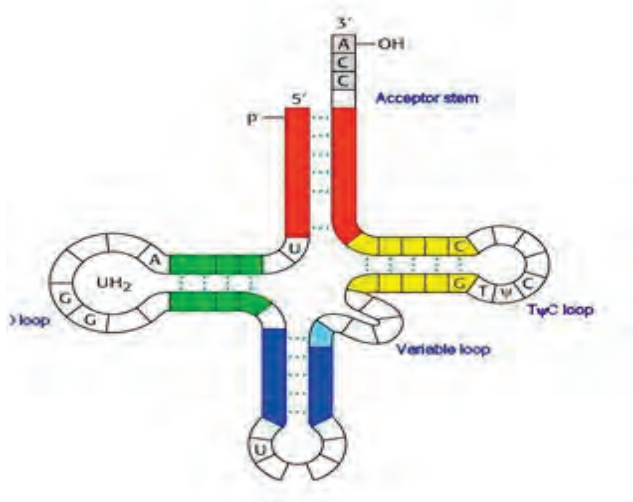
Ribosomal RNA

Cell growth is intimately linked to ribosome biogenesis. The ribosome is a cytoplasmic nucleoprotein structure which acts as the machinery for the synthesis of proteins. Ribosome is essentially made up of ribosomal RNA and protein. Ribosomal RNA constitutes 80% of total RNA present in the cell. In prokaryotic cell three (i.e. 5S, 16S and 23S) types of rRNA are found, whereas in eukaryotic cells four (i.e. 5S, 5.8S, 18S and 28S) types of RNA are found.

Micro RNA

Micro RNAs are endogenously encoded approximately 20-24 nucleotide (nt) long (Fig. 2) single-stranded RNAs (Winter *et al*., 2009), expressed in a highly tissue or developmental-stage-specific fashion that specifically control translation of target mRNAs by binding to sites of antisense complementarily in 3′ untranslated regions (Grishok *et al*., 2001). Evidence also indicates that miRNAs regulate gene expression at posttranscriptional levels in various organisms (Reinhart *et al*., 2002). One of the first miRNAs discovered is let-7. The let-7 family of miRNAs is highly conserved and functions as a master temporal regulator of development and differentiation, both in early embryos and complex adult tissues (Roush and Slack, 2008).
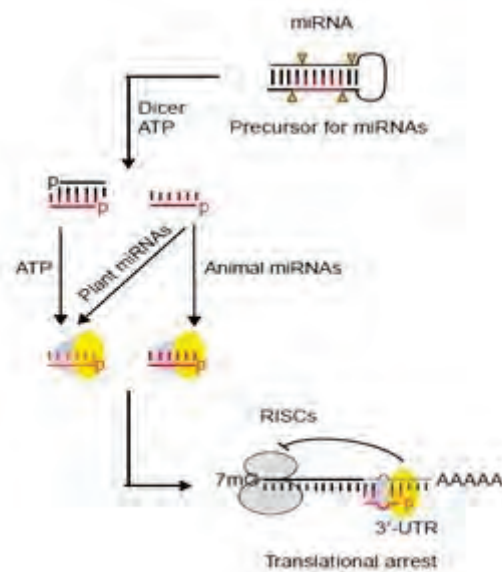

