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MicroRNA: from fundamental research to their application

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MicroRNAs (miRs) are small non-protein-encoding RNAs of 20-30 nucleotides long. In eukaryotic cells miRs play the role of bioregulators of gene expression through the mechanisms of translation repression/modulation. Here we both familiarize the readers with miRs biogenesis, functioning mechanisms, and strategy of their discovery and present the list of biological processes, regulated by miRs. We also list the publications, dedicated to miRs role in human pathologies (carcinogenesis in particular) and their application for marking, prevention, diagnostics, and therapy of cancer.

Key words: microRNA, biogenesis, expression profile, bioinformatic, microRNA-prediction, bioregulation, carcinogenesis, therapy.

Introduction. The beginning of the century was renowned for one of the greatest discoveries, which could be compared with the discovery of double stranded DNA by James Watson and Francis Crick or with the discovery of reverse transcription by Howard Temin and David Baltimore. This discovery can be considered to be the revolutionary one as it not only supplements our ideas on growth regulation and differentiation of cells and widens the ideas on various cell metabolism and the processes of development of the organism but also helps to perceive the paradigm of medical treatment of various diseases, especially cancer diseases and diseases of development, based on the aforementioned knowledge. This is the discovery of minor RNA molecules, capable of inducing RNA-interference.

Two groups of minor interfering RNA. The two groups differ in biogenesis and in the role they play in organisms, yet have many common features in the mechanisms of their functioning. The class of minor RNAs is represented by small non-coding RNAs (snRNAs), 20–30 nucleotides long. Functioning of snRNA results in silencing of gene expression at transcriptional and post-transcriptional levels due to complementary interactions as a part of ribonucleoprotein (RNP) effector complexes with their DNA- (level of transcription) and RNA- (level of translation) targets [1]. In this paper we describe only the second (from the point of view of chronology of discovery) group of snRNAs, *i.e.* microRNAs, miRNAs, or miRs.

However, prior to discussing miRs we need to mention the first group of snRNAs – small interfering RNA or siRNAs. This group is represented by double-stranded spiral RNA, 22 and 28–30 nucleotides long which are due to occur after splitting of large double-stranded RNA by RNAase III endonuclease, also known as Dicer [2, 3]. According to the source of dou-

ble-stranded RNA in the cell, siRNAs can be classified into two sub-groups, which are specific for different biological effect and different functions. Unlike double-stranded RNA, which are delivered into the cell by viruses and transgenes or occur after aberrant synthesis of RNA, "diced" siRNAs of 22 nucleotides long function as the mechanism of cell protection from non-specific allogenic RNA, and present a sort of immune response at the level of RNA [2]. If double-stranded RNA is synthesised in the cell in the natural way from genome region, which includes centromeres, transposons, telomeres or repeats, "diced" siRNAs of 28–30 nucleotides long take an active part in the epigenetic processes, resulting in silencing of genes at the level of transcription [4].

That is about all we wanted to mention in regard to the first group of snRNAs – siRNAs – to emphasize the principal differences from the second group of small interfering RNA – miRs.

Different aspects of genome organisation, biogenesis, regulation of transcription, functioning of miRNAs and their role in the regulation of differentiation and cell growth, as well as the development of organism and various cell processes are the subject of reviews [5–7]. Hence, the aim of current review is to turn the attention of molecular biologists onto these tiny bioregulators, which, apparently, take part in all cell processes.

Distribution and localisation of miRs genes. The principal difference of miRs is their endogenic origin, *i.e.* cell genomes contain miR genes. The latter were discovered in almost all representatives of eukaryotes and in large DNA-containing viruses (except for RNA-containing human immunodeficiency virus (HIV)) [8], genome of which is incorporated into the host genome. Usually miR genes are localized in the intergenic region of encoding chains as single genes or their clusters [9]. They are located in the intron regions of encoding genes (intronic miRs) [10, 11] and in transposon elements [12].

miRs biogenesis. There is hardly any information on the initiation and regulation of transcription of primary transcript (pri-miR) for miR as well as on the factors, regulating expression of miRs. Regulation of miR-155 expression was shown in Burkitt's lymphoma to take place at two levels: i) level of transcription, involving proteinkinase C and nuclear kappa B factor and ii) level of processing via yet undiscovered mechanism [13].

