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Small Non-Coding RNAs in Regulation of Course and Therapeutic Efficacy in Acute Myeloid Leukemia

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Abstract

Small non-coding RNAs (sncRNAs) are small regulatory molecules, which play key roles in fine-tune of all cell functions. In late 1970s and early 1980s, it was first determined that non-coding RNAs contribute to the cellular regulatory processes. The kingdom of sncRNAs is very numerous and it is clear that functions of different members of this family is different from each other and may be involved in normal and pathologic processes in cell. Recently it was investigated that sncRNAs and long non-coding RNAs play roles in cellular differentiation, proliferation, metabolic processes, bioenergetic regulation, cell death and inter-cellular communications, etc. In embryos, non-coding RNAs control maternal-zygotic transition, the maintenance of pluripotency, the patterning of the body axes, the specification and differentiation of cell types and morphogenesis of organs. Development of hematologic malignancies in humans, their course and regulation of resistance and sensitivity of tumorous cells to therapy are under the control of sncRNAs.

Keywords: small non-coding RNAs, micro-RNAs, antago-miRNA, nano-sized polymer carriers, leukemic cell transformation

1. Introduction

1.1. Small non-coding RNAs

Small non-coding RNAs (sncRNAs) are oligonucleotides with length less than 200 nt. This is numerous family of non-coding genomic regulators. The most investigated sncRNAs are micro-RNAs (miRNAs) and small interfered RNAs (siRNAs). Less studied sncRNAs are piwi-interacting RNAs (piRNAs), small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs) [1, 2].

1.2. Biogenesis of micro-RNAs and piwi-interacting RNAs

All small non-coding RNAs before they become functionally active undergo different processes of biogenesis from their precursor form. This multistep maturation is necessary for normal functionality of small non-coding RNAs. Imbalance of one or more steps of sncRNAs biogenesis may result in development of different pathologic disorders and carcinogenesis [3].

1.3. micro-RNAs

miRNAs are small, single-stranded RNAs (ssRNAs) that are less than 24 nucleotides in length. They control translation of more than 60% of protein-coding genes. Four different mechanisms of regulation exist: inhibition of translation initiation, suppression of translation elongation, degradation of co-translational protein and initiation of translation termination [4–8].

The biogenesis of miRNAs was previously described [9–13]. Primary miRNAs (pri-miRNAs) are mostly transcribed by RNA Polymerase II (RNA Pol II). After that, pri-miRNAs undergo nuclear processing by the microprocessor complex of RNase III enzyme Drosha/DGCR8 (DiGeorge syndrome critical region gene 8), followed by export into the cytoplasm as pre-miRNAs complexed with exportin5 and RAN GTP [9–11]. In the cytoplasm, immature miRNAs are duplexed by the cytoplasmic RNase III Dicer together with its catalytic partner Trans-activator RNA (tar)-binding protein (TRBP). Dicer/TRBP cleavage pre-miRNAs in duplex RNA (dsRNA) is loaded onto Argonaute (AGO) proteins to generate the RNA-induced silencing complex (RISC). RISC contains a single-stranded miRNA and guide them to their target mRNAs [12, 13].

1.4. Piwi-interacting RNAs

PiRNAs, 26–32 nt long small non-coding RNAs that are associated with the piwi-class AGO protein family, are generated independently of Dicer from single-stranded precursors [14]. The primary function of these sncRNAs is silencing of transposable elements through de novo DNA methylation [15]. Some piRNAs are silencing target protein-coding genes [16]. Recently two models of piRNA biogenesis were proposed: the primary processing and the secondary amplification (ping-pong amplification loop) pathways. In the germline, piRNA biogenesis involves both pathways. Two putative RNA helicases, Armi and FS(1)Yb (Female Sterile (1) Yb; also known as Yb) and a nuclease, Zuc (Zucchini), as factors of primary piRNA biogenesis. PiRNA precursors or intermediates obtained from uni-strand clusters are cut by Zuc to produce piRNAs that bind to piwi proteins. Amplification of loop pathway is activated by piRNA derived from primary biogenesis pathway. There should be a relative increase in abundance of complementary piRNAs due to the amplification. The primary pool of piRNAs amplifying sequences is silencing active transposons in the secondary ping-pong amplification loops cycles. The ping-pong amplification loop characterized in many animal species requires piwi subfamily proteins: piwi and Aub [17–19]. Sense-strand piRNAs react with Ago3 [20], whereas antisense piRNAs bound to Piwi or Aub [21]. In the ping-pong

amplification loop model of piRNA biogenesis, antisense piRNAs in complex with Aub directly cleaves sense-strand transposon sequences, generating sense piRNAs for Ago3. The Ago3-piRNA complex then directs cleavage of antisense piRNA precursors, generating antisense piRNAs for Aub. The 5'-ends of amplified secondary piRNAs are determined by Aub and Ago3 Slicer [22–25].