Fig. 1. Transfer RNA

Fig.2. Micro RNA

Small interfering RNA

Small interfering RNAs (siRNAs) are 21-25 nucleotide (nt) long double stranded RNA and bear 2 nt, 3' overhanging ends. Each siRNA has a 5' phosphate and 3' hydroxyl termini. RNase III family enzymes such as Dicer cleave double stranded RNA into 21 nt fragments (Ghildiyal and Zamore, 2009). Small interfering RNAs act as functional intermediate in RNA interference (RNAi) (Brodersen and Voinnet, 2006) to induce target mRNA cleavage by RNA-induced silencing complex (RISC) (Fig. 3). RNA-induced silencing complex then uses unwound antisense siRNA strand as a guide to find target mRNA and induces its endonucleolytic cleavage (Carthew and Sontheimer, 2009). Although exogenous siRNAs were discovered a decade ago, endogenous siRNAs have only recently been identified in fruit-flies and mammals (Okamura and Lai, 2008, Okamura *et al.*, 2008).
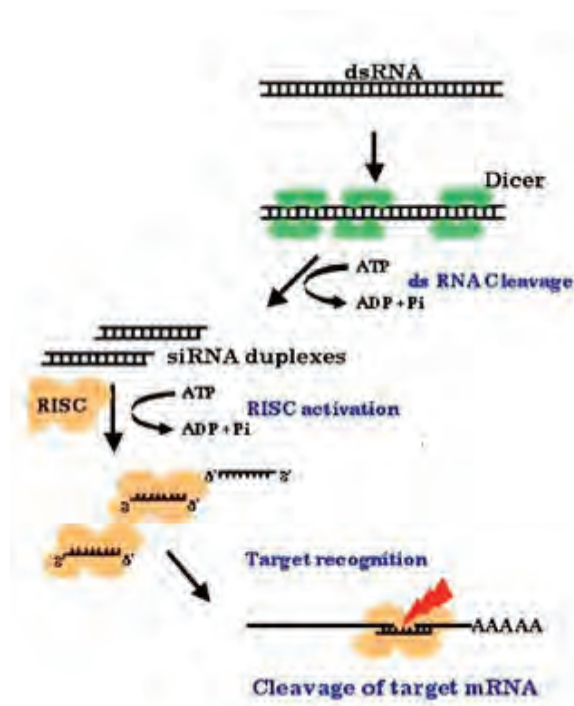

Fig. 3. Small interfering RNA

PIWI-interacting RNAs

PIWI-interacting RNAs (piRNAs) are the Dicer-independent 26-30 nt small RNAs. They are mostly restricted to the border of germ line and somatic cells and associated with PIWI-clade Argonaute proteins regulating transposon activity and chromatin state (Malone and Hannon, 2009). Mutations in Piwi lead to defects in oogenesis and a depletion of germ line stem cells (Cox *et al.*, 1998). In human millions of unique piRNA sequences are identified.

MicroRNA-offset RNAs

MicroRNA-offset RNAs (moRNAs) are small RNAs of 20 nt long. They are derived from the regions next to pre-miRNAs without any known function until the date (Shi *et al.*, 2009, Langenberger *et al.*, 2009).

Ribonuclease P and Ribonuclease mitochondrial RNA processing

Ribonuclease P (RNases P) and mitochondrial RNA processing (MRP) are ribonucleoproteins act as endoribonucleases in tRNA and rRNA processing, respectively. Ribonuclease P helps generation of the mature 5' ends of tRNAs (Fig. 4) (Walker and Engelke, 2006). Ribonuclease MRP is eukaryote-specific, which cleaves leading to the maturation of the 5'end of 5.8S rRNA, generates RNA primers for mitochondrial DNA replication, and is involved in the degradation of certain mRNAs. The high similarity of P and MRP RNA secondary structures and the protein contents suggest that P and MRP RNAs are paralogs. RNase P RNA is found almost ubiquitously. However, MRP RNA is only found in plants, including green algae, and red algae (Piccinelli *et al.*, 2005).
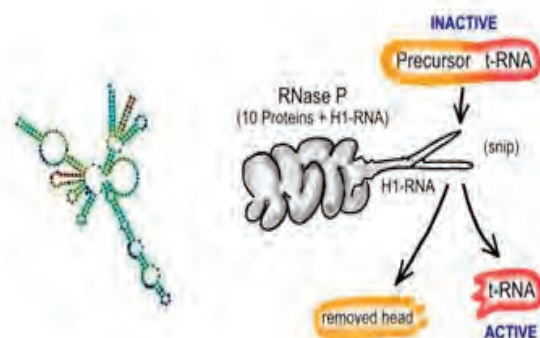

Fig. 4. Ribonuclease P and its mechanism of action.

