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Ancient RNA World Roaming Across the Human Body (Cancer as an Evolutionary Model)

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ABSTRACT

Now exist strong evidence in a favor of "RNA-first" view of life's origin. With discovery of extracellular vesicle-mediated microRNA (miRNA) transfer in cancer cells, it is possible to trace evolution of life till the origin of genetic code. Thus, cancer cells can be used as a model to investigate retrospective evolution of life on Earth. In this complexity to simplicity approach, miRNAis seen as a basis for molecular genetics, and vesicles as the origin of cellular membrane systems, cytoskeleton structures, and energy production. This article proposed that "RNA World" was made primary of hairpin miRNA molecules wrapped into extracellular-like vesicles protector, and that oldest genetic code consist of miRNA, i.e. piecemeal of tRNA minihelixes. More precisely, everything begins with the miniRNA (mnRNA)-miRNA seed – like region. This was, at the same time, the beginning of biotic era.

Keywords: *archaea, mnRNA and cancer, origin of biotic era, retrospective evolution.*

INTRODUCTION

At the molecular level, biochemistry of the human cell affected by cancer resembles that of a prokaryotic cell in terms of energy consumption, cell proliferation, and loss of contact inhibition, leading to the "prokaryotic individualism". All these characteristics are the results of reverse evolution, in which the genes for normal cellular functions play a secondary role to the prokaryotic genes causing cancer, undermining human genome. This fact raises interesting question: "At which point in evolution the eukaryotic carcinogenic cell goes backwards?" .In the previous hypothesis (1), biochemistry and molecular genetics of eukaryotic cancer cell coincides with the emergence of the proto-eukaryotic cell after the separation of two archaeal replicons, raising nucleus and mitochondrion. It was thought to be a limit until the cancer cell can follow retrospective evolution.

Emerging evidence shows that extracellular vesicles (EV) associated miRNA play pivotal role in a wide range of diseases, particularly in cancer (2). "RNA World" model itself (3) cannot explain the evolution of metabolism. So, these two evolable hyper-structure entities, miRNA and extracellular vesicles, should exist in a vestigial form of living system.

Numbers of evidences has begun to accumulate that tumor cells have the ability of secreting a variety of extracellular vesicle (EV) containing miRNA (2,4, 5, 6, 7). Several studies have suggested a functional role of extracellular regulatory RNA in cell-to-cell communication (8). In this manner, the extracellular RNA-based communication is widespread biological process. Thus, miRNA can be identified as a biomarker for human cancer diagnosis. To perfectly match idea that cancer cell can serve as a model for evolutionary approach, tumorogenesis are attributed two-way interaction, between cancer cell and microenvironment. miRNA may function as a either oncogenes or tumor suppressor under certain conditions, depends on their target mRNA(7). miRNA share its role in cancer through various mechanisms, including amplification or deletion of miRNA genes, as the Human papilloma virus 16 (HPV 16) does (9). miRNA has been found in vesicles by many of the cell types. EV- associated miRNA can travel long distances, in accordance with this, B and T cells release EV-associated miRNA, which increase significantly in the blood after vaccination with Influenca virus (10).miRNA and tRFs (tRNA derived fragments) predict the transformation of myeloid dysplastic syndromes to acute leukemia (6). miRNA has important role in the pathogenesis of B cell lymphoma (5). miRNA is abundantly expressed in normal germinal center cells, which are the cell of

origin for the majority of B-cell lymphomas. But, miRNA is down regulated in lymphoma cell lines and primary biopsies. They are abundant in both invertebrates and vertebrates species. Specific tRNA, tRNA for Glu – UUC, and tRNA for Arg – CCG, promotes metastatic progression by enhancing EXOSC2 expression (4).

This match idea that this type of cells can serve as a model for evolutionary up-down approach, going even deeper into the origin of genetic code and metabolism. Thus, all of this reminds to the origin of life on Earth based on mini-metabolic active membrane systems associated with small RNA fragments. To give some sense to it, the parallel between the surface metabolism (11), archaeal membrane system, and contemporary vesicles containing miRNA, has to be found, having in mind origin of metabolism. At the same time it has to compare primordial RNA (mnRNA) with miRNA seed region. Because both of them, RNA and membranes, co-evolved, making pivotal role in the living organisms. So that the application of this model, with the new adding hallmarks of cancer, moves to the pre-archaeal period, till the origin of biotic era. During the cancerogenesis, the eukaryotic functions slowly extinguish revealing ancient bricks of life. In this case, the retrospective point of view of growing cancer cell, as a model, could move up to 4-4,2 by backwards, until the appearance of small RNA molecules trapped in micro vesicles, i.e. some 200-400 million of years before origin of genetic code (12).

