Non-Coding RNAs in Myelodysplastic Neoplasms

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Myelodysplastic syndromes or neoplasms (MDS) are a heterogeneous group of myeloid clonal disorders characterized by peripheral blood cytopenias, blood and marrow cell dysplasia, and increased risk of evolution to acute myeloid leukemia (AML). Non-coding RNAs, especially microRNAs and long non-coding RNAs, serve as regulators of normal and malignant hematopoiesis and have been implicated in carcinogenesis.

myelodysplastic syndromes | non-coding RNA | microRNA | lncRNA | circRNA

1. Introduction

Myelodysplastic neoplasms (MDS) are a group of myeloid neoplasms characterized by clonal proliferation of hematopoietic stem cells (HSCs) and genetic and epigenetic abnormalities leading to ineffective hematopoiesis, peripheral cytopenias, and a propensity to the development of acute myeloid leukemia (AML) [1][2]. Diagnosis is based on full blood count parameters, bone marrow morphology and blast count, and the presence of cytogenetic and molecular abnormalities, mainly mutations [2]. The most recent World Health Organization (WHO) classification, the fifth edition, recognizes two main groups: a. MDS with defining genetic abnormalities and b. MDS, morphologically defined [3]. Following correct diagnosis and accurate classification, prognosis estimation and risk stratification are crucial to tailor therapy. The revised International Prognostic Scoring System (IPSS-R) is widely used for the risk stratification of MDS patients considering the number and depth of cytopenias and cytogenetic abnormalities [4]; while most recently the molecular IPSS (IPSS-M) combined genomic aberrations with hematologic and cytogenetic abnormalities and provided improved risk stratification of patients with MDS [5]. In general, low-risk patients are managed either expectantly or with recombinant human erythropoietin or luspatercept [6], whereas high-risk patients are offered hypomethylating agents (HMAs) and/or allogeneic hematopoietic stem transplantation (AlloSCT), which remains the only curative modality. Despite all this progress, there is currently no widely accepted predictive model nor a serviceable biomarker of response that can offer a timely and valid estimation of the expected benefit from these available treatment options.

In terms of pathophysiology, genes regulating epigenetic modifications seem to be the most commonly mutated in patients with MDS [7]. Among epigenetic modifiers, non-coding RNA molecules, especially microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have recently attracted research interest. Until recently, it was believed that the molecules important for the functioning of a cell are those described by the “Central Dogma” of biology, namely messenger RNAs and proteins. However, almost three decades ago, the discovery of microRNAs (miRNAs) in plants [8] and animals [9][10] changed this perception. Subsequent research efforts have demonstrated that large

parts of an organism's genome are transcribed into RNA at one time point or another but are not translated into an amino acid sequence. These RNA transcripts have been referred to as non-coding RNAs (ncRNAs). There are many recognizable classes of ncRNA, each having a distinct function. These include the abovementioned miRNAs, transfer RNAs (tRNAs) [11], ribosomal RNAs (rRNAs) [12], PIWI-interacting RNAs (piRNAs) [13], small nucleolar RNAs (snoRNAs) [14], long intergenic ncRNAs (lincRNAs) [15], etc. The full extent of distinct classes of ncRNAs that are encoded within the human genome is currently unknown but is believed to be numerous.

Functionally, ncRNAs are divided into two main categories: housekeeping ncRNAs, which are involved in generic cellular functions, and regulatory ncRNAs, which primarily regulate gene expression in multiple levels. Hence, their regulatory role in cellular physiology, including normal hematopoiesis, is important, as is their participation in initiation and progression of neoplasia. Indeed, several studies have demonstrated the role of ncRNAs in solid and hematological malignancies, either from a pathophysiologic point of view or as prognostic biomarkers [16][17].