U7 small nuclear RNA

The U7 small nuclear RNA (snRNA) is the smallest polymerase II transcripts that play the key role

in 3' end processing (Fig. 5) of histone gene transcript (Spycher *et al.*, 1994), which is not polyadenylated, ending instead in a conserved stem-loop sequence. A detailed analysis shows that each of its three major domains, the histone binding region, the Sm-binding sequence, and the 3' stem-loop structure, exhibits substantial variation in both sequence and structural details across the species (Mowry and Steitz, 1987).
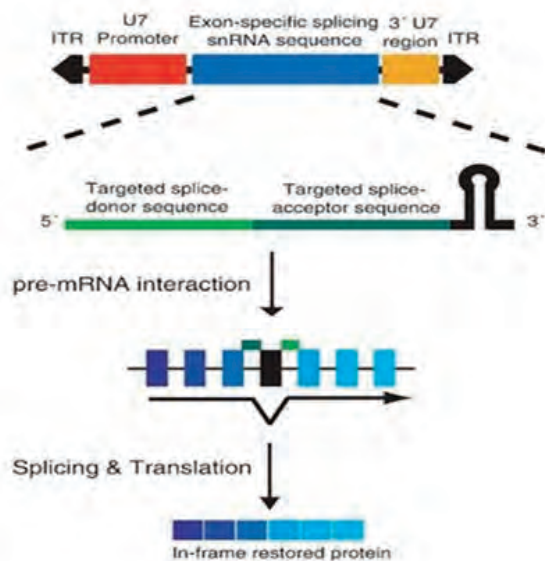

Fig. 5. Processing of histone gene transcript by U7 Sn RNA.

Promoter-associated RNAs

Promoter-associated RNAs (PARs) are broadly defined as short transcripts (250-500 nucleotides) within a few hundred bases of protein-coding or non-coding RNA transcription start sites (Fejes-Toth *et al.*, 2009). Promoter-associated RNAs were first identified in yeast and until the date, they are described in all major eukaryotes (Taft *et al.*, 2009b).

Telomere small RNAs

Extensive studies (mostly in yeast) demonstrated that small RNA-dependent processes are central for the formation of constitutive heterochromatin (Moazed *et al.*, 2006, Grewal and Elgin, 2007). A methylation mechanism for heterochromatin assembly in mammalian cells by telomere small RNAs (tel-sRNAs) were suggested, but have yet to

be firmly established. It remains controversial whether they are Dicer-dependent small RNAs in association with repeat sequences and heterochromatin (Cao *et al.*, 2009).

Centrosome-associated RNAs

Centrosome-associated RNAs (crasiRNAs) are group of 34-42 nt small RNAs, derived from centrosomes that show evidence of guiding local chromatin modifications (Carone *et al.*, 2009).

Small nucleolar RNAs (snoRNAs)

Small nucleolar ribonucleoprotein (snoRNP) particles are nucleolus-localized complexes consisting of snoRNAs and a few associated proteins. Most snoRNPs function in the modification and processing of pre-ribosomal RNA. There has been also report that several snoRNAs may as well target tRNAs and other snoRNAs (Zemann *et al.*, 2006). Known snoRNAs can be grouped in two major classes referred to as 'box C/D' and 'box H/ACA' snoRNPs based on a conserved sequence elements and secondary structure (Fig. 6). C/D snoRNAs exhibit the "boxes" C and D with consensus sequence (A) UGAUGA and CUGA respectively. They frequently contain a second copy of these two boxes, usually designated C' and D', in the region between the C and D box. The H box of the H/ACA snoRNAs has the consensus sequence ANANNA. The ACA motif located at the 3' end of the molecule is highly conserved. The two major classes direct distinct chemical modifications.
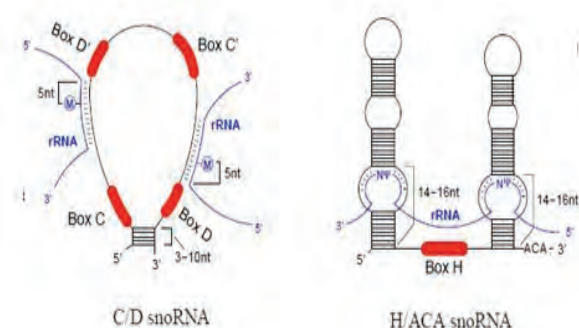

Fig. 6. Small nucleolar RNA

Most C/D snoRNAs determine specific target nucleotides for methylation of the 2'-hydroxyl posi-

tion of the sugar, while most of the H/ACA snoR-NAs specify uridines that are converted into pseudouridine by rotation of the base.