Lee *et al.* [14] identified numerous regulatory elements, located in 5 -positions towards miRs genes, known to be significant for transcriptional and post-transcriptional regulation of expression of miRs. Fukao *et al.* [15] revealed that miRs are predominantly controlled by unique *cis*-regulatory elements, which co-develop with miRs sequences. These data reveal the possible participation of well-characterized transcription factors, protein-encoding genes, in the expression of miRs genes. miRs along with transcription factors make the regulatory networking, controlling thousands of genes, possibly including expression of miRs genes [16]. The latter were shown to be co-expressed with their mRNA-targets. At the same time mammalians were demonstrated to have two classes of cyclic expression co-regulation of miRs and their targets with positive and negative feedback [17], which involves miRs as stabilizing and destabilizing factors in the dynamics of the gene expression [18]. Apparently, transcriptional regulation of miRs gene expression is controlled via some epigenetic mechanisms [19–21]. The mechanisms, based on single nucleotide polymorphism [22–24] and A I-editing of the predecessors and mature miRs [25–29] can be possibly included to the list of mechanisms of post-translational regulation of expression of miRs genes.

In case if miRs genes are located within the intergenic region, pri-miRs are transcribed with RNA-polymerase II [30, 31], at the same time, if they are localized in introns, then the production of pri-miR is also supplemented by the mechanism of RNA splicing [10, 11]. In some cases miRs are transcribed by RNA-polymerase III. Thus, authors of [32] demonstrated that the cluster of miRs genes, located among *Alu*-repeats on human chromosome 19, is transcribed by RNA-polymerase III but not RNA-polymerase II.

It remains unknown whether it is a unique case or a rule for miRs genes, located in genome regions, transcribed by RNA-polymerase III. Authors in [33] determined the majority of the investigated miRs genes of nematode, human, and two plant species to possess the same type of promoter specific for protein-encoding genes (TATA). However, a significant number of

genes are of indefinite type. The authors developed a new method of foreseeing the promoters, reminding *cis*-acting elements, for transcription initiation. The value and the secondary structure of transcribed pri-miRs may vary significantly [31]. Length-wise they may be from 100 to several thousand nucleotides long. There are cases of pri-miRs, specific for poly-A-sequences and cap structure, *i.e.* capable of performing functions of mRNA [34]. The specificity of secondary structure of pri-miRs is the presence of hair-loop structure – hairpins – regardless of their length [35]. In some cases, they may contain 1–2 hairpins [36] or several as in the case of cluster localization of pri-miR genes [9, 37, 38].

The next stage of miR biogenesis is the splitting of pri-miR in the nucleus by RNAase III, also called Drosha [35]. Scheme of miR biogenesis is presented in Fig.1. Drosha chips off the hairpin out of pri-miR – miR precursor, pre-miR. Certain rules have to be abided regarding the structure of pre-miR hairpin as a part of pri-miR for successful chipping off by Drosha. Split takes place between several (1–5) non-paired bases, then hairpin stem, containing not less than 10 b.p., is split. Hairpin stem may include non-paired bases as well. The most successful splitting occurs at the presence of branchy non-paired chains at the hairpin base. Chipping off takes place at the base and captures 1–2 nucleotides of the hairpin stem. The length of pre-miR may usually vary (50–80 nucleotides). Hairpins may include non-paired bases of both arms (5 and 3), forming symmetrical loop, and of one arm only – asymmetrical loops (up to 10 b.p.). Yet exceptions may occur. The presence of pri-miR hairpins in plants is not considered to be the rule. pre-miR hairpins, if they are processed, vary significantly in length (from 60 up to 300 nucleotides) and in shape [39, 40]; *e.g.* pre-miR-169, 196 nucleotides long, contains one asymmetrical loop, 44 nucleotides long, in each of the stem arms [39]. In most of the cases, mature miRs are chipped off double-stranded extended pri-miR regions, which do not necessarily form hair-pin loop structure [40]. Later on we will discuss some possible reasons of such exceptions.