2. Circular RNAs

Circular RNAs (circRNAs) are closed-loop single-stranded RNA molecules that have proved to be important regulators of gene expression at multiple levels although initially considered transcriptional byproducts [18]. CircRNAs function as miRNA sponges or traps that indirectly modulate transcription, interact with intracellular proteins, regulate splicing, and travel in extracellular vehicles called exosomes, enabling intercellular communication [19][20]. In the context of normal hematopoiesis, circRNAs show cell-type specificity and are considered as regulators of blood cell differentiation and maturation [21].

The hypothesis of circRNAs interfering with MDS pathophysiology was supported by the observation that exogenous inhibition of the spliceosome components, commonly affected by MDS mutated genes, can cause an imbalance between circular and linear RNA concentrations within affected cells towards overexpression of the circular molecules [22][23]. Wedge et al. recently reported that specific cancer-associated circRNAs, such as circZNF609 and circCSNK1G3, are upregulated in MDS patients with U2AF1 mutations compared to unmutated controls [24]. Additionally, global circRNA expression has been found to be upregulated in the continuum from normal hematopoiesis to clonal cytopenias of undetermined significance (CCUS) and further to MDS. Even among MDS patients, a higher risk group was correlated with increased global circRNA expression and a "Myeloid Circ Score" was developed based on 14 specific circRNAs with potential prognostic value to stratify patients in terms of risk and disease outcomes [25]. Another research group found 145 circRNAs to be upregulated and 224 downregulated in MDS patients compared to healthy controls. Researchers also suggested that of all these circRNAs, hsa_circRNA_100352, hsa_circRNA_104056, and hsa_circRNA_102817 could be used as MDS prognostic biomarkers, since their increased expression was significantly correlated with poorer OS. Bioinformatics network analysis indicated that these three circRNAs are probably associated with multiple cancer-related molecular pathways, including Wnt/β-catenin and PTEN/Akt/mTOR [26][27]. Additionally, circ-ANAPC7 might be another promising circRNA biomarker, as its expression in MDS patients has recently been shown to be upregulated, along with the increasing risk group, by IPSS-R [28]. Finally, several circRNAs are differentially expressed between responders and nonresponders to azacytidine, although only one circRNA, hsa_circ_0006595,

is considered a potential predictor for response to azacytidine treatment [29]. Whether circRNAs will soon be used in clinical practice for diagnostic, prognostic, or predictive purposes remains to be answered, given the need for bone marrow sampling, since the reproducibility of findings in peripheral blood has not been proven yet.

3. Long Non-Coding RNAs

Long non-coding RNAs (lncRNAs) are a functionally heterogeneous class of thousands of RNA molecules, each containing more than 200 nucleotides, which are not translated into functional proteins. They are produced through DNA transcription, either from genes or intergenic regions (lincRNAs), and have multiple functions including epigenetic chromatin modifications, regulation of neighboring and distant gene transcription, RNA splicing, response to DNA damage, sponging miRNAs, and participation in signaling pathways [30][31]. In the field of normal hematopoiesis, from murine models to humans, it is known that lncRNAs are expressed in a stage-specific and lineage-specific pattern from hematopoietic stem cells (HSCs) to mature blood cells in a way that they enable self-renewal of HSCs, such as H19 lncRNA, but also determine lineage commitment of progenitor cells, e.g., EGOT lncRNA for eosinophil maturation, in cooperation with transcription factors [32][33][34][35][36][37][38].