Signal Recognition Particle RNA

The signal recognition particle (SRP) is a RNA polymerase III transcript ribonucleoprotein complex that interacts with the ribosome during the synthesis and translocation of secretory proteins. It helps co-translational targeting of proteins that contain signal peptides to membranes, including the prokaryotic plasma membrane and the endoplasmic reticulum. The assembled SRP consists of two structurally and functionally distinct domains (Fig. 7). The small domain (Alu-domain of the SRP RNA and the proteins SRP9 and SRP14) modulates the elongation of the secretory protein and the larger domain (S-domain of the SRP RNA and several specific proteins) captures the signal peptide. Eukaryotic SRP RNA is also known as 7SL RNA

Telomerase RNA

Maintenance of linear chromosomes requires a specific mechanism to compensate for the terminal sequence loss that occurs pursuant to conventional DNA replication in eukaryotes. Eukaryotes rely on a cellular reverse transcriptase, telomerase that synthesizes tandem tracts of a short guanine-rich se-

quence onto the 3' overhangs of chromosomes (Schoeftner and Blasco, 2008). The main components of telomerase are its reverse transcriptase and telomerase RNA containing a short template sequence. The RNA component varies dramatically in sequence composition and size (Podlevsky *et al.*, 2008). Although several telomerase RNAs have been identified, the known examples are restricted to four narrow phylogenetic groups: vertebrates, yeasts, ciliates, and plasmodia (Fig. 8).
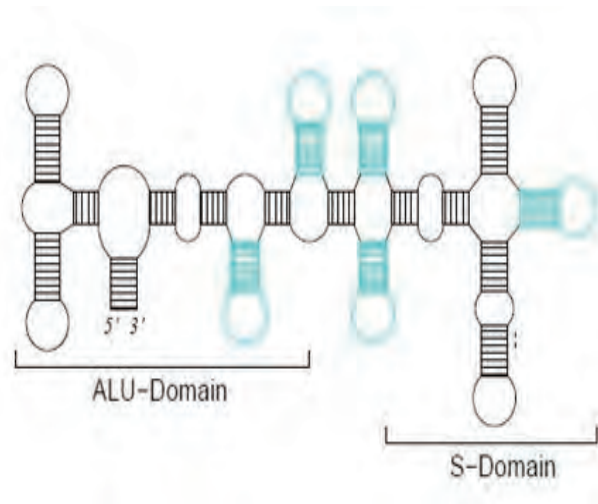
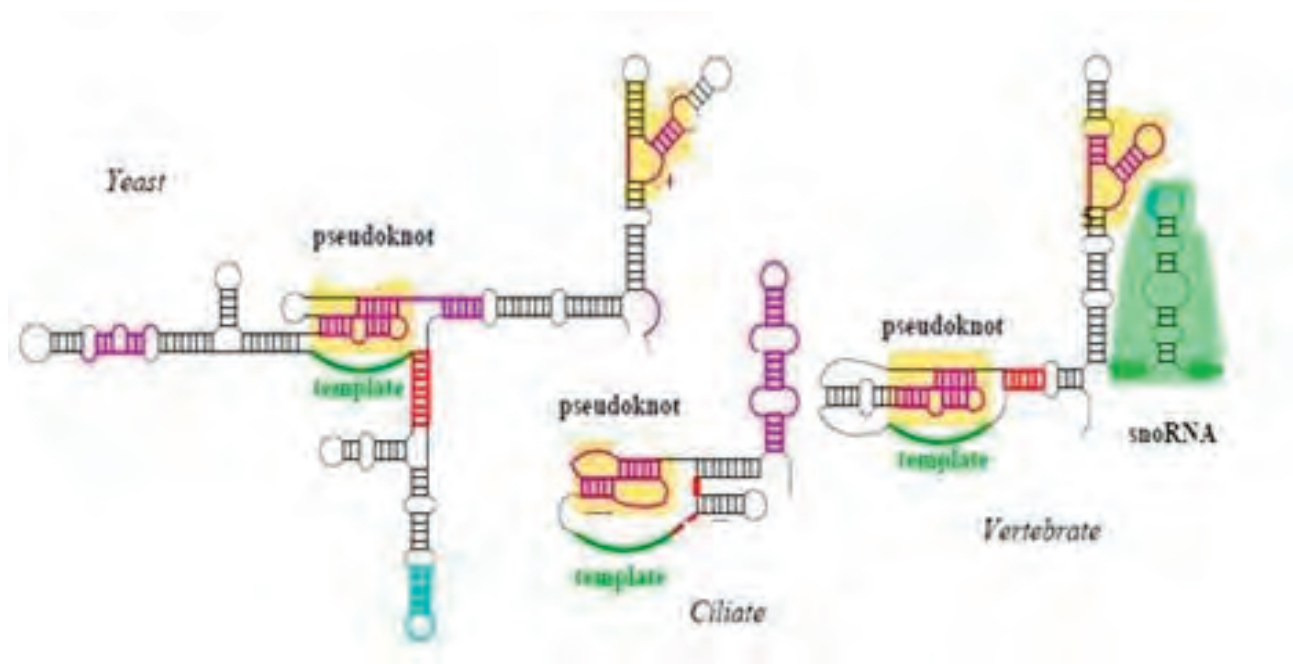

