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Review

Molecules derived from tRNA and snoRNA: Entering the degradome pool

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ABSTRACT

Molecules built of RNA have been the subjects of numerous studies, which have made known new functions and structures that these molecules can create. In recent years, thanks to next-generation sequencing, it is possible to observe very small RNAs and the number of newly discovered RNA molecules is rapidly increasing. Among other small oligonucleotides, structures derived from tRNA and snoRNA molecules have been observed, and these molecules were determined to not be precursors of known RNA molecules. These structures have attracted the attention of researchers because the level of accumulation of tRNA or snoRNA fragments was relatively high. Additionally, other parts of the parent molecules were absent. Derivatives of well-known RNA molecules also have functions that are different from their parent molecules. They are mainly involved in regulating the expression of genetic information in a similar way to miRNA. In addition, some of the miRNAs that have been described are derivatives of tRNA or snoRNA. Most of the research on these newly discovered molecules is based on their detection and on the study of the macro effects that they exert, in the absence of a description of the molecular mechanism by which they arise and work.

1. Introduction

RNA molecules are a very important group of compounds in living organisms. At first, it was thought that they play the role of an intermediate product in the translation of genetic information from DNA into proteins and nothing else. Until the discovery of ribosomal RNA (rRNA) and transfer RNA (tRNA), which showed that RNA can have other functions in cells [1], it was thought that non-coding RNA was useless and non-functional. Further research led to greater understanding of RNA [2]. RNA was then divided into two groups: coding (mRNA) and non-coding (ncRNA). Initially, ncRNA included those RNAs that had a seven-nucleotide cap and no open reading frame (ORF). This view has changed, and now the ncRNA designation includes all RNAs that do not encode proteins [3]. Among ncRNA, two groups are distinguished: housekeeping RNA and interference RNA. Housekeeping RNA includes those molecules whose expression is constitutive in the cell and necessary for its normal functioning, i.e., rRNA, tRNA, small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), transfer-messenger RNA (tmRNA) and a few others. MicroRNA (miRNA) has been assigned to the group of interference RNA and has the function of post-transcriptional gene silencing [3]. It is possible that the coming years will bring information about increasingly newer RNAs, and there is a need to revise the RNA nomenclature as some of the names, such as long non-coding RNA, small RNA, and microRNA may cease to be appropriate. This must be considered in combination with the names under which the RNA is described in this work, i.e., unusually small RNA. The most frequently described molecules from this RNA group are the tRNA and snoRNA fragments.

Transfer RNA is responsible for the supply of amino acids to the ribosomes. They bind in a specific way to free amino acids and transport them to places of translation. In addition to their main function of transporting amino acids to the ribosomes, they also transfer amino acids to other biochemical pathways, regulate cell apoptosis by cytochrome binding and may be a retrovirus primer [4]. All tRNAs have the shape of a four-leaf clover because all tRNA molecules must be able to interact with the rRNA in a similar manner. In addition to the anticodon loop, rRNA can also distinguish D loops and T-loops (Fig. 1). These are important elements from the point of view of the molecules discussed later.

Transporting RNAs are highly conserved in evolution, and this may suggest that molecules prepared in the process of their degradation are one of the first formed regulatory elements [5].

Small nucleolar RNA has been given an analogous name, small nuclear RNA (snRNA), which illustrates the specific location of these molecules. They occur mainly in the nucleolus but also in Cajal bodies, and their length varies from 60 to 300 nucleotides. This type of RNA

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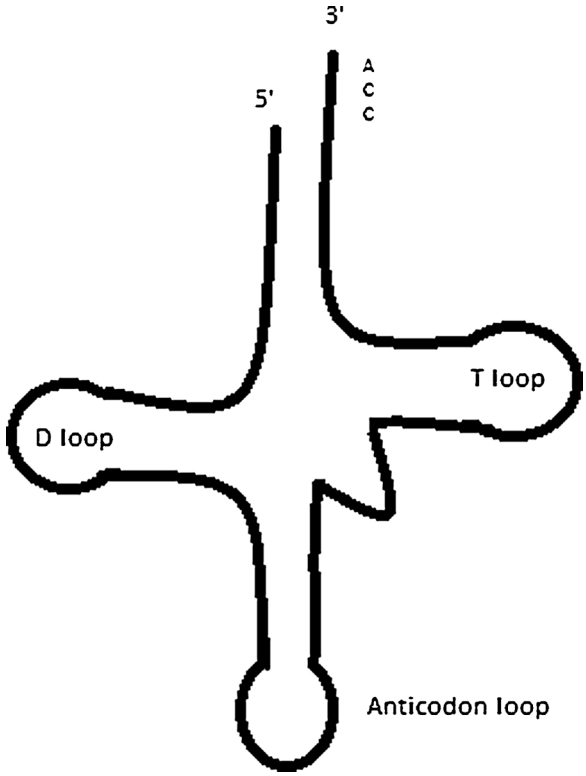

Fig. 1. The anticodon loop contains seven bases (5′-pyrimidine-pyrimidine-XYZ-modified purine-variable base-3′) where the centre has an anticodon, a D-loop that contains several dihydrouracil molecules, and a T-loop that contains the sequence ribotimine-pseudouracil-cytosine.

can be found in archaea as well as in eukaryotes, which is why they evolved probably 2–3 billion years ago. In humans, snoRNA is most often coded in introns. Usually, after mRNA splicing, introns are degraded; however, snoRNAs avoid this fate by forming complexes with proteins, which we call snoRNPs [5]. We divide the small nucleolar RNA into two families, which are characterised by different structures and functions. There are C / D and H / ACA snoRNPs; both groups are involved in the chemical modification of nucleotides in RNA, mainly in ribosomal RNA in regions important for translation such as the peptidyl transferase centre or mRNA decoding centre, but they can also modify other RNAs, such as snRNA in eukaryotes, tRNA in archaebacteria, and possibly brain-specific mRNA in mammals (Fig. 2). For the proper functioning of spliceosomes, an appropriate modification of snRNA by snoRNA molecules is necessary [5]. The C / D family, due to the presence of fibrillarin methyltransferase, may methylate 2′-O-ribose, whereas the H / ACE family is associated with pseudouridine synthetase. The specific hybridisation of snoRNA fragments with the appropriate RNA fragment helps in the modification of a particular nucleotide [5]. There are over 200 unique snoRNA molecules; however, not all have been matched to specific target tRNA or snRNA molecules. These are called orphan snoRNAs and have uncharacterised functions in the body.

2. Degradation of RNA

The degradation process is extremely important for maintaining the cell in a state of homeostasis. Cells can properly control all reactions and levels of proteins. RNA degradation involves the removal of normal RNA that is no longer necessary, RNA maturation (processing precursor molecules), quality control by removing improperly folded or synthesised particles, post-transcriptional regulation of gene expression, and protection against foreign RNA (Fig. 3) [6,7]. The degradation process is a very complicated and extensive system and has not been completely characterised. The enzymes known as ribonucleases are responsible for the cleavage reaction, and we can divide them into 3 groups depending on the place of hydrolysis of phosphodiester bonds. The endoribonuclease catalyses the cleavage of bonds within the RNA molecule, 5′-3′ exoribonuclease catalyses the detachment of a single nucleotide from the 5′ end, and the 3′-5′ exoribonuclease provides the analogous function on the 3′ end. In each subgroup, there are several families of enzymes that recognise other substrates. Some of the enzymes are very specialised, and others can be used with more degenerate target sequences [7,8]. Such a diversity of ribonucleases is supposed to ensure the highest reliability of the degradation system and proves the importance of this process in the proper functioning of the cell and organism [9]. More than 60 different RNA-degrading enzymes belonging to several families have been estimated to exist in humans

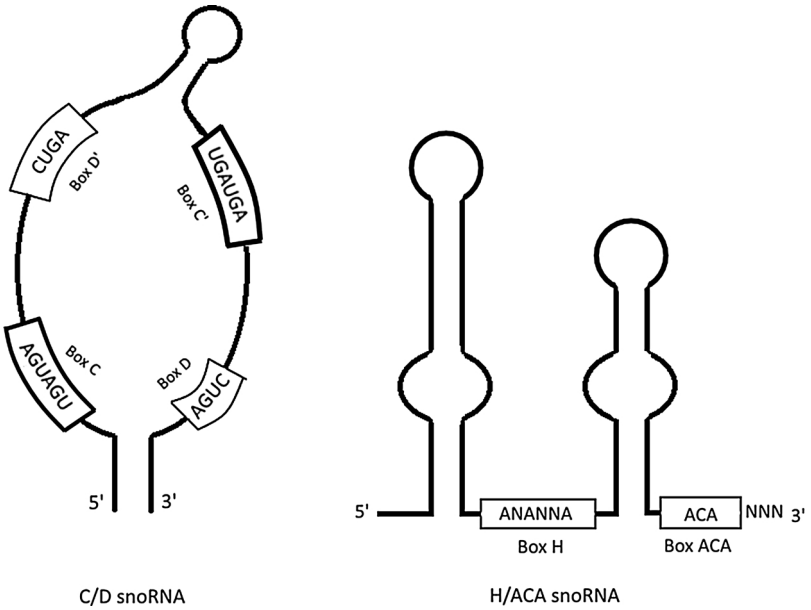

Fig. 2. C/D snoRNA has two pairs of distinctive conserved sequences named box C and box D. Sequences between boxes C and D are the site of the RNA chain binding to be modified. H/ACA snoRNA also has two conserved H and ACA structures that are located between the beta-hairpin structures.