After the identification of MEG3 (maternally expressed gene 3) lncRNA hypermethylation in many MDS patients, evidence that linked aberrant expression of lncRNAs with multiple hematological malignancies, including MDS, began to accumulate. The aforementioned lncRNA is considered a tumor suppressor whose downregulation has been associated with poor OS in several solid neoplasms [39][40][41][42][43][44]. While scientific interest in lncRNAs was increasing, researchers identified a positive feedback loop in MDS cells involving lncRNA bc200-miR-150-5P-MYB, which resulted in sustained cell proliferation. On the other hand, the inhibition of this axis seemed to suppress neoplastic growth of bone marrow MDS cells, implying potential therapeutic targeting of BC200 [45]. Additionally, increased expression of the lncRNAs KCNQ10T1 and HOXB-AS3 has been associated with adverse prognosis in MDS, with the latter pertaining to only lower-risk patients [46][47]. Further basic research and computational analysis revealed a vast number of differentially expressed lncRNAs between MDS patients and healthy controls, with functions including cell adhesion, differentiation, and chromatin modifications, mainly through functional interaction with DNA methylation processes [48][49]. Of these lncRNAs, H19 emerged as one of the most promising prognostic biomarkers in MDS patients. Interestingly, a set of 14 lncRNAs were considered as reliable predictive biomarkers to inform about potential patients' response to azacytidine [29][49][50]. To improve MDS risk stratification by connecting laboratory research with clinical practice, Yao et al. developed a scoring system based on the expression of four lncRNAs with the highest prognostic potential (TC07000551.hg.1, TC08000489.hg.1, TC02004770.hg.1, TC03000701.hg.1). A higher lncRNA score was significantly associated with higher bone marrow blast percentage, higher-risk subtypes by WHO, complex karyotypes, high-risk gene mutations (RUNX1, ASXL1, TP53, SRSF2, and ZRSR2), as well as shorter OS [51]. Consequently, lncRNAs overall appear to be promising prognostic and predictive biomarkers for patients with MDS, probably awaiting their future incorporation in widely accepted prognostic scoring systems to assist in decision-making.

4. PIWI-Interacting RNAs

PIWI-interacting RNAs (piRNAs), the third major class of small non-coding RNAs, are single-strand 26–31 nucleotide-long RNA molecules. Their main function, apart from epigenetic modifications, was first believed to be the maintenance of germline DNA integrity through the guidance of PIWI proteins (P-element-induced wimpy testis proteins) towards silencing transposons, which are mobile parasitic genomic elements [52][53]. Further research indicated that aberrant expression of specific piRNAs is associated with the development and progression of several solid and hematological cancers, as these molecules are considered to play a role in continuous proliferative signaling, resistance to apoptosis, tumor invasion, angiogenesis of malignant tissues, and even resistance to antineoplastic treatment [54][55]. On the other hand, though, there has been increasing evidence that aberrant expression of piRNA pathway genes alone might not be adequate for the formation of piRNA–PIWI silencing complexes with biological impact on tumorigenesis [56].

Although the importance of piRNAs in other hematological malignancies such as multiple myeloma and classic Hodgkin lymphoma has gathered research interest, data on MDS have been scarce. The first study of piRNAs in bone marrow cells of patients with MDS demonstrated a higher expression (9%) of piRNAs in patients with MDS with refractory anemia (low-risk MDS) compared to patients with MDS with refractory anemia and excess of blasts—2 (high-risk MDS) and healthy controls (2% and 1%, respectively), assuming a DNA-protective role of piRNAs in lower-risk MDS [57][58]. Small non-coding RNA analysis from plasma and extracellular vesicles also showed an upregulation of specific piRNAs (hsa_piR_019914/gb/DQ597347 and hsa_piR_020450/gb/DQ598104) in MDS patients compared to controls. Two other piRNAs, hsa_piR_000805/gb/DQ571003 and hsa_piR_019420/gb/DQ596670, were differentially expressed between patients with low- and increased blasts—MDS. The latter piRNA was also shown to be correlated with OS with a protective role, but no piRNAs were found to have predictive value about patients' response to azacytidine [59]. The biologic interpretation of these findings as well as the extent to which they can be incorporated in everyday clinical practice remain to be further elucidated.

5. Ribosomal RNAs

Ribosomal RNAs (rRNAs) are indispensable components of ribosomes, the cell's protein-producing machinery. Ribosomes in human cells comprise four rRNAs (28S, 5S, 5.8S, and 18S) and approximately 80 proteins that are assembled into a small (40S) and a large (60S) subunit through a multilevel process, which mainly takes place in the nucleolus [60][61][62][63].