Drosha enzyme is known to function in the human body with RNA-binding protein, called Pasha or DGCR-8 [41] (Fig.1). In this tandem Pasha acts as pri-miR binding protein, while Drosha provides nucleolytic activity of the complex. Pasha protein consists of 773 amino acid residues and contains N-terminal domain (1–275), responsible for nuclear localization, two domains in C-terminal region, responsible for pri-miR binding and one domain (692–750) is responsible for binding with Drosha [41]. Authors of [42] suggested the model of recognition of pri-miR by DGCR-8 protein on crystallographic structure of core region of 429–720. Crystallographic structure of C-terminal domain of Dicer, responsible for production of miRs, was studied by Takeshita *et al.* [43]. Drosha in mice is represented by a complex of two subunits, one of which is DEAD-containing helicase subunit which recognizes pri-miR [44].

The next stage of miR biogenesis is export of pre-miR hairpins, chipped off pri-miR, from the nucleus to cytoplasm [45–47] (Fig.1), carried out with the participation of protein translocation factor Exportin 5. In cytoplasm pre-miR interacts with Dicer endonuclease, which cuts double stranded intermediate product miR/miR*, 20–25 nucleotides long, out of the hairpin. This product initiates the formation of effector RNA-induced complex, resulting in silencing of genes, *i.e.* RISC – RNA induced silencing complex, the main protein components of which are Dicer, helicase, RNA-binding protein, and argonaute-protein, responsible for the formation of RISC [5–7, 48–52]. In *Drosophila* Dicer-processing enzyme as a part of RISC-complex functions in tandem with RNA-binding protein Loqs, which results in the formation of intramolecular dimer [48]. Authors describe "functional anatomy" of Dcr-1/Loqs-complex and details of pre-miR splitting mechanism.

Helicase is known not only to untwist miR/miR*-duplex but also to be a significant component of miR metabolism. Along with other components, helicase takes part in "loading" of RISC-complex [49].

Plants are specific for a different mechanism of splitting. They possess four Dicer-like enzymes [50]. In *Arabidopsis*, DCL-1 protein and two other proteins HYL-1 and SE form an intramolecular complex, which is included into SmD3/SmB-body, localized in the nucleus [51]. The authors put forward a supposition that DCL-1/HYL-1/SE-complex is involved into miR pro-

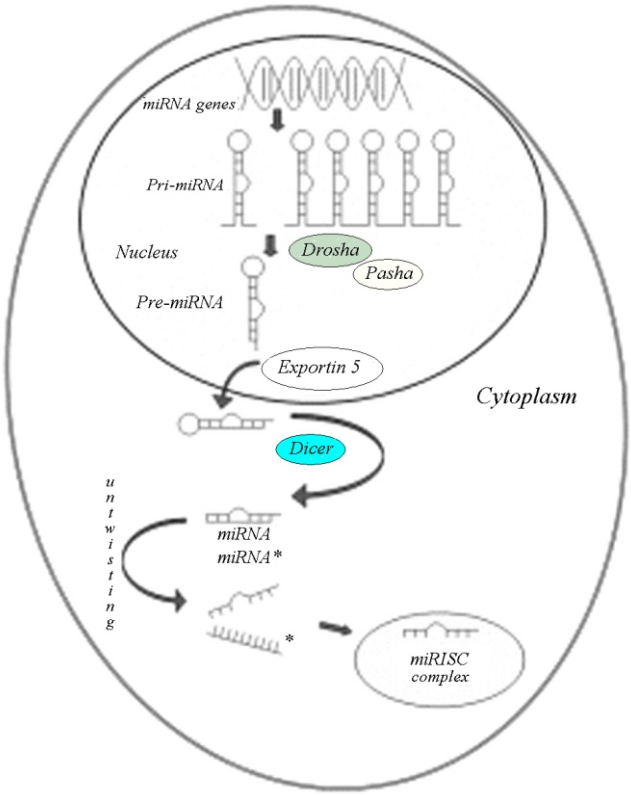

Fig. 1. Scheme of miR biogenesis. See text for details.

duction in the nuclear SmD3/SmB-bodies. These data are confirmed by results in [52]. Dicing (D)-bodies, as defined by the authors of [52], take part in "symphonic" processing of pri-miR–pre-miR–miR in nuclei of plant cells. The facts mentioned (the existence of four DCL-enzymes, nuclear localization of D-bodies) allow supposing that plants are specific for the absence of intermediate product of miR-metabolism – pre-miR – and the above mentioned abnormal hairpins are the discovered pri-miRs.