The central features for membrane composition isa invention of isoprenoid lipids before the advent of fatty lipids domain. In both cases, in archaeal lipids or in eukaryal fatty lipids, the membrane consist of macrocyclicbis-glycerol, either tetraetherisoprenoid lipids or tetraester fatty lipids. It is likely that both go back to a common biochemical precursor invented in early semi cellular form of life with isoprenoid lipids membranes (11), with a role in membrane metabolism and energy production. Surface-bonding chain extension proceeds through mevalonic acid ->isopentenyl pyrophosphate ->dimethylallyl pyrophosphate ->geranyl pyrophosphate ->farnesyl pyrophosphate ->geranylgeranyl pyrophosphate. In archaea, preny l transferases catalyse sequential condensations of isopentenyldiphosphate with alylicdiphosphate. The presence of fernesylgeranyldiphosphatesynthase (FGPP) synthesizing C25 isoprenyldiphosphate in archaea was proven, having C20 – C25 diether lipids in addition to C20 – C20 diether lipids commonly occurring in archaea (13). Farnesylgeranyldiphosphate synthase is clearly encoded from archa ealgerany lgeranyl diphosphate (GGPP), suggesting that FGPP synthase evolved from archaeal GGPP (13). This pathway is an enzymatically modified successor of a more ancient precursor. Archaealisoprenoid lipids chain are synthesized through the classical mevalonate pathway, as in eukaryotes, as a vestige of the primordial pyrophosphate, or even more ancient monophosphorylated pathway. Primordial cells are differentiated into archaea and bacteria by segregation of enantiomeric phospholipid membranes. Results indicate that common phospholipid polar head groups were present in surface metabolist, before differentiation into archaea and bacteria (14).

The amino acid sequence of archaeal GGR have a high similarity with these of FAD/NAD (P)H-dependent oxidoreductase, and these coenzymes have been shown to be sufficient for the activity of GGR. Genes responsible for the reductive conversion of a geranylgeranyl group into phytyl groups (chlP, bclP) have been identified in higher plants and bacteria (15), and in archaea (16, 17). This archaealreductase action is similar to the mechanism of reductase involved in the biosynthesis of fatty acids and chlorophyl. Thus, the evolutionary aspects of the sereductase might be intriguing, possible sharing same evolutionary capacity to construct membranous compartments, without needing to invoke undefined stochastic events (like symbiosis …). Saturated prenyl groups were found not only in respiratory quinines but also in membrane lipids in archaea. Thus, all above may be a denominator for membrane biogenesis, energy production, and coenzyme evolution.

The evolution of eukaryotic GTPase families can be explained by serial gene duplication event of the arhcaeal genes (18). In eukaryotes, the expansion of GTPase families through serial gene-duplication events has also been linked to an increase in compartments diversity over evolutionary time. The presence of large numbers of small GTPase in the Loki's genome provides strong evidence of ancestry in membrane identity, dynamics, and especially incompartmentalization (19). The ancient isoprenoid chain pathway was anon-enzymatic (no-genes) event. Connection between addition of lipid tails in surface metabolist and in eukaryotic "vesicles" with GTPase influence

confirm dictum: "Where there are genes for a given biochemical process, this means that this process is in a state of advanced development". Thus, membranes biogenesis, energy production, coenzyme evolution, was started at the same time, and at the same place; in the membrane composition of primordial membrane vesicles.

MICRO VESICLES

EV are small lipid bi-layered "roaming shuttles" released by normal or diseased cells which spread signals between them. The structure of the extant vesicles membranes can be seen as a vestige of primordial autothrophycally grown lipid membranes. EV are nanosized , membrane-bound body realized from cells. They consist of a lipid bi-layer similar to that of plasma membrane (20). The cargo of EVs includes, among others, the nucleic acids, especially miRNA. In archaeon *Ignicococcusislandicus*, cytoplasmic vesicles of 30-90 nm in diameter, and tubules up to 300 nm long, have been observed (21). The presence of these structures indicates that the capacity to construct membraneous compartments exist in archaea.