The dependence of highly proliferative cells, such as the hematopoietic cells, upon protein synthesis has provided the rationale for extensive research on the role of aberrant ribosomal synthesis in several human diseases including hematopoietic neoplasms. In this context, mutation of Nol9 a ribosomal biogenesis protein required for 28S rRNA processing was found to affect hematopoiesis in animal models by reducing proliferation of hematopoietic stem and progenitor cells [64]. Moreover, *DNAJC21* mutations were associated with bone marrow failure with increased tendency to malignancy, attributed to impaired biosynthesis and cytoplasmic maturation of the 60S ribosomal subunit [65]. Similarly, a whole group of diseases termed "ribosomopathies" arising from congenital or acquired genetic abnormalities that lead to impaired ribosomal construction and function have been associated with bone marrow failure and increased risk of hematological malignancies, such as Shwachman–

Diamond syndrome or congenital dyskeratosis [66][67]. Further data supporting the correlation of rRNA deregulation with myeloid neoplasms indicate the potential role of *DDX41*, whose germline mutations predispose to myeloid malignancies, in the processing of pre-ribosomal rRNA to mature rRNA [68]. *U2AF1* somatic mutations, commonly detected in MDS patients, apart from altered splicing, are also believed to cause aberrant ribosomal synthesis, mediated by NPM1, which is considered a ribosomal biogenesis factor [69]. Finally, bone marrow CD34+ cells from patients with MDS show decreased rRNA expression compared to controls, which is probably driven by increased promoters' methylation of DNA loci coding for these rRNAs (rDNA). Interestingly, this hypermethylation can be reversed by hypomethylating agents such as azacytidine and it is therefore implied that methylation status of rDNA could be used as a predictor of response to treatment with such agents, instead of genome-wide methylation status, although this hypothesis is yet to be proven [70][71]. Researchers have recently focused on the study of short RNA fragments cleaved from rRNA, called rRNA-derived fragments (rRFs), as they are believed to regulate cellular functions and show sequence overlap with miRNAs and piRNAs [72][73].

6. Small Nuclear and Small Nucleolar RNAs

Small nucleolar (snoRNAs) RNAs are 60–300 nucleotide-long RNA molecules derived from coding and non-coding genes and are in the nucleolus of eukaryotic cells. Their main function is processing of other RNA molecules such as ribosomal RNAs and small nuclear RNAs (snRNAs) via pseudouridylation and 2′-O-methylation. In turn, snRNAs are vital components of the spliceosome, the cell machinery that catalyzes pre-mRNA splicing through intron excision and joining of exons, to form functional mature mRNAs [74]. Additionally, snoRNAs are involved in regulation of alternate splicing and also act like miRNAs to selectively suppress gene expression [75][76].

In HSCs, snoRNAs expression is supposed to be cell-type-specific and play an important role in cell homeostasis, self-renewal, and stress response, while their aberrant expression has been linked to several hematological malignancies, MDS included [77][78][79]. For example, *DDX41* regulates snoRNA processing, ribosomal biogenesis, and protein synthesis in hematopoietic stem and progenitor cells (HSPCs) and its germline mutation is known to confer predisposition to clonal myeloid disorders. More specifically, monoallelic DDX41 mutations, as in germline predisposition, increase the risk for age-dependent hematopoietic defects and confer competitive proliferation advantage to HSPCs. On the other hand, biallelic DDX41 mutations deregulate snoRNA processing, causing intracellular accumulation of inappropriately processed snoRNAs; impair protein synthesis; and finally result in cell cycle arrest. Most of the affected snoRNAs belong to the SNORA family and are typically involved in RNA pseudouridylation [80]. Similarly, snoRNA U33, which is a mediator of cell metabolic stress, has been found to be upregulated in MDS patients. More importantly, this snoRNA was shown to be significantly associated with OS of patients, albeit no relevant biological explanation is provided [59][81].