Helicase in RISC-complex or in D-bodies untwists miR/miR*, passenger miR* chain is eliminated, and RISC remains with complementary chain of 20–25 nucleotides long, *i.e.* mature miR. Mature miR may be processed from either 5 - or 3 -arm of pre-miR, or from both arms. The latter fact is supposed to depend on thermodynamic stability of 5 - or 3 -arms of pre-miR. The cells usually choose the least stable miR and destroy the other one. Nevertheless, Ro *et al*. [53] demonstrated that in some tissues both chains may be accumulated as paired miRs until they are not subjected to the selection in other tissues. Both miRs are capable of suppressing expression of their genes in such tissues. Mammalian miRs may be imported back to the nucleus in some cases.

Thus, authors of [54] revealed that specific miRs sometimes contain additional hexanucleotide element in 5 -terminal sequence, which determines their subcellular localization. The same authors demonstrated that having joined miR-296, the mentioned terminal motif controls its nuclear import. The accumulation of mature miR in the nucleus was also shown in [55], where the authors defined that rat miR-206 is associated with forming ribosomes, as well as with 28S rRNAs of functioning ribosomes in cytoplasm. This is a short review of the mechanism of miR gene expression. We may also suppose that plant miRs, formed in the nucleus, are exported into cytoplasm.

Mechanism of miRs functioning. How does the mature miR function? The model of miR functioning is presented in Fig.2. Having remained in RISC-complex miR becomes a "guide" for miRISC-complex. It guides effector RNP-complex to the target, which is presented by mRNA and where mature miR finds its complementary region. Due to miR complementarity with RNA-target the complex is retained on mRNA, inhibiting the process of translation [45, 46]. Long *et al.* [56] revealed the influence of secondary structure of mRNA-target on recognition of its miRs. They also supposed the existence of two-step reaction of hybridization of miR and mRNA. A I-editing of miRs and their targets influences the repertoire of mRNA-targets for miRs and redistribution of targets [26–29]. The mechanism of inhibition is of two sides and is known to depend on the degree of miR complementarity to its target. If miR is complementary in its 5 - and 3 -terminal sequences, 5–7 nucleotides long, and is not complementary in the center (5–7 nucleotides), forming a ledge, then the complex is placed on 3 -untranslated region (3 UTR) of mRNA. In this case the process of translation is inhibited. The selection of targets is influenced by some specificities of 3 UTR [57–59]. It was shown that successful inhibition is achieved with 5 miR end, while 3 -end variability is possible [60–62]. There may be several binding centers on 3 UTR. For instance, mRNA lin-14, encoding nuclear protein, necessary for transition of *Caenorhabditis elegans* larva