1.5. Role of sncRNAs in carcinogenesis

sncRNAs may play double-faced roles in carcinogenesis as oncogenes and tumor suppressors. As oncogenes sncRNAs function in tumor initiation, progression and resistance to therapy; as tumor suppressors, sncRNAs inhibit cell growth, induce apoptosis, block cell cycle and promote cell differentiation [26, 27]. In every pathologic condition, its own biomarker sncRNAs exist which indicate prognosis, course of disease and resistance or sensitivity to ongoing treatment. These biomarkers may be a basis for creation of new drugs for epigenetic therapy of cancers.

2. sncRNAs in AML

In acute myeloid leukemia (AML), some sncRNAs may play roles in oncogenes and other sncRNAs may be tumor suppressors. Oncogenic sncRNAs are miRNA-155, miRNA-17-92 cluster, miRNA-221, miRNA-21, etc. Tumor suppressive functions have miRNA-15a/16 cluster, miRNA-29b, miRNA-181b and members of let-7 cluster [28]. These sncRNAs may be determined as biomarkers and prognostic markers in AML.

2.1. sncRNAs as biomarkers and prognostic markers of AML

Acute myeloid leukemia (AML) is a heterogeneous hematologic disease, which characterizes with disturbances of differentiation and maturation of hematopoietic stem cells or progenitor cells and appearance of immature blasts in periphery blood. Any classifications of AML are existing (WHO, 2008 with corrections in 2016) [29]. Classification of AML in dependence of genetic abnormalities is one of the basic classifications for this disease. All genetic changes in AML are also associated with imbalance of expression of different sncRNAs. These sncRNAs can be determined as biomarkers of particular type of AML. In **Table 1**, presents the most comprehensive analysis of dysregulated sncRNAs in dependence of AML type. All displayed sncRNAs profiles were taken from clinical investigations in AML patients.

2.2. Role of separated miRNAs and piRNAs in AML

miRNA, which most often involved in pathologic processes in AML are let-7 family of miRNAs, miRNA-16, 17–92 cluster, miRNA-29, miRNA-30, miRNA-146, miRNA-150, miRNA-155, miRNA-196 and miRNA-223. The oncogenic markers are miRNA-17-92 cluster, miRNA-155 and miRNA-196; the tumor suppressive are miRNA-15/16, let-7 family, miRNA-29, miRNA-30, miRNA-146, miRNA-150 and miRNA-223 (**Figure 1**).