Fig. 7. Signal Recognition Particle RNA

Fig. 8. Telomerase RNA

Spliceosmal snRNAs

Removal of the intervening sequences (introns) from pre-mRNAs is a crucial and ubiquitous step in eukaryotic gene expression (Fig. 9). The process of intron splicing takes place in a massive ribonucleoprotein complex known as the spliceosome which consists of up to 300 proteins and five small non-coding RNAs (Nilsen, 2003).

Three distinct variants of spliceosomal machinery may be present in eukaryotic cells. The major group of spliceosome contains U1, U2, U4, U5 and U6 snRNAs and removes introns delimited by the canonical donor-acceptor pair GT-AT. The minor group of spliceosome is composed of U11, U12, U4atac, U5 and U6atac snRNAs (Patel and Steitz, 2003) and acts on AT-AC introns (Sheth *et al.*, 2006). The snRNAs U11, U12, U4atac, and U6atac take on the roles of U1, U2, U4, and U6. Whereas, both U6 and U6atac are polymerase-III transcripts, all other spliceosomal snRNAs are transcribed by polymerase-II. The snRNAs themselves are not only part of the spliceosomes but are also involved in transcriptional regulation (Kwek *et al.*, 2002).
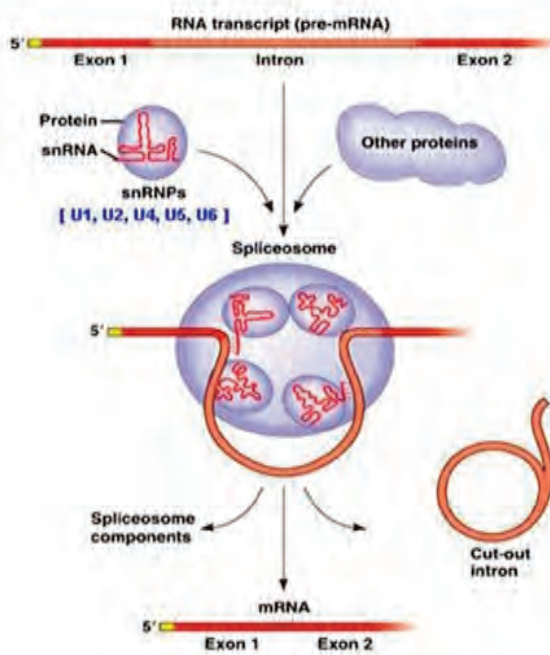

Fig. 9. Spliceosmal snRNA

Small nucleolar-derived RNAs

Small nucleolar-derived RNAs (sdRNAs) are small RNAs (some of which are Dicer-dependent), which are processed from snoRNAs. Some sdRNAs have

been shown to function as miRNA-like regulators of translation (Taft *et al.*, 2009a).

Transfer-messenger RNA

Translation of a messenger RNA (mRNA) lacking a stop codon often results in a ribosome stalled at the end of the mRNA with a peptidyl-tRNA in the P site and with an empty A site (Fig. 10). The transfer-messenger RNA (tmRNA) which is also known as 10Sa RNA or SsrA rescues these stalled ribosomes, promoting release factor binding and thus providing the template for a peptide-tag that then causes the rapid degradation of the incomplete translation product (Marzluff, 2005).
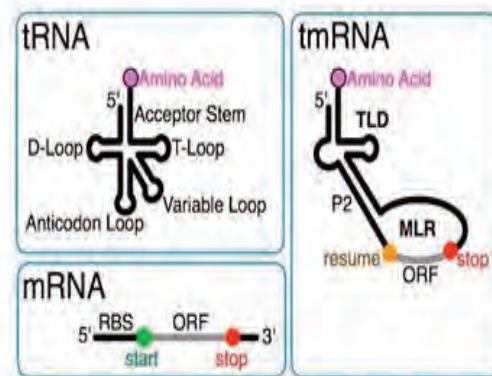