Table 1. ncRNAs with prognostic value in MDS.

Class of ncRNAs	ncRNA	Sample	Prognostic Value	Reference
miRNAs	miR-125a	BM	Decreased survival	Gañán-Gómez 2014 [82]
	miR-22	BM and PB (plasma)	Decreased survival	Ma 2020 [83]
	miR-196b-5p	BM	Increased risk of transformation to leukemia	Wen 2017 [84]
	miR-29b	BM	Increased risk of transformation to leukemia	Kirimura 2016 [85]
	miR-320c, miR-320d	BM	Decreased survival	Wan 2021 [86]
	miR-194-5p	BM	Decreased survival	Choi 2015 [87]
	miR-661	BM	Decreased survival	Kang 2019 [88]
	miR-126, miR-155, miR-124a	BM	Decreased survival	Choi 2019 [89]
	miR-181a-2-3p	BM	Decreased survival	Liang 2022 [90] Kontandreopoulou 2022 [91]
	miR-125b-5p, miR-155-5p	BM	Higher risk MDS	Kontandreopoulou 2022 [91]
	miR-451a, miR-223-3p	PB (plasma)	Decreased progression-free survival, decreased survival	Dostalova-Merkerova 2017 [92]
	let-7a, miR-144, miR-16, miR-25, miR-451, miR-651, and miR-655	PB (plasma)	Association of clusters with overall survival	Zuo 2015 [93]
	miR-1237-3p, miR-548av-5p	PB (extracellular vesicles)	Decreased survival	Hrustincova 2020
circRNAs	hsa_circRNA_100352 hsa_circRNA_104056 hsa_circRNA_102817	BM and PB (MNCs)		Wu 2020 [27]
lncRNAs	KCNQ10T1	PB (serum)		Zhang 2020 [46]
	HOXB-AS3	BM		Huang 2019 [47]

Class of ncRNAs	ncRNA	Sample	Prognostic Value	Reference
	H19, WT1-AS, LEF1-AS, TCL6	BM		Szikszai 2020 [50]
	TC07000551.hg.1 TC08000489.hg.1 TC02004770.hg.1 TC03000701.hg.1	BM		Yao 2017 [51]
piRNAs	hsa_piR_019420	PB (EVs)		Hrustincova 2020 [59]
snoRNAs	U33	PB (EVs)		Hrustincova 2020 [59]
tDRs	tDR-Asp family	FFPE preparations		Guo 2017 [94]

BM: bone marrow; PB: peripheral blood; MNCs: mononuclear cells; EVs: extracellular vesicles; FFPE: formalin-fixed paraffin-embedded.

ntially the elieved to have additional functions such as modulation of gene expression and control of cell death. Cleavage of pre- or mature tRNAs produces the tRNA-derived fragments (tRFs) or tRNA-derived small RNAs (tsRNAs) or tRNA-derived RNAs (tDRs), which are involved in multiple biological processes including translational regulation with gene silencing, intercellular communication, cellular stress response, and immune cell activation, rather than being useless byproducts of tRNA degradation [95][96][97][98].

Specific tRNAs (chr2.tRNA27-GlyCCC, chr.18Trna4-LysCTT) as well as overall tRNA to rRNA ratio have been found upregulated in marrow cells from MDS patients compared to controls, and it was assumed that this increase might contribute to decreased programmed cell death and increased leukemic transformation, since tRNAs are known to inhibit cytochrome c activated apoptosis [35][57][59][99]. On the other hand, the SF3B1^{K700E} mutation commonly seen in MDS seems to reduce translational machinery components, primarily tRNA synthetases [100]. Another somatic mutation in the mitochondrial tRNA repertoire, MtRNA$^{Leu(UUR)}$, in bone marrow cells is suspected to contribute to ineffective hematopoiesis [101].