Type of AML [29, 32]	Downregulated	Upregulated
AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1	miRNA-9, 18a, 19a–b, 20a, 92, 193a, 196 [34]; miRNA-196b [36]; 21, 26a, 125a, 142-3p, 196a, 494 [37]; 133, 17-3p, 17-5p [38]; let-7b, c [40]	miRNA-126, 130 [33, 36]; let-7a-3, 30a, b, c [34]; 27a, 146a, b, 150, 155, 181a, b, 223 [37]; 17–92, miRNA-24a, b [40]
AML with inv.(16)(p13.1;q22) or t(16;16)(p13.1;q22); CBFβ-MYH11	miRNA-30b, d, 335 [36]; 196a, b [37]; let-7b, c [40]	miRNA-126 [36]; 126 [40]
AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A	miRNA-22, 24, 29a, b, 30a, 124, 132, 133a, 133b, 146a, b, 150, 155, 193b, 221, 222, 424, 503, 542 [33]; 23a, 181b, 210, 495 [34, 35]; let-7c, miRNA-26a, 30c, d, 100, 125b, 126-3p, 143, 181a, d [37]; 16, 29s, 34a [38]; let-7b, miRNA-29c [40]	Let-7a-3, miRNA-30a, b, c, 17h, g, 196b, 328 [34, 35]; 21, 196a, b [37]; 17–92, 196a, 219, 326 [38, 40]
APL (M3) with a translocation between chromosomes 15 and 17 (PML-RARA)	Let-7c, miRNA-15b, 107, 143, 210, 223, 342 [33]; miRNA-16 [34]; 23a [35]; 485-5p [36]; let-7b, 18b, 22, 24, 27a, 126-3p, 150, 196a, b, 378 [37]; 17-5p, 20a [39]	Let-7a, let-7d, miRNA-142, 181b [33]; let-7a-3, miRNA-30a, b, c, 337-3p [34]; 125b [35, 37]; 29a, 100, 146a, 146b-5p, 181 a, b [37]; 127, 299, 323, 368, 382 [38, 40]
AML with t(6;9)(p23;q34.1); DEK-NUP214		
AML with inv.(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM	miRNA-449a [35]	
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1	miRNA-29a [37]	miRNA-335, miRNA-375 [37]
AML with BCR-ABL1	miRNA-203 [41]; 150 [42]; 451 [43]; 120, 151, 155, 31, 564 [44];	miRNA-23a [41]; 125b, 96 [44];
AML with mutated NPM1	miRNA-424, 181a, b [46]; 320, 145, let-7c [47]; 10b, let-7, miRNA-29, 181a, 124, 128, 194, 219, 220a [48]; 204, 126, 130a, 451 [38]	miRNA-10a-5p [45]; 155 [46]; 196a, b [47]
AML with biallelic mutations of CEBPA	miRNA-34a [49]	miRNA-328 [44]; miRNA-181a [38, 48]; 335 [38]
AML with mutated RUNX1	Let-7, miRNA-223, 99a, 100 [48]	miRNA-24, 23, 27, 155, 211, 220, 595 [48]

Table 1. AML with recurrent genetic abnormalities [30, 31].

Let-7. The let-7 is a 13-member family of miRNAs expressed in human tissues. This sncRNAs are induced in embryogenesis and then its high levels are detected in different tissues. Down-expression of let-7 was obtained in early embryogenesis and its suppression was observed in many types of cancers. The main functions of let-7 miRNA are tumor suppression and supporting of cell differentiation. Let-7 targets a human rat sarcoma (RAS) ortholog, a high-mobility group AT-hook 2 (HMGA2) and MYC. These factors are human oncogenes. Let-7 regulates

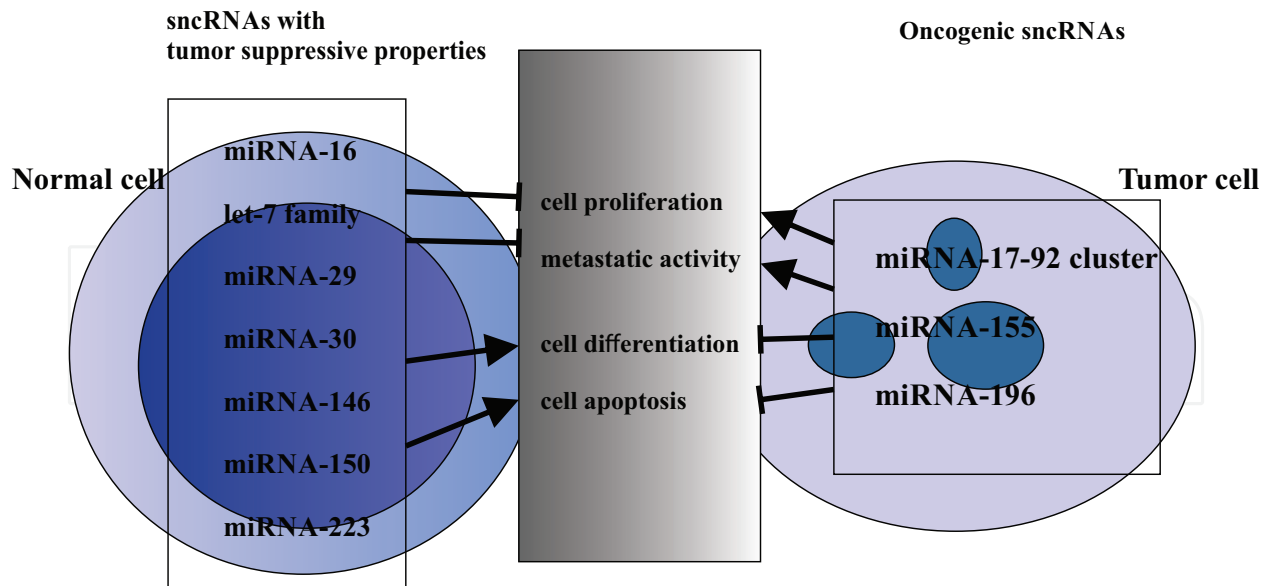


Figure 1. Influence of tumor suppressor sncRNAs and oncogenic sncRNAs on main functions of cells.