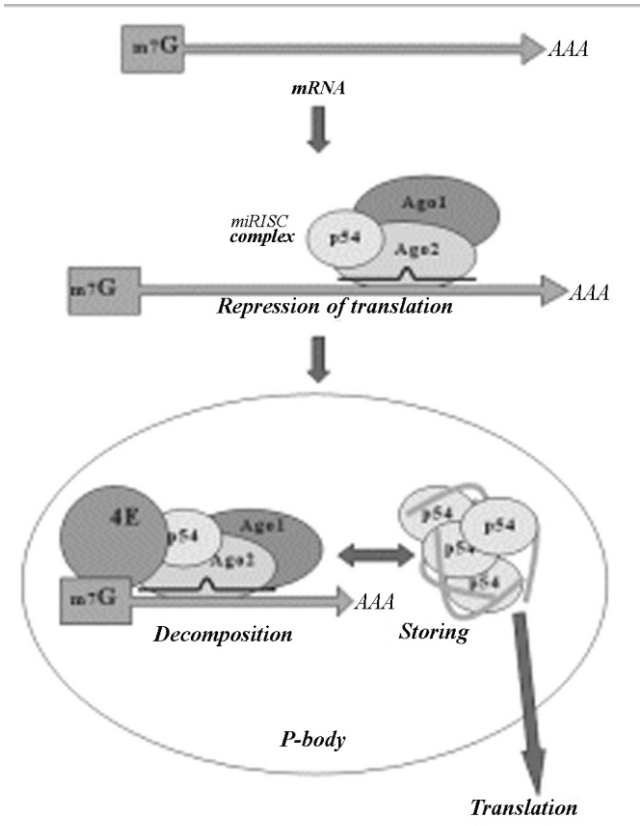

Fig. 2. The model of miR functioning. See text for details.

from age 1 to age 2, is known to contain seven binding centers with miR-lin4 [63]. The investigation of the mechanisms of inhibition has been commenced only recently [64] and it is far from giving clear results. There are several mechanisms, different in fine details of molecular interaction of RNA and protein components – the participants of this complicated process [47, 65]. We will not take time to describe the details but will name only some stages of this process. Repression is known to require cap-structure and poly-A-sequence [66-69], and to occur after translation initiation [70]. Evident is the fact that binding of miRISC with mRNA-target takes place in polysomes. Thus, exponentially growing HeLa cells showed the majority of three miRs to be associated with actively translated mRNA, while human miR-let7a blocks protein synthesis on actively translating lin-41 mRNA polysomes, assisting in accumulation of growing polypeptides [71, 72]. Polysomes were precipitated in saccharose concentration gradient together with miR-let-7a and Ago-protein. Supposedly, miRISC blocks protein synthesis, contributing to fast descent of ribosomes with growing polypeptide chains during translation elongation [47, 65]. The destiny of the latter remains uncertain, yet some suppositions are presented in [47, 65]. Later on it has been determined that inhibited mRNA along with miRISC is associated with P-bodies (Fig.2) [45–47]. The authors of [73] showed that realization of mRNA out of polysomes is insufficient for the initiation of P-bodies assembly – released mRNA should take part in inhibition of metabolism, initiated by miR. The authors made the conclusion that P-bodies are not obligatory for functioning, but are the consequences of metabolism of silencing of genes with the participation of miR. P-bodies contain high concentrations of enzymes and factors, necessary for repression of translation or mRNA turnover. In this situation two variants are possible: i) miRISC interacts with decapping proteins and translation initiation factor 4E, at the same time assisting in the inhibition and splitting of mRNA; ii) mRNA interacts with helicase protein p54, oligomerisation of complex p54–mRNA takes place and mRNA is preserved till better times. When necessary, this preserved mRNA may enter the translation cycle again [45, 74]. However, it remains unknown how the cell selects the way of realization. Besides, this scheme was determined for miR-let7, which is commonly known to split mRNA-targets, regardless of its incomplete complementarity (poly-A-sequence is chipped off) [47, 65, 75].

This is the first supposable mechanism of inhibition of translation with miR, which is based on incomplete complementarity of miR and mRNA target, as a part of miRISC-effector complex, which engages miR "guiding" role, and effector protein p54 determines whether RNA should be split or preserved for further repeated translation [45].

The second mechanism of inhibition of miR translation in plants is the cutting of mRNA-target according to siRNA mechanism [39, 76, 77]. Similar mechanism was shown on one of miRs of BART2 of Epstein-Barr virus (EBV) [78]; it is performed in the cases when miR is completely complementary to its target. The splitting takes place via the centers of complementary regions. It is obvious that the selection of mechanism of inhibition depends on the complementarity of the central region of

miR ~7 nucleotides long. Interestingly, in some cases the splitting, initiated by miR, results in the formation of siRNA out of mRNA splitting products [40, 76, 77]. Sometimes 5 -product of mRNA splitting does not synthesize siRNA. Some scientists believe that these unsplit 5 -products may be functionally necessary for plants. It is supposed that splitting of mRNA, resulting in siRNA formation, takes place outside of P-bodies.

The data of the type and place of miR splitting are rather controversial. There are some works that claim that splitting in some points takes place in endonuclease containing P-bodies [79]. However, it contradicts the data, obtained on miR-166 in *Arabidopsis*, the target for which is mRNA of PHV gene [77]. This work demonstrates that miR-166, completely complementary to its target, assists in splitting of mRNA, 656 nucleotides long, and the accumulation of 5 -terminal product of splitting, 500 nucleotides long. Dicer of RISC-complex, initiated by miR-166, acts as multiple-use enzyme, as one complex splits ~30 target molecules. This mechanism is unlikely to be the same if the complete splitting took place in P-bodies with endonuclease assistance. It is the most likely that the split in one point takes place in P-bodies according to the second type, with the accumulation of 5 -half of mRNA, as it has been shown for let-7 [45].

Up to this moment we reviewed the works, proving down-regulation of translation in case of miR binding to 3 -UTR mRNA (mammals, invertebrates) or to the encoding mRNA region (plants). However, miRs may also up-regulate mRNA, modulating the process of translation [80–82]. miRs can modulate binding centers for proteins, interacting with mRNA [80, 82]. It is supposed that binding of one or more miR to mRNA may result in conformational changes in mRNA, and consequently, to revealing or masking of additional regulatory elements on mRNA. This may occur in case of location of miR binding centres within 5 -non-coding region of mRNA-target. Up-regulation of expression of hepatitis virus type C was demonstrated during the interaction of miR-122, specific for host liver, with 5 -region of viral RNA [81]. Two miRs, interacting with 5 -region of their mRNA-targets, were discovered in plants (*Arabidopsis*) [83]. Evidently, modulation of translation process is performed when miR is bound to 3 -UTR mRNA and is accumulated in P-bodies for recurrent translation, which was demonstrated for human let-7 miR [45].

On the basis of revealed mechanism of miR functioning a definite conclusion can be made that biological effect of miR depends on proteins, encoded in their mRNA-targets, as well as on the processes these proteins participate in. But before proceeding to that we need to mention the methods of discovery and identification of miR.

The strategy of discovery and investigation of miRs. As of today some strategies of discovering and investigating individual miR have already been developed, and some are still being elaborated, mainly including two basic approaches, namely biochemical and bioinformatical [84, 85]. Biochemical approach uses total RNA, extracted from tissues, divided by either gel-filtration or electrophoresis in 15% polyacrylamide gel, containing sodium dodecyl sulfate and 7M urea, in order to isolate and to identify miR. The zone of low-molecular RNA (20–30 nucleotides) is modified and amplified with subsequent cloning and sequencing. The methods developed allow identifying miRs, different in one nucleotide, in 25 pmoles [86]. Thus, this is the way individual miRs are isolated and numbered. Besides, there is one work on isolating a specific 15S-complex of miR from RNP, containing 40 individual miRs, from HeLa cells [87]. Some methods developed are aimed at the identification of miRS expression profiles [88, 89], *i.e.* identification of time of appearance, synthesis, and elimination of miRs in the organs and tissues during carcinogenesis. Wang *et al.* [88] developed accurate and sensitive method of miRs profiling, which allows discriminating RNA in the cell degree- and sequence-wise and determining individual miRs in tissues, held by formalin and covered with paraffin. Work [90] can be an example of description of expression profiles of 23 miRs in carcinogenesis of *Drosophila* at the embryonic stages, and larvae of three different age groups *i.e.* prepupal, pupal, and adult female. This work demonstrates that some miRs are synthesized constitutively during carcinogenesis (miR-1, miR-8), others at the stage of embryo only (miR-2, miR-3), and some – miR-34 – at the stage of larva, and are synthesized intensively in adult specimen, whereas miR-125 and let-7 – only at the stages of pupa.

Let us have a look at the bioinformatical approach to investigation of miRs. Computer programs are being developed to predict the presence of hairpin-loop structures (pre-miR) and mature miRs as parts of these hairpins [91–94], as well as the presence of mRNA targets for miR [61, 85, 95–102]. The prediction of pre-miR and mature miR hairpins is based on one criterion: candidates for pre-miR should possess specific secondary structure of hairpin-loop shape, 60–100 nucleotides long, with several symmetrical or asymmetrical "bubbles" (several unpaired bases). Mfold computer program is the most wide spread [91]. There is also RNA fold-L-100 program [92], which is capable of differentiating real hairpins from pseudo ones among numerous pre-miR candidates with free folding energy >23.00 ccal/mol. To predict the presence of mature miR among pre-miR candidates there some computer programs like miRSeeker and miRScan, which select hairpins of 100 nucleotides long and total rating of >10. miRSeeker [93] and miRScan [94] are based on the criterion of conservatism of adult miRs, thus they select candidates after obligatory comparison of two related hairpins. This is main disadvantage of the mentioned computer programs and thus, the reason of their limited application, especially in the investigation on miRs, encoded in the genome of viruses. Biochemical approach confirmed that these computer programs do not identify many real miRs, they select the most probable ones, and then "real" hairpin-candidates, containing mature miRs. However, pri-, pre-, and mature miRs, predicted using this method, require additional confirmation of the fact that the precursors are the substrates for processing enzymes (Drosha, Dicer) [103]. Authors consider miRs, successful in passing this sort of selection, can be named the real miRs and unsuccessful ones – precursors. Bioinformatical investigation is usually confirmed by biochemical one (profiles of miRs expression, isolation of individual miRs and their sequencing) and visa versa.

Participation of miRs in cell process regulation. What are the results obtained for the last five years since the discovery of miRs in 2001 [104]?

First of all, all eukaryotic genomes investigated up to date contain miRs genes. The number of different miRs in different organisms is tens and hundreds in one organism. E.g. the number of miRs genes in human genome is supposed to exceed 1 000 and may even reach 20 000, which is over 3% of encoding genome capacity, they may also control 30+% of genes [5–7, 105, 106]. Even such small size-wise genomes as genomes of viruses contain up to several tens of miRs [8, 107, 108]: EBV – 32 miRs [8]; rhesus lymphocryptovirus – 22 miRs; Kaposi sarcoma associated virus – 17 miRs; human cytomegalovirus – 14 miRs; mouse gamma herpes virus – 10 miRs [8]; human immunodeficiency virus – 10 miRs [107]; Marek's disease virus – 8 miRs [108]; simian SV40 – 8 miRs; herpes simplest virus – 1 miR [8]. At the same time one miR may have tens and hundreds of different targets [5–7, 109]. Different transcription factors and many other protein-factors prevail among miR targets. Protein synthesis is regulated indirectly via the processes of transcription – down-regulation (suppression of synthesis) and up-regulation (restoration of synthesis). However, miRs are capable of not only suppressing translation (down-regulation) but also restoring it (up-regulation) [81, 82, 110].

Due to the effect on the process of transcription, miRs act as real regulators of numerous processes. Taking into account the fact that profiles of miRs expression are specific to various tissues, organs, and stages of carcinogenesis, it is clear why miRs are involved into control and regulation of processes of development, starting from embryogenesis [111–115] and up to adult organism [116–118], processes of differentiation [119–121] and cell growth [122–124], processes of tissue formation [111, 119, 125] and of separate organs [115, 116, 118, 125–127]. miRs control self-identification and differentiation of stem cells [113–115, 128], processes of proliferation and apoptosis [121, 129–134], they take part in the signaling systems of cells [135], in the regulation of endocrine [119, 136] and nervous [5, 119, 137–141] systems, they function in hematopoiesis [5, 119, 120, 142–144], spermatogenesis [145], immunogenesis [146–151]. miRs possibly take place in alternative splicing [152] and together with siRNAs in epigenetic processes [153–156]. They are also involved into the metabolism of low-molecular compounds [157–161] (amino acids [158], lipids [159], glucose [160], phosphates [161]) and in the regulation of cell osmotic pressure [162]. miRs were shown to participate in the

regulation of protein-protein interaction networking in humans [163].

miRs play the significant role in virus-cell interactions [8]. Generally these are miRs, encoded by large DNA-containing viruses, integrated into host genome, and retroviruses. Yet this is a whole different topic, which requires special attention.

miRs and diseases. Fundamental investigation of biogenesis and functioning of miRs attract special attention due to their involvement in various pathologies [105, 121, 131, 155, 164–170], inflammatory processes [171] and stresses [167, 169]. Nowadays the methodology of studying the expression profiles of cell miRNAs in norm and pathologies is in progress [104, 106, 121, 131, 172–180]. There also occur some papers on the role of miRNA as a tool in the management of embryonic development and classification of human tumours [121, 174]. On the basis of these works the supposition can be put forward that programs of development in all investigated organisms represent specific examples of miRNA expression profiles and disorders in these profiles correlate with different pathologies, in particular, virus infections [181] and carcinogenesis [106, 132–134, 173–179, 182–192]. Currently it has been shown that neoplasias are characterized by specifically changed profile of miRNA expression [121, 173–179, 189, 190, 193–198]. Not only changes in expression profiles but also the occurrence of specific miRs have been detected in various tumours [190, 193, 199–203]. Interestingly, both oncogenes and tumour suppressors may be considered as miRs [131, 176, 177, 185, 199–212].

RNAi-therapy. Totally new strategy of marking, diagnostics, prevention, and treatment of diseases is being developed due to the study of new miRs and their expression profiles [106, 121, 169, 175–180, 184–187, 203–205, 213–218] which involves the application of genetically and chemically modified miRs (antogomirs) along with siRNAs [191, 219–224]. The main task for the new generation of medical preparations for different types of pathologies is the determination of optimal modifications of chemically synthesized sense and antisense oligonucleotides. Delivery of oligonucleotides, vector selection, chemical modifications for protection from nucleases, elimination of side effects (interferon stimulation) – this is the list of the most important problems, waiting for their solution on the way to the introduction of fundamental knowledge on miRs into medical practice. *In vivo* toxicity of short hairpin RNA, conditioned by the saturation of metabolism of endogenic miRs, may hinder the implementation [225–226]. Researchers inquire whether these data would limit therapeutic application of short hairpin RNA.

John *et al.* try to answer this question [227]. These authors revealed that the silencing of target genes does not result in significant changes in levels of miR-122, mir-16, and let-7a, expressed in cells of rats and hamsters, via the application of synthetic siRNA, aimed at two hepatocyte-specific genes (apoliprotein B and factor VII). Scientists concluded that the application of synthetic miRs should not result in the disorders in the organism and thus, antogomirs may be considered "safe and effective silencing tool of gene transcripts". Stating on the abovementioned we may suppose that synthetic minor RNA can be applied as medical preparations. The key role in diagnostics and drug discovery within the new paradigm of development of personalized medicine, based on RNA-interference with miRs and siRNAs, belongs to miRs [228]. Although not even one single commercial medical preparation has been developed and only some are being clinically tested, future market of RNA-interference-based drugs is estimated to be $3.5 \cdot 10^9$ USD in 2010 and up to $10 \cdot 10^{10}$ USD in 2015 [228].

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МикроРНК: от фундаментальных исследований до их приложения

МикроРНК – малые, некодирующие белок РНК длиной 20–30 нуклеотидов. В клетках эукариотов микроРНК выполняют роль биорегуляторов экспрессии генов через механизм ингибирования или модуляции процесса трансляции. Цель обзора – проанализировать механизмы биогенеза и функционирования микроРНК, стратегию их открытия, предоставить краткий перечень биологических процессов, в регуляции которых принимают участие микроРНК, а также ознакомить с новейшими публикациями, посвященными причастности микроРНК к различным патологиям (особенно канцерогенезу) и использованию их для маркирования, диагностики, профилактики и терапии раковых болезней человека.

Ключевые слова: микроРНК, биогенез, функция, профили экспрессии, биоинформатическое предсказание, биорегуляция, канцерогенез, терапия.

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