The minimal division machinery in crenarchaeota consist of an operon with three genes – cdv A, cdv B, and cdv C. Cdv B and Cdv C are related to the eukaryotic ESCRT-III protein sorting machinery (22), indicating shared common ancestry and similarities to endosomal vesicle formation and viral budding in eukaryotes. Cdv B homologs are implicated in formation of membrane vesicles and might be involved in excretion of enzymes (or probably small RNA) into environment. It seems likely that Cdv machinery is employed in cell division and/or vesicle membranes formation (23).

Archaea are capable of attaching glycan moieties to selected proteins (24). Like eukaryal glycoproteins, archaeal S-layer glicoproteins can undergo N- and O- glycosilation. N- linked glycan moieties of archaeal S-layer glycoproteins has released the wide variety of saccharides for glycosilation, suggesting the common origin of membrane systems for both archaea, and eukaryotes.

Only recently, it was shown that the oncogenic form of epidermal growth factor receptor, specific to glioblastoma, is released from brain tumor cells as cargo of EVs (7). Oncogene-carrying EVs of cancer derived EVs, was coined the therm – "oncosomes", found to emanate from protrusion of cellular plasma membrane (25). Oncosomes have recently been described as membrane-derived microvesicles secreted by cancer cells, which transfer oncogenic signals (miRNA), and protein complexes across boundaries (26). The ability to mediate the extracellular exit of transforming macromolecules can be used as a new hallmark of cancer. EV-associated miRNA (with the length of app. 22 nt) can both promote and suppress cancer progression. This fact provides basis for the hypothesis that cancer cells specifically package suppressive miRNA into oncosomes to promote cancer initiation (2).

MICRORNA

Recent results establish that functional active miRNA can be derived from tRNA, defining a new class of genetic entities. tRFs produced under hypoxic stress acts as a tumor suppressors through a post-transcription mechanism that lead to destabilization of many pro-oncogenic transcripts (27). Highly metastatic cells are capable of evading this mechanism by blunting the induction of tRFs during hypoxic conditions associated with cancer progression (27). This tRFs have been found in Argonaute protein complexes, and have thus been suggested to functions as miRNA. Ago2 is able to cleave target RNAs that are fully complementary to the small RNAs, suggesting ancient role of miRNA for the origin of tRNA(28). The functional characteristics of miRNA include: DROSHA-, and DICER- dependent biogenesis, physical association with Argonaute proteins, and ability to repress mRNA transcripts in a sequence specific manner. RNA folding determines the maturation of non-coding RNA. pri-miRNA are transcribed by RNA polII, and are usually capped and polyadenilated. They contain one or several hairpin secondary structure (29), making colorful world of the miRNA myriad molecules. Correct folding of pre-tRNA is assisted by the Lupus antigen, to prevent alternative folding going back to miRNA pathway, by mis-chaneling (29).

miRNA repress mRNA post-transcriptionally through binding to the 3' UTR of the mRNA with the miRNA seed region. Canonical, or core, seed region comprise a contiguous string of at least 6nt beginning at position two of the 5' miRNA. More precisely, the core seed region have been described as a 6-mer, 7-mer, or 8-mer. The 7-mer-A1, and 8-mer seeds required an adenine as the first nucleotide (30). The longer seeds, seeds of 7- or 8- nt, were more

evolutionary conserved than shorter ones (31). The seed types were termed by the start position relative to the 5'-end of the miRNA and the length of the consecutive seed match (32). 6-8 nt long seed sequence of the miRNA represent important feature for base-pairing with target 3'-mRNA UTR. In contrast to canonical targeting, non-canonical targeting did not lead to significant target down regulation at the mRNA level (33). miRNA suppress target expression at both the transcriptional and translational levels (34, 35).