cell cycle suppression of any cyclins, such as cyclin A, cyclin D1 and cyclin-dependent kinase 4 (CDK4). It may indirectly suppress LIN28 by the direct inhibition of MYC [23, 24]. Let-7c induces megakaryocytic cell differentiation as the result of targeting of PBX2 in myeloid cells. This factor in cooperation with Meis1 and HoxA9 are required for MLL-dependent leukemogenesis. Acute promyelocytic leukemia (APL) decreases let-7c levels and cooperation of KRAS with PML-RARA results in poor prognosis of disease [25, 26, 50, 51]. One more novel axis was determined in poor prognosis leukemia. This is protein tyrosine phosphatase of regenerating liver 3: PRL-3/LIN28B/let-7 axis. PRL-3 induces activation the PI3K/AKT pathway and Src-ERK1/2 pathways. PRL-3 phosphatase activity upregulates LIN28B, a stem cell reprogramming factor, which in turn represses the let-7 mRNA family, inducing a stem cell-like transcriptional program. These pathways support epithelial-mesenchymal transition and results in metastatic processes. PRL-3 is detected in more than 50% of patients with AML [27, 52].

miRNA-16. miRNA-16 is tumor suppressor sncRNAs. miRNA-16 targets anti-apoptotic gene Bcl-2 (B-cell lymphoma 2) and numerous genes, which are involved in cell cycle regulation. Those genes are cyclin D1, D3, E1 and cyclin-dependent kinase 6 (CDK6). miRNA-16 regulates genes supporting Wnt-signaling pathway, such as WNT3A (wingless-type MMTV integration site family, member 3A). As a result, miRNA-16 can fine-tune cell cycle, support cell apoptosis and inhibit cell proliferation [28, 53]. Erythropoiesis is supported by miRNA-16 and its expression positively correlates with the appearance of erythroid surface antigens (CD36, CD71 and CD235a) [29, 54]. Its level is downregulated in APL. After treatment, ATRA levels of miRNA-16 increase [26, 51].

miRNA-17-92. miRNA-17-92 is one of the most investigated oncogenic miRNA complex in leukemia. Cluster 17-92 is complex of seven co-operating miRNAs. Members of this cluster are miRNA-17, miRNA-17*, miRNA-18a, miRNA-19a, miRNA-20a, miRNA-19b-1 and

miRNA-92a-1. These miRNAs are located at 13q31. The majority of miRNAs from this cluster are overexpressed in MLL-rearranged AML. These miRNAs can support cell proliferation, cell viability, inhibit apoptosis, suppress cell differentiation and induce malignant transformation. In normal hematopoiesis, this complex plays essential roles in monocytopoiesis and megakaryocytopoiesis. Targets for 17–92 complex are factors of cellular proliferation E2F1, E2F2, E2F3, PTEN (tumor suppressor phosphatase and tensin homolog), BIM (pro-apoptotic molecule), AML1, TGFBR2, NCOA3, RBL2, DOCK5, THBS1 and CTGF. RASSF2 and RB1 genes are target genes in leukemia [29–33, 38, 54–57]. In vivo cluster 17–92 expression significantly decreases leukemia latency [34, 40].

miRNA-29. The miRNAs-29 family consists of miRNA-29a, miRNA-29b and miRNA-29c, and is encoded and transcribed in tandem by two genes located on chromosome 7q32.3 (miRNA-29a/b1 locus) or chromosome 1q32.2 (miRNA-29a/b2 locus), respectively. As was shown recently, miRNA-29a and miRNA-29b regulate critical anti-apoptotic genes, such as myeloid cell leukemia-1 (MCL-1) and play tumor suppressor role. These results indicated that miRNA-29a and miRNA-29b target Mcl-1 and play roles in regulation of apoptosis in AML. Bcl-2, Mcl-1 and Bcl-Xl are anti-apoptotic proteins and promote cell survival and proliferation. Both miRNA-29a and miRNA-29b not only directly target anti-apoptotic genes but also upregulate pro-apoptotic genes, such as BIM (BCL2L1), p53 and the tumor suppressor programmed cell death-4 (PDCD4) [35, 36, 58, 59]. Overexpression of miRNA-29a, miRNA-29b or miRNA-2c markedly inhibited cell proliferation and promoted cell apoptosis by targeting protein kinase B2 (AKT2) and cyclin D2 mRNAs.