When it comes to tRFs, some of them show enhanced expression while others are downregulated in MDS cells. Interestingly, the combined expression of 4 tRFs (chr6.tRNA157.ValCAC, chr11.tRNA17.ValTAC, chrM.tRNA12.TS1, and chrX.tRNA4.ValTAC) in treatment-naïve patients was found to have predictive value regarding the likelihood of response to treatment, and this is also the case with one mitochondrial tRNA (MT-TSI), while it is suggested that tDR-Asp family members could be used as predictors for progression to AML [94][102].

Even posttranscriptional modifications of these non-coding RNAs are suspected to interfere with MDS pathophysiology. Pseudouridylation by PUS enzymes, for instance, of mini tRFs containing 5-terminal oligoguanine, was found to regulate the renewal of human embryonic stem cells and also promote the differentiation of impaired HSPCs in MDS, indicating a potential therapeutic approach [103][104][105].

8. Short Interfering RNAs

Short or small interfering RNAs (siRNAs) are 21–25 nucleotide-long RNA molecules with a crucial role in gene silencing, primarily through mRNA degradation and by promoting heterochromatin formation. These interfering RNAs are produced via the procession of long double-stranded RNAs or short hairpin RNAs by the DICER endoribonuclease. The produced double-stranded siRNA is then packed with proteins to form the RISC. One strand of the RNA is discarded, and the remaining strand guides the RISC towards the targeted mRNA, which is recognized with perfect complementarity with the siRNA and is finally cleaved by Ago2 protein of the RISC [106][107][108].

The well-established way of action of RNA interference has not only made it possible for researchers to better understand its implications in cancer pathogenesis but also provided the possibility to utilize siRNAs towards gene expression knockdown with research and therapeutic purposes. For instance, siRNAs have been used in basic research as tools to knockdown expression of genes that are commonly mutated in MDS patients, such as ZRSR2 and antiapoptotic “survivin”, so as to better investigate their role in MDS pathophysiology [109][110]. Additionally, Mackin et al. showed that compared with azacytidine, which is a hypomethylating pharmacologic agent, siRNAs targeting *DNMT* expression (DNA methyltransferase) proved more efficient at overall demethylation within the genomic transcription units [111]. Another clue to the potential therapeutic role of siRNAs came when the siRNA-mediated inhibition of p38*a* MAP kinase, a mediator of apoptosis that is constitutively activated in low-risk MDS bone marrow cells, led to in vitro improvement of hematopoiesis from MDS myeloid and erythroid progenitors [112]. It is therefore implied that siRNAs could provide a means of therapeutically targeting multiple genes that are aberrantly expressed in MDS patients, although no such agents have been tested in MDS patients to date.

Table 2. ncRNAs with predictive value of treatment response in MDS.

Class of ncRNAs	ncRNA/Gene	Sample	Reference
miRNAs	miR-143, miR-145	BM	Venner 2013 [113]
	miR-145, miR-146	BM	Oliva 2013 [114]
	miR-34a, and miR-34a*	PB (MNCs)	Merkerova 2015 [115]
	miR-17-3p, miR-100-5p, miR-133b miR-10b-5p, miR-15a-5p/b-5p, miR-24-3p, miR-148b-3p	BM	Krejcik 2018 [116]
	miR-124	BM	Wang 2017 [117]
	miR-21	PB (serum)	Kim, 2014 [118]

Class of ncRNAs	ncRNA/Gene	Sample	Reference
	miR-423-5p, miR-126-3p, miR-151a-3p, miR-125a-5p, miR-199a-3p	PB (plasma)	Hrustincova 2020 [59]
	miR-192-5p	BM and PB (MNCs)	Mongiorgi 2023 [119]
	miR-92a	PB (plasma)	Li 2022 [120]
circRNAs	hsa_circ_0006595	BM	Merkerova 2022 [