Archaeal small regulatory RNA (sRNA), between less than 50 to more than 5OO nucleotides long, are able to target both the 5'-UTR or the 3'-UTR of respective mRNA. In archaeal genome hundreds of antisense RNA genes were identified (36). Complementarity of endogenous small non-coding RNA, especially miRNA, and seeds miRNA with intronict RNA, mature mRNA, with all over transcribed non-coding genome region were found. This points to the idea of the role of small RNA molecules in the construction of the DNA genome. It seems that origin of contemporary genome was originated from joined RNA fragments. From this one can conclude, or say, that robust DNA molecule did not replace RNA during the course of evolution, but that RNA subordinate DNA to its needs (Fig. 4.).

Long Cluster of Tandem Repeats (LCTR), which is typical for archaea, provided them with immunity against viruses. LCTR, also known as a CRISPR, arrays are transcribed into small RNA molecules (crRNA) which base-pair with invading viral nucleic acid (37). In archaea, crRNA matches mostly with viruses. These viruses carry anti-CRISPR based genome sequences (38). It is evident that viruses had means of baypassing that immunity, or vice vesa, that prokaryotes had means of "viral like" invading sequences present already somewhere in the nature. Thus, archaea are obliged to carry this part of sequences in their genome. It is evident that this part of sequences is older than prokaryotic counterparts, and that this sequences is one of the basis for RNA quided DNA genome development.

Cloverleaf tRNA appears to represent at least a second generation scheme (after mini-helix) and probably a third generation scheme, after microRNA seeds, that precede robust 31-nt minihelix. Evolutionary analysis of proto tRNA support the mini-helix model. The D and V loops show similarity to the acceptor stems, Ac and T loops are very similar in sequence. D loop is derived from a 17 nt micro-helix, part of 31 nt mini-helix. Ac loop (in position: 30-46) may had the ancestral sequence, the T loop also (39). Because of high conservation of the T loop in archaea, tRNA probably evolved in a single event, followed by acquisition of different anti-codon loops which have existed in the 31-nt proto-tRNAmini helix world (39). Ac and T loop (30-46, 52-68) are relicts of proto-tRNA probably after different anti-codons, joined by ligation.

The universal presence of A at the charging end of tRNA bespeaks the origin of the tRNA as replacement for A-bearing mono -ribonucleotide adaptors. This suggests that tRNAare at least a second generation of the RNA molecules. The end of tRNA is universally made of CCA sequence, so that the first tRNA arose by joining a CCA domain to a hairpin pre-tRNA, a process conserved in eukaryotes and archaea. The CCA sequence at the 3'-end of miRNA (mini helix) is acquired by nucleotide addition of future tRNA molecule (40). This piece of tRNA- an amino acyl mini helix, mixed with oligonucleotide that contained piromycine, and with imidazole as a catalyst, is capable of peptide bond formation (41). Which would be additional proof that mini helix is ancient part of tRNA. Overlapping between the detecting archaeal miRNA seeds, typically of 2-8 nucleotides (nt) of mature miRNA, and eukaryotic seeds, shows that miRNA evolve before the divergence of these two domains of life (42). This testified in favor that tRNA is a third evolutionary generation, after miRNA seeds, and miRNA mini helix world.

SCENARIO

In the following schematic presentations it can be seen the purpose of this proposal. Two pivotal entities guiding the evolution of life on the Earth: micro (extracellular) vesicles and mnRNA (seed miRNA – like sequences), Fig. 1.In humans, the pre-miRNA contains the hairpin structure, similar to that on Fig. 2 III, that is cleaved by Drosha. After the single – stranded miRNA was obtained, multiple possibility exist, including dsRNA synthesized on a complementary strand by elongation a small RNA bound to its target RNA, or DNA by reverse transcriptase using the miRNA as a guide. Similar situation exist after mini helix formation in Fig. 2.

Invagination of the endosomal membrane, catalyzed by the ESCRTsystem, leading to the extracellular vesicles formation. In animals, ESCRT pathway is caused by viruses, in the

process equivalent to the budding, similar to the Fig. 2.and 3.

Polynucleotide ligase join a diverse array of nucleic acids, including nicks that are present in single- and double- stranded breaks, by formation of phosphodiester bounds between the 3'-hydroxy group and 5'-phophate termini at the break. This protein ligate 20 bp double-stranded oligonucleotides, containing a single strand break, and also the RNA nicks present during miRNA processing. The ability of some ligase to nick joining for some RNA-DNA hybrid support the ideas that all nucleotidyl transferase, also present in archaea, are derived from a common ancestor (43).

This type of enzymes can be used during the DNA repair (44). Several reports demonstrated acritical role for RNA-processing enzymes and small RNA molecules in DNA repair, indicating an evolutionary conserved mechanism. This small RNAs appeared to be produced from the degradation of longer RNA molecules. A number of reports implicated RNA in double-stranded DNA repair, connecting novel species of small RNA, which appears to be derived from the vicinity of DSB. The same situation is with miRNA-processing, connecting these two pathways. In the human genome app. 98% sequences belong to the non-coding region. Rest of the genome is transcribed into premature mRNA. Huge majority of the non-coding DNA is transcribed into the myriad of non-coding RNA, further processed in large and small RNA, including miRNA, reverse situation from that on the beginning of "RNA-first" genome development (Fig. 4.).

It is interesting to compare place of miRNA processing and miRNA seed region, with mn RNA, and mini helix RNA biogenesis, many reciprocal details can be observed (Fig. 5.).

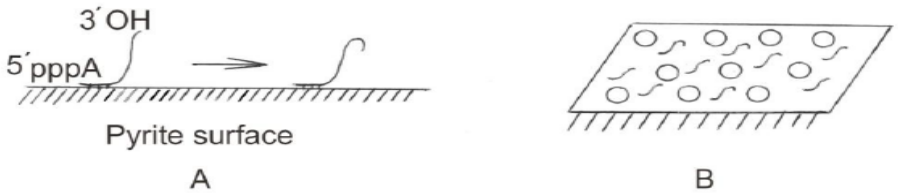

Fig1. *Starting position. The ancient "miRNA seeds region" can found it complementary mRNA sequences in the extant genome. This fact speak in the favor that first genetic code was that region. In many cases, miRNA-target mRNA interaction is mediated by the seed region of 6 to 8 nt long fragments that are complementary to the cognate target. These mini RNA (mnRNA) seed fragments are at the 5'-end of miRNA. It can be that these mnRNA are ancient part of mini helix, this is in frame of the present model of retrospective evolution, making of tRNA third generation of RNA world.*

A) 6 nt sequence of seed region, mostly situated at position 2 – 7 from the miRNA 5'-end, play crucial role in miRNA targeting. Extention of the mnRNA, evolution of mini helix tRNA, by monoribonicleotide terminal extension or oligoribonucleotide addition, ligation, to app. 22 nt. Network of different functional mini helix RNA sequences, making colorful origin of geneticcode.

B) Carpet of the surface membranes with mini helix RNA sticks on the pyrite surface, in the life favorable microenvironment.

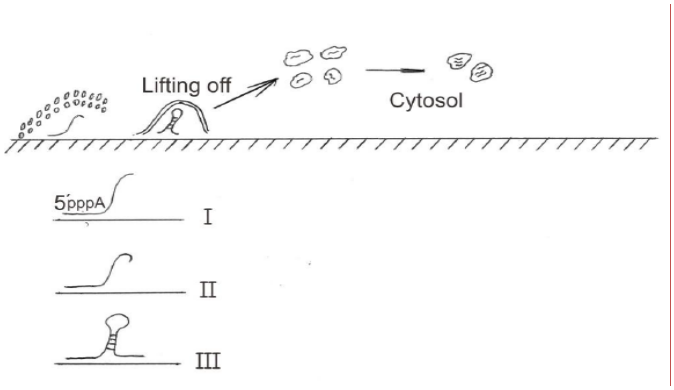

Fig2. *Future development. RNA have a tendency to self protection by wrapping into the membrane vesicles. The first folded RNA molecule have hairpin or miRNA mini helix –like structure. Membrane system of surface metabolist are detached, wrapping hairpin miRNA mini helix and lifted off the pyrite surface. From this point,*

several possibilities exist, making colorful origin of life. One of them is a basis for gene compartmentalization, like in the Influenza virus. The resulting hairpin RNA in the vesicles is similar to the event after viral budding. At this very moment the EV contain mnRNA helixes, few FeS molecules, and cytosol with the same salt concentration like in the contemporary cytoplasm.

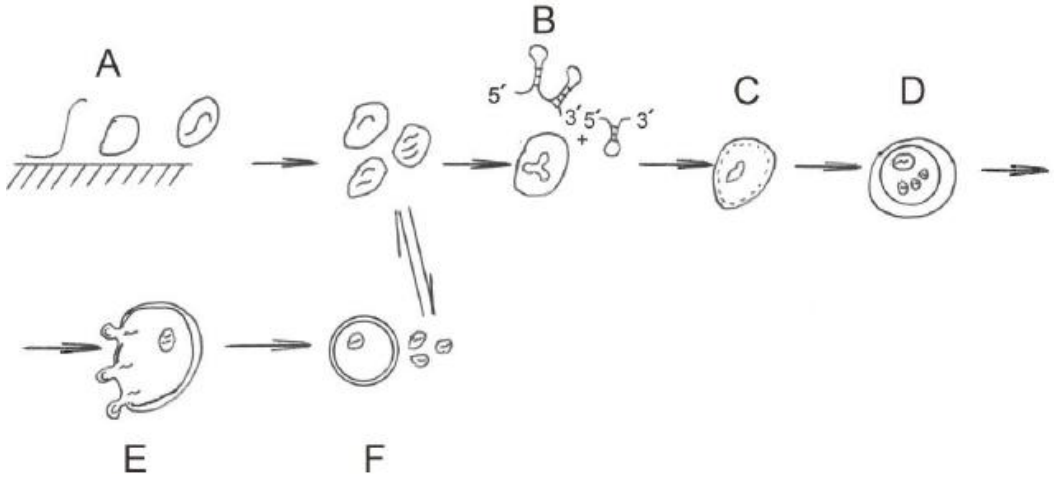

Fig3. *Simplicity to complexity development, from the cancer cell point of view*

A) 0,3 by after Earth formation, miRNA seed region and vesicles establishment;

B) 0,7 by after tRNA maturation;

C) 1,7 by origin of Archaea;

D) Origin of eukaryotes;

E) Budding and liberation of the oncosomes from cancer cells, launching off the miRNA;this remaining themini helix RNA wrapped into membrane vesicles.

F) identical situation with vesicles containing mini helix and oncosomes;

Above B), formation of double-stranded RNA complex from few single-stranded mini helix RNA molecules (like in the 45).

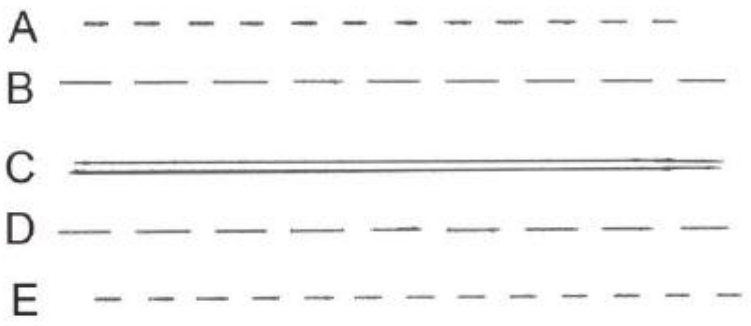

Fig4. *DNA did not "replaced" RNA during the course of evolution. It is better to say that RNA is underpinned DNA during the course of evolution.*

A) myriad of different mnRNA,, miRNA seed;

B) RNA oligomerisation;

C) DNA;

D) whole genome transcription;

E) myriad of different small and big RNA, miRNA, snRNA , miRNA seed,..., as a result of RNA processing.

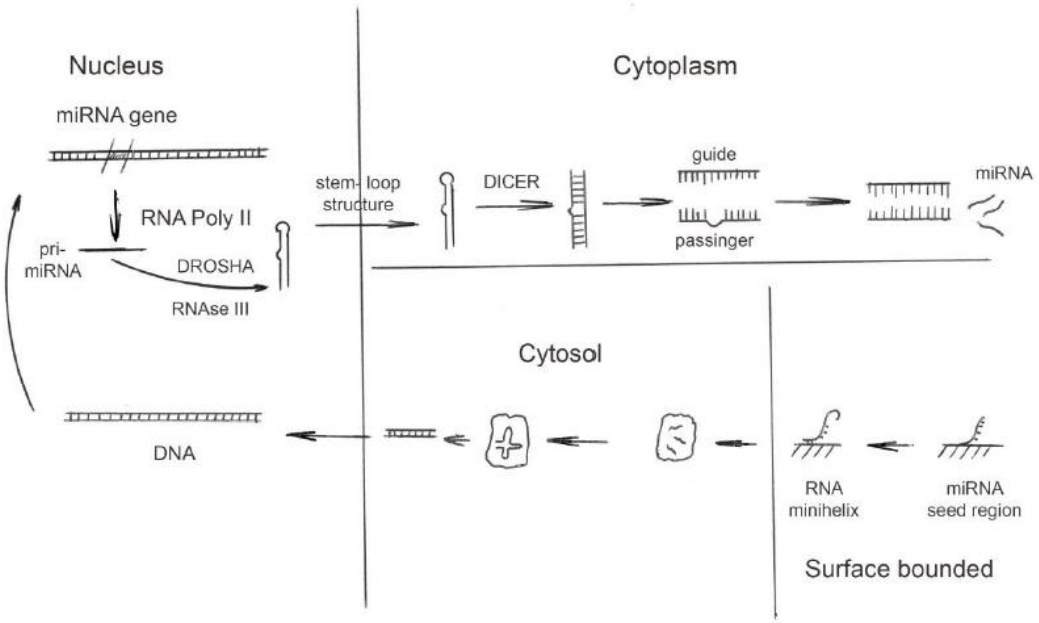

Fig5. *Comparation between miRNA processing and miRNA biogenesis. Records of molecular evolution are preserved from deepest antiquity (4 – 4,2 by) in miRNA primary, secondary, and tertiary structures, til the cancerogenic cells status. miRNA processing, in normal and tumor cell, start in nucleus (app. 20 – 22 nt in lenght) and terminated in the cytoplasm. mnRNA biogenesis starts in cytosol and terminated in the nucleus (app. 20 nt in length). Pre-miRNA can be seen as a mini helix, and miRNA seed region as a surface bounded small mnRNA.*

CONCLUSION

Organisms evolve from ancestral to extant entities, inherited biological pathways for four billion of years. In multicellular host, archaeal form of life subvert the "host" biochemical reactions and induce eukaryotic cell to provide growth factor for them. During the cancerogenesis, the eukaryotic functions slowly extinguish revealing ancient bricks of life. The malignant cells emerge as selfish individuals, independent from a cell community.

The miRNA processing is under multiple levels control: at the level of miRNA transcription, DICER, DROSHA, DEAD-box helicase, SMAD, KSRP, methyl transferase, DGCR8 action, etc. The underlying mechanisms of miRNA dysregulation in human cancer include defects in miRNA biogenesis, chromosomal abnormalities, changes in transcription, epigenetic changes, including mitochondrial dysfunction. Cancer, as a phenomenon, is engaged in all panoply of the fundamental biochemical reactions. After all, which kind of biological manifestation, or sobering, the cancerogenesis is? This phenomenon cause its own consciouslysuicide. Message from cancer cell can be seen in the miRNA processing, and miRNA – vesicles biogenesis.By this way,with hairpinned miRNA wrapped into vesicle's protection system = miRNA wrapped into oncosomes, ancient RNA world roaming across the human body. Thus, the cancer cell can help in investigation of the development of life, taking in mind dysfunction of all fundamental pathways in the cell. There are no investigation in this direction, but it will be useful to go in that way.

The origin of life is not a simple transition from non-living to the living entities. To known exactly how life occurs on the Earth, first of all we have to known the definition of life, what life is it. In the previous article there is statement for the origin of life: "Aquatic polymerization of the essential tricarbonate molecules on the mineral support at 100°C, 20 m beneath the ocean, and light driven membrane protection assembly" (46). Contemporary, by the cancer as a model for retrospective study of life's development it is possible to go back up to 4,2 by. To go deeper into the origin of life principle, before it appearance on Earth, another approach has to be used. Definition forthe life is than: "String, water, and nucleic acid, united by mislion, results in life" (47). To understand what is going on, it is important to wait till the ribosomal organelle evolution (48).

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