miRNA-29b targets DNA methyltransferases (DNMTs) and downregulates DNA methylation in malignant cells. In AML cells, enhanced expression of miRNA-29b results in the reduction of the expression of DNMT1, DNMT3A and DNMT3B. miRNA-29b downregulates DNMT1 indirectly by targeting Sp1, a trans-activator of the DNMT1 gene due to a decrease in global DNA methylation and re-expression of p15 (INK4b) and ESR1. Moreover, miRNA-29 family members may downregulate the active DNA demethylation pathway members tet-methylcytosine dioxygenase (TET1) and thymine DNA glycosylase (TDG) [37, 60]. miRNA-29 targets CCNT2 that is a component of the positive transcription elongation factor b (P-TEFb). P-TEFb is essential for the elongation of transcription and co-transcriptional processing by RNA polymerase II. Different P-TEFb complexes can regulate subsets of distinct genes that are important for the embryonic development. miRNA-29 family miRNAs downregulate cyclin-dependent kinase 6. It provides a differentiation promoting activity of Runx proteins to be selectively activated in terminally differentiating cells [38, 61].

miRNA-30. miRNA-30 as was shown is tumor suppressor miRNA in AML. miRNA-30 downregulates NOTCH1 gene expression to promote granulocytic differentiation [39, 62].

miRNA-146. miRNA-146a and miRNA-146b are two miRNA, which are highly expressed in primitive bone marrow cells (lineage negative). In mature blood cells, their expressions are different. miRNA-146a is highly expressed in blood cells maturation lineage. The expression of miRNA-146a is regulated by a combination of PU.1 (spleen focus-forming virus proviral integration 1) and c-ETS. It was supposed, that miRNA-146a controls maturation of blood marrow stem cells in adults and plays role in the self-renewal of long-term hematopoietic

stem cells. The decrease or deletion of miRNA-146 levels could result in development of AML in adults [40, 63]. miRNA-146a negatively regulates NF- κ B by suppressing two signal transducers, TRAF6 (TNF receptor-associated factor 6) and IRAK1 (IL-1 receptor-associated kinase 1). Absence of miRNA-146a expression is due to NF- κ B hyper-expression, which involves miRNA-146a/TRAF6/NF- κ B/IL-6 pathway resulting in depletion of hematopoietic stem cells and the development of myeloproliferative diseases [41, 64]. miRNA-146a also downregulates CSF1R. Increased expression of this factor is strongly associated with the development of AML [42, 65]. Furthermore, high expression of miRNA-146a impaired bone marrow reconstitution in mice and reduced survival of hematopoietic stem cells. Treatment of AML patients with ATRA results in downregulation of miRNA-146a, which is associated with upregulation of Smad4 pathway [43, 66]. miRNA-146a is downregulated in MLL rearrangements. MLL-rearranged AML MEIS1 and HOXA9 are key target genes of MLL-fusion proteins. MEIS1/HOXA9 downregulate PU.1 expression, which is essential for miRNA-146a expression. Low levels of miRNA-146a result in high levels of SYK and its activation. SYK expression and activation is switch leukemic cellular transformation [44, 67].

miRNA-150. miRNA-150 is one of the main regulators of hematopoiesis. It is expressed in normal hematopoietic stem cells. The known target for miRNA-150 is Myb, which regulates differentiation of progenitor cells toward megakaryocytes and erythrocytes, supporting c-KIT expression. In majority of cases of patients with AML this miRNA is downregulated [45, 68]. Downregulation of miRNA-150 is associated with misbalance of regulatory factors. MLL-fusion proteins bind to the promoter regions of miRNA-150 and directly promote its expression, however, blocking maturation and biogenesis of this miRNA [46, 47, 69, 70]. Repression of miRNA-150 maturation is associated with expression of Myc protein. Myc is a direct target for MLL-fusion protein, which binds to the promoter region of LIN28 and activates its transcription [48, 71]. miRNA-150 is an important regulator of hematopoietic recovery after treatments with chemotherapeutic drugs. miRNA-150 targets other genes that are necessary for leukemogenesis. These genes are HOXA7, Meis1 and cyclin-dependent kinase 2 [38, 72].

miRNA-155. miRNA-155 expressed in high levels in normal HSC and in low in mature hematopoietic precursors. It controls early maturation of HSC until common myeloid progenitor stage. miRNA-155 supports the leukemogenesis by downregulation of SH2 domain-containing inositol 5'-phosphatase 1 (SHIP1) translation, activating SHIP1-mediated PI3K-Akt pathway. This event is due to myeloproliferation and decrease of erythropoiesis. SHIP1 downregulation results in activation of IL-6 signaling pathway and induces a reactive proliferation of the relatively apoptosis-resistant myeloid precursor cells [49, 73]. Key targets of miRNA-155 are PU.1 and Cebpb in myeloid progenitors. PU.1 transcriptionally activates miRNA-155, forming positive regulatory loop. PU.1 and CCAAT/enhancer-binding protein b (C/EBPb) transcriptionally regulate expression of myeloid-specific miRNA-223, which upregulates myelopoiesis by indirectly regulating C/EBPa [50, 51, 74, 75]. miRNA-155 promotes production of inflammatory cytokines in mature myeloid cells. It negatively regulates anti-inflammatory factors, such as SHIP1 and SOCS1 [52, 76]. miRNA-155 reduces apoptotic activity of myeloid cells in vitro and in vivo by the regulation of Akt-signaling pathway [53, 54, 77, 78]. In silico target prediction identified a number of putative miRNA-155 target genes, and the

expression changes transcription factors of myeloid proliferation and apoptosis, such as MEIS1, GF1, cMYC, JARID2, cJUN, FOS, CTNNB1 and TRIB2 [55, 79].

miRNA-196. miRNA-196 is a member of homeobox regions (HOX) clusters family miRNAs: miRNA-10, 196 and 615. HOX genes encode transcription factors, which control embryonic development. miRNA-196 are highly expressed in AML. MLL-fusion proteins directly upregulate expression of miRNA-196, which is necessary for leukemic cells immortalization. miRNA-196 blocks granulocyte colony-stimulating factor-induced granulopoiesis [56, 80]. Recently it determined double-faced regulation by the miRNA-196 of MLL-associated AML. miRNA-196 may be double-faced Janus in MLL-rearranged AML. On the one hand, it targets MLL-associated HOXA9/MEIS1 oncogenes; on the other hand, it regulates first apoptosis signal (FAS) (also known as Apo-1 or CD95) tumor suppressor gene. High expression of miRNA-196 is associated with the more aggressive leukemic phenotypes and worse prognosis for patients with leukemia [38, 57, 81, 82].

miRNA-223. miRNA-223 is an intergenic miRNA, which is highly expressed in human peripheral blood granulocytes and bone marrow-committed myeloid precursors. It is regulated by two factors PU.1 and C/EBP β [40, 58, 59, 83–85]. miRNA-223 has tumor-suppressive role in AML, and its expression is downregulated in this disease. Targets for miRNA-223 are erythrocyte membrane protein band 4.1 like 3, septin 6, FBXW7, ataxia teleangiectasia mutated, insulin-like growth factor 1, paired box 6 and caprin-1. FBXW7 (F-box protein in the SCF E3 ligase complex) protein leads to ubiquitination of binding proteins and proteasomal degradation. It regulates cell proliferation, differentiation, cell cycle, migration and invasion. miRNA-223 downregulates this factor and results in inhibition of cell proliferation and enhancing apoptosis [60, 86]. Other target genes for miRNA-223 are LMO2, NFI-A, MEF2C (myocyte enhancer factor) and E2F1 (adenovirus E2 promoter-binding factor 1). In normal conditions, increased expression of miRNA-223 promotes differentiation toward granulocytes. Its repression associated with differentiation to erythrocytes and monocytes/macrophages [40, 61, 83, 87]. C/EBP α regulates miRNA-223 that blocks myeloid cell cycle progression by targeting E2F1. Overexpression of E2F1 results in repression of miRNA-223 gene expression by the negative feedback [62, 88].

2.3. Piwi-interacting RNAs

Piwi-interacting RNAs is the most numerous class of sncRNAs, whose action in normal and malignant hematopoiesis is less studied. Piwi-regulatory proteins are Argonaute family proteins, which are essential for germ stem cells self-renewal and maintenance. They are encoded by highly conserved PIWI genes. Human genome has four piwi-coding genes: HIWI, HILI, HIWI3 and HIWI2. Piwi proteins are associated with piRNAs and they act in cooperation with each other. Firstly, piwi proteins were identified in germ cells and then in somatic cells [63, 89]. A growing number of studies have found that piwi proteins in humans and mice, specifically, HIWI, PIWIL2 and PIWIL2-like proteins, are expressed in various types of tumor cells. In addition, piRNAs were also detected in these cells [64, 90].

In AML, piwi proteins and piRNAs are deregulated. Recently, it was shown that high expression of piwi-like protein 4 in leukemic cells in 72% of the patients with different types of AML

compared to healthy controls, and in 90% of the patients with MLL-AF9 rearranged AML [13, 65]. PiRNAs act as sequence-specific guides for piwi proteins, and they support biogenesis and stability of piRNAs. Piwi and piRNAs are involved in the intra-nuclear processes such as heterochromatin formation, mobile transposable elements (TE) silencing and repressive histone modifications (H3K9me3). The piwi protein PIWIL4 is overexpressed in a large proportion of AML leukemia patients. This knockdown results in gross changes in histone methylation and slowed leukemic growth. It suggests a tightly regulated piwi pathway is essential for normal hematopoiesis [66, 91].

Mobile transposable elements, which are under the control of piwi and piRNAs constitute approx. 44% of the human genome. TE could actively contribute to genetic heterogeneity, to alter the behavior during adaptation, and responses to stress. Somatic retrotransposition and its associated insertional mutagenesis have particularly important implications for carcinogenesis and are often associated with different cancers. TE activity can generate a wide spectrum of genomic mutations, ranging from point mutations to gross rearrangements. These events may be due to development of different diseases. Mobile transposable elements such as duplications caused by Alu-Alu (SINE type of TEs) recombination in intron 1 and 6, result in a duplication of exons 2–6 of gene MLL1 [67, 68, 92, 93]. Chromosomal rearrangements in MLL are result of Alu recombination. In partial duplication events, TEs are inserted near the translocation breakpoints. MYB and MLL duplications were also obtained in healthy controls, whereas leukemogenesis is induced by TE insertions during blood cell differentiation [69, 94]. Knockdown of the murine piwi protein MIWI2 leads to abnormal hematopoiesis and erythroid precursors take on characteristics of more differentiated erythroid cells [70, 71, 95, 96]. The roles of piRNAs in hematopoiesis have only just begun to be explored and it seems likely that more will be uncovered in the near future. Certainly, regulation of mobile transposable elements, histone modifications, DNA methylation processes by piwi and piRNAs are important for leukemogenesis and for tumor suppression. Investigation of new piwi/piRNAs biomarkers will be a novel diagnostic tool and possible hopeful epigenetic treatment of patients with AML in future.

2.4. SncRNAs as markers of therapeutic resistance or sensitivity to AML treatment

All sncRNAs from the view of chemoresistance and sensitivity of AML patients to the current treatment can be assigned to the two groups. Group 1 characterized with high level of expression of sncRNAs, which associated with sensitivity to therapy. This group members are miRNA-181a, b; let-7f, miRNA-9*, miRNA-96, miRNA-135a, miRNA-409, miRNA-10, miRNA-29b and miRNA-217 [72, 73, 97–100]. Group 1 members act through activation of cellular differentiation, inhibition of leukemic cells proliferation and survival, regulation of cell cycle, inducing of apoptosis and suppression of migration and invasion. Group 2 characterized with high expression of sncRNAs, which associated with resistance to therapy. Group 2 members are miRNA-155, miRNA-125b, miRNA-126, miRNA-210, miRNA-3151, miRNA-196b, miRNA-199a, miRNA-191, miRNA-644, miRNA-363, miRNA-532-5p and miRNA-342-3p [74, 101].

miRNA-181a is the most investigated miRNA with its chemosensitive action on leukemic cells. Investigations of samples from cohort of patients of different ages, miRNA-181a was

identified as marker of chemosensitivity [75, 102]. The main function of this miRNA is activation of apoptotic activity in cells and inducing sensitivity of leukemic to native immunity action. Direct targets for this miRNA are KRAS, NRAS, transcription factor Prospero home-box protein 1 (Prox1) and HMGB1, a member of the high-mobility group box DNA-binding proteins. The CD4 co-receptor is another target for miRNA-181a. Anti-proliferative effect of miRNA-181a is associated with targeting of FBJ murine osteosarcoma viral oncogene homolog (FOS), which is involved in Moloney murine sarcoma viral oncogene homolog (MOS)/dual specificity mitogen-activated protein kinase (MEK)/mitogen-activated protein kinase (ERK) pathway [76, 103]. miRNA-181a can sensitize leukemic cells to natural killer (NK) cell action [77, 104]. miRNA-181a regulates mechanisms of cell proliferation, differentiation and apoptosis of normal cells. All regulated targets for miRNA-181a are aberrantly expressed and are frequently mutated in acute myeloid leukemia. Promotion of high expression of miRNA-181 in the case of AML may have partial positive effect for chemosensitivity of leukemic cells and for anti-leukemic activity [78, 79, 105, 106].

Other miRNA, which enhances chemosensitivity of leukemic cells is miRNA-217. This sncRNA decreases leukemic cell proliferation via the cell apoptosis pathway. It targets KRAS regulator of signaling links from extracellular space to the nucleus. KRAS connects multiple upstream signals to various downstream signaling pathways [97].

miRNA-155 is oncogenic miRNA, whose high expression is able increase chemoresistant effects of anti-leukemic drugs. Its increased expression is correlated with decreased CR rates and a shorter overall survival (OS) of patients with AML. In our laboratory, primary in vitro leukemic cells were transformed into megakaryocytes after using complexes of polymer carrier with antago-miRNA-155 [80, 107].

Another miRNA from the second group is miRNA-126. High expression of this miRNA correlated with decreased CR rates and shortened OS. Treatment with nanoparticle-based antagonist of miRNA-126 results in strong anti-leukemic effects in murine leukemia models and chemo-sensitizing effects of cytarabine and idarubicin in AML cell lines.

Recently determined miRNAs predict the prognosis of AML. From the amount of miRNAs were indicated miRNAs, which expression is dysregulated in patients with poor prognosis of AML. miRNA-107, miRNA-155, miRNA-25, miRNA-29b and miRNA-196a are associated with short OS of patients. The worse prognostic marker was miRNA-25 expression dysregulation [76].

3. Conclusion

The normal bone marrow stressor or injury factors act as dysregulators of epigenetic and genetic program of hematopoietic stem cells, which is due to downregulation of separated sncRNAs and upregulation of other sncRNAs. These events result in the development of imbalance of regulating cell program and consequent transformation of normal hematopoietic cells into leukemic. In this case, genotypic and phenotypic markers of pathologic cells

are changing. These cells change its functions. They lose possibility to normal lifecycle: to differentiation, maturation and death. As a consequence, leukemic cells produce abnormal proteins and express particular palette of sncRNAs, which worsens the negative impact into development of AML.

The chemotherapy may change expression map of sncRNAs in the advantageous or in the disadvantageous position. The study of this map may be useful tool for hematologists and hemato-oncologists in the diagnostic of course, efficacy and prognosis of AML in the particular case. In the course of chemotherapy, downregulation of oncogenic sncRNAs and inducing of tumor suppressor sncRNAs associates with favorable prognosis of disease. On the contrary, inhibition of sncRNAs with tumor suppressive properties and high expression of oncogenic sncRNAs due to unfavorable prognosis of AML.

Reversing of changed epigenetic program of cells and its supporting may be the novel tool for the treatment of different hematological malignancies even which have poor prognosis. Treatment with anti-oncomiRNAs and inducing of producing, biogenesis and maturation of miRNAs with tumor suppressive properties may be new therapeutic benefit in complex therapy of AML. However, limitations to this treatment modality include the instability of free-floating anti-miRNAs in the plasma and their vulnerability to breakdown by nucleases, nonspecific tissue uptake and renal clearance. These limitations can be overcome by nanoparticle-based delivery of the anti-miRNAs to target tissues.

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