Fig. 10. Transfer-messenger RNA

Transfer-messenger RNA that combines the functions of a tRNA and a mRNA has two distinct domains tRNA-like (TLD) and a mRNA-like (MLD) domain linked by RNA-helices and RNA-pseudoknots (Keiler *et al.*, 1996). Transfer RNA-like domain binds to the protein SmpB and then aminoacetylated by an alanyl-tRNA synthetase. A quaternary complex that contains elongation factor EF-Tu recognizes ribosome stalled at the 3' end of a nonstop mRNA and like tRNA, enters the ribosome's A site. The nascent polypeptide is transferred to the alanyl-tmRNA, which now switches to its mRNA-like mode of action by translocating to the P site of the ribosome where it places a TAG codon in the ribosome's mRNA channel. This leads to the release of the defective mRNA and its subsequent selective degradation by RNase R. The ribosome continues translation with the tmRNA ORF as a surrogate template and terminates at a tmRNA-encoded stop codon, thereby releasing the nascent protein with the 11-amino acid degradation

tag, which contains epitopes for ubiquitin proteases for degradation.

Y RNAs

Y RNAs have so far been reported only in vertebrates, the nematode Caenorhabditis elegans and the prokaryote Deinococcus radiodurans. They are short RNA polymerase-III transcripts with characteristic secondary structure (Fig. 11) without any known function yet (Farris *et al*., 1999). However, Y RNAs are seemed to be component of Ro RNP particle and Y5 that are implicated in 5S rRNA quality control (Hogg and Collins, 2007).

Fig. 11. Y RNA

6S RNA

The 6SRNA is one of the bacterial small RNAs that binds specifically to the bacterial RNA-Polymerase (RNAP) holoenzyme and selectively inhibits σ70 dependent transcription (Maeda *et al*., 2000). It seems to mimic the open σ70 dependent promoter complex (Cavanagh *et al*., 2008). This RNAP-6S complex is present when NTP concentrations are low and as soon as new NTPs become available to the RNAP-6S complex, the 6S RNA serves as a template for the transcription of the 14-20nt pRNAs (Wassarman, 2007). This results in the formation of an unstable 6S RNA-pRNA complex which releases the RNAP-holoenzyme (Wassarman and Saecker, 2006). 6S RNA has three domains closing stem central bubble and terminal loop (Fig. 12).

Vault RNAs

Vaults are large ribonucleoprotein particles that are ubiquitous in eukaryotic cells with characteristic barrel-like shape with poorly understood function in multi-drug resistance (van Zon *et al*., 2003). Vault RNAs are short (Fig. 13) polymerase-III transcripts having two internal polymerase-III promoter sequences, Box A and Box B, and a typical terminator sequence at the 3' end (Mosig *et al*., 2007). The terminal stem is conserved among all known examples. They exhibit little sequence conservation beyond their Box A and Box B internal promoter elements.
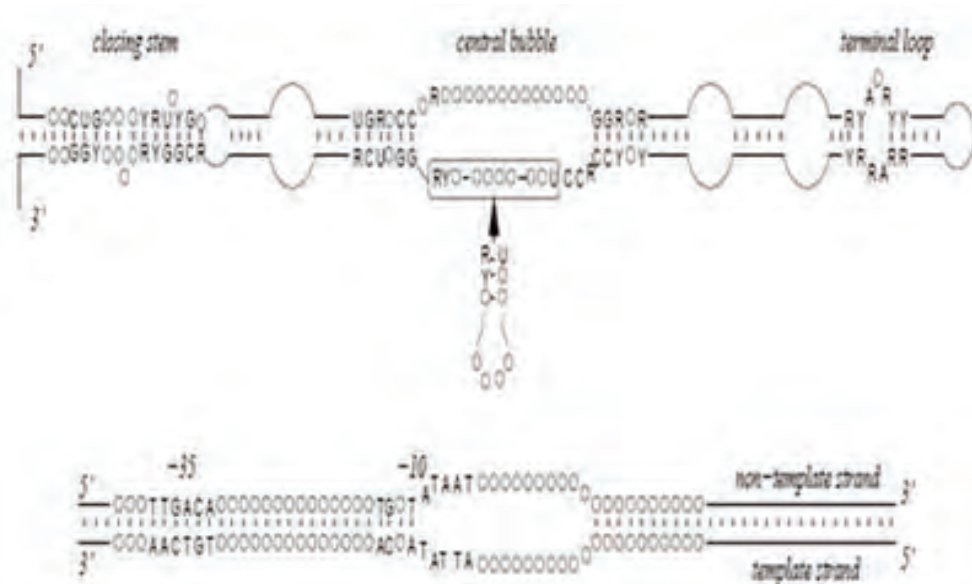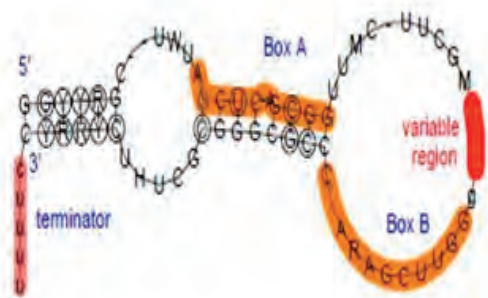

Fig. 12. 6S RNA

Fig. 13. Vault RNA

7SK RNA

The 7SK snRNA is one of the polymerase-III transcripts, with a length of about 330nt (Wassarman and Steitz, 1991). It is highly abundant ncRNAs in vertebrate cells and function as a transcriptional regulator by inhibiting the transcription elongation factor P-TEFb, a critical regulator of RNA polymerase-II. 7SK RNA is highly variable in both sequence and structure (Fig. 14). Only two stem-loop structures, towards the 5' and the 3' end, are conserved. The 5'-terminal hairpin is responsible for HEXIM1 and PTEFb binding (Egloff *et al.*, 2006), the 3'-stem interacts with P-TEFb.
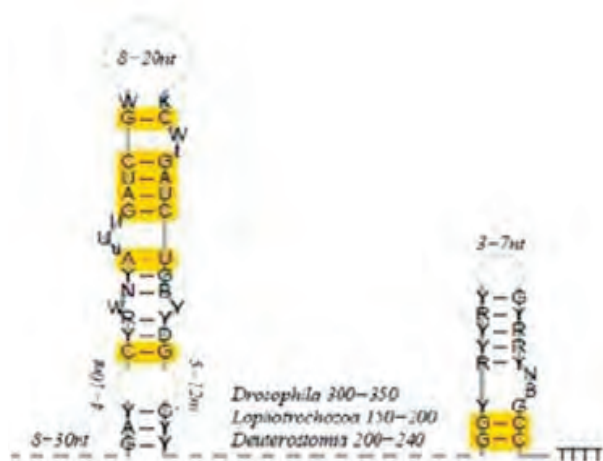

Fig. 14. 7SK RNA

Ornate large extremophilic RNA

The "ornate large extremophilic" (OLE) RNA with a length of approximately 610nt is highly conserved in both sequence and secondary structure non-coding RNA (Fig. 15).

Fig. 15 Ornate large extremophilic RNA

Ornate large extremophilic is found predominantly in extremophilic Gram-positive eubacteria. A functional link between OLE RNA and membrane protein has been suggested (Puerta-Fernandez *et al.*, 2006).

Guide RNAs

Mitochondrial mRNAs of some protozoa need to undergo a post-transcriptional editing process before translation. Kinetoplastids of the trypanosomatid group possess two types of mitochondrial DNA molecules: Maxi-circles bear protein and ribosomal RNA genes. Mini-circles specify guide RNAs (gRNAs), with a typical length of about 50nt that mediate uridine insertion/deletion RNA editing. Following the hybridization of the 5'-anchor region of a gRNA to the 3' end of its target mRNA, a U insertion and deletion is directed by sequential base pairing (Alatortsev *et al.*, 2008).

Conclusion

Everyday there are new class of non-coding RNA are discovered. So it is very difficult to conduct both qualitative as well as quantitative study of non-coding RNA genes. However, completion of genome sequencing will help understand the genome in a more comprehensive way that may ease our effort to identify the non-coding RNA. New generation of sequencing technology will lead to understand the insight of non-coding RNA genes in a much better way. However, sharing of information should not be overlooked.

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