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The Ribosome as a Source of Genome Hypervariability?

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Abstract—In this report it is suggested that at early stages of evolution ribosomes were responsible for synthesizing short oligonucleotide cDNA packets which formed the protogenic tandem repetitive sequences. Ribosomal RNA (rRNA) could have been the most probable template for such a synthesis. rRNA has homology with the monomers of tandem hypervariable repetitive elements of the genome. A model for the proposed participation of rRNA in the genesis of genomic fragments is provided by analysis of the active center of GTP-binding proteins. The role of oligonucleotides, synthesized by the ribosome, in the context of mechanisms of genome regulation, genes responsible for disease and human longterm memory formation are also discussed.

Introduction

The discovery of RNA enzymes, namely, ribozymes, along with the application of genetic engineering in the study of ribosomes revived an interest in alternate functions of ribosomes. Recently the groups of Noller and Cech (1, 2) have stressed the significance of ribosomal RNA (rRNA) in the functioning of ribosomes.

In the present report it is suggested that the mechanisms of protein synthesis are also involved in the synthesis of oligonucleotides. For example, three of four subunits of RNA-replicase of both phages Q-β and f2; elongation factors EF-Tu, EF-Ts and the ribosomal protein SI, are related to ribosomes (3, 4). Ribosomal protein L3 has been demonstrated to independently replicate RNA molecules (5). Furthermore RNA molecules are able to synthesize a complementary RNA, thus increasing the number of their copies in vitro (6, 7). Ribosomes and the elongation factor EF-G interact with RNA-polymerase of B. subtilis (8, 9). Genomic ribosomal operons include genes for the EF-G, EF-Tu, EF-Ts, subunits of RNA-polymerase, DNA-primase, and RNAse P (10–15). Interestingly, self-splicing RNA introns may contain genes for the site-specific DNA-endonuclease and sequences analogous to the gene for reverse transcriptase (16). Genes present for nucleotide metabolism in the ribosomal operons and the ability of proteins connected with the ribosome to synthesize oligonucleotides suggest that earlier in evolution, ribosomes were capable of synthesizing short oligonucleotides on the rRNA template, which in turn formed the tandem genomic repetitions.

Results

Homologies of various sequences of the human rRNA were found when compared to monomers of both

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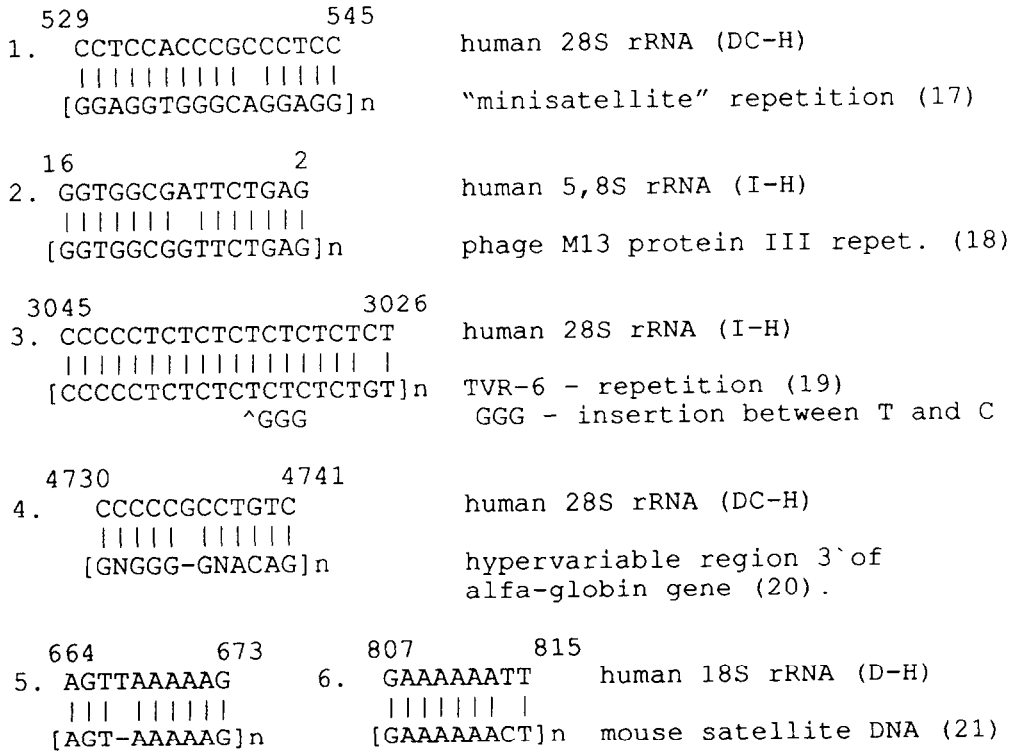

Fig. 1

human and mouse hypervariable genomic repetitive elements. Alignment of gene and protein sequences were prepared by a computer algorithm (provided by Dr A. Ageev). This algorithm compared sequences in 4 variants: direct-homology (D–H), invert-homology (I–H), direct complement homology (DC–H) and invert complement homology (IC–H) (Fig. 1).

CGC repetitions occur quite frequently in the 28 rRNA sequence. This may serve as a source of GTG (CAC) repetitions (CG→TG transition) (22). (CT)n fragments, used in DNA 'fingerprint' technology, are also present in 28S rRNA. The 3' end of 28S rRNA contain many GACA and GATA-sequences, repetitions of which are dispersed along the genome (23). It can be speculated that rRNA is the origin of certain exons. A correlation between the two spatially distinct peptides of the active center of the GTP-binding proteins (GTP–BP) and 28S rRNA are present.

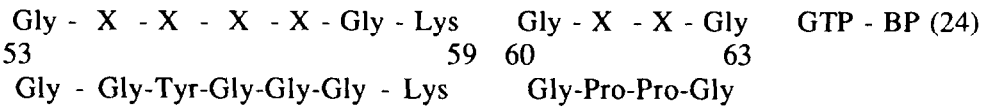

Fig. 2

Figure 2 represents the position in the 'peptide' at nucleotide 679 of the 28S rRNA. The genes, encoding these two peptides follow each other in the rRNA sequence.

Discussion

The appearance of homology between rRNA and many peptides, leads to the possibility that the rRNA is not only the origin of the hypervariable repetition but may also be a progenitor of these peptides. These peptides are components of the proteins: keratinis, helix-destabilising proteins, informatin, tubulins, dihydrofolate reductase, insulin-like growth factor, calcium-dependent protease, TRK-oncogene, androgen receptor, NADP-cytochrom B5 reductase, DNA-methylase and many others (25–31). Tandem repetitions like (GTG)n, (GT)n, (CT)n, (GGC)n, (GC)n,

(CCG)n are characteristic to both rRNA and genes encoding protein (31). Thus, one can assume that the genes of some proteins were formed by the rRNA-derived oligonucleotides. According to Bostoc and Samner 'a considerable part of so-called (genome) unique sequences is likely to consist of repeating sequences' (32).

It is suggested in this report that the transition from the RNA-world into the DNA-world may have been mediated through the ribosomes. Proto-ribosomes may construct oligonucleotides by the cutting and splicing (by rRNA) of parts of the proto-tRNAs. Thus tRNAs may be bringing not only peptide monomers (amino acids), but monomers for oligonucleotides as well (proto-anticodons). These oligos were being translated into DNA-form by reverse transcriptase.

The generation of oligonucleotides by ribosomes may take place in cells. In this scenario, ribosomes synthesizing both oligonucleotides and peptides that correspond to these oligonucleotides, and could control both cytoplasmic and nuclear activity, thus performing cellular monitoring. This monitoring could be dependent on changes in cytoplasmic ion concentration and, ultimately, on extracellular signalling.

Synthesis of these oligonucleotides could take place in the ribosomes bound to the endoplasmic reticulum (ER). The ER is the ramified external nuclear membrane, and its channels might be used by the oligonucleotides to penetrate into the nucleus.

Ribosomal oligonucleotide synthesis can be associated with a series of diseases. For example GGN- and CGG-repeated elements are involved in genesis of spinal and bulbal muscular atrophy, also known as Kennedy disease and fragile X syndrome (33).

Possible ramifications of ribosome mediated synthesis of oligonucleotides could be the following:

a) regulation of gene expression (Considerable portion of the active genome regions, TATA-box, GCC-, (CT)n-blocks, Hinf-repetitions, Shi-sites and others (17, 34, 35) are homologous to rRNA);

b) supply of the inert genetic material, which later will be used in chromosomal reduplication;

c) heterochromatinization of the genome by oligonucleotides may cause the mechanism of cell division to turn on. In this case ribosomes could work as a genetic timer of the cell. Involvement of inert material of heterochromatin in the rapid reduplication of euchromatin may lead to both the increase in the level of the latter and decrease in the level of heterochromatin, thus maintaining the genetic status of the cell, namely, the euchromatine/heterochromatine ratio.

This hypothesis concerning simultaneous synthesis of oligonucleotides and corresponding peptides may shed light on the problem of long-term memory in both humans and animals. Existing hypotheses may involve either the reverberation of the electric current in the neuronal networks, or the chemical modification of macromolecules, mainly proteins (36). However, the physiological alterations of electric current by electricshock therapy or by chemical methods does not lead to the long-term memory loss. The relatively short life-time of peptides in comparison with the time of existence of the long-term memory, makes the significance of the proteins in this process highly dubious.

One can speculate that consecutive synthesis of oligonucleotides and placement into the genome with the concurrent expression of the given tandem motif may restore metabolic processes in neurons. Thus long-term memory may be recorded by the genomic tandem repets, generated in ribosomes, utilizing rRNA as a synthetic matrix. Since this hypothesis is applicable to any cell in the organism, it implies that the usual cellular structures, conciliating cellular metabolism with its genome fixation, may explain the possible reproduction of the long-term memory engram and preservation of information in the cell.

Furthermore, it may be understated that the function of ribosomes is not exclusively in translation of nucleotide sequence. The ribosome has given birth to the genome and continues supplying it with its 'ideas', thus regulating genomic function and setting the life term of the genome, cell, and ultimately the organism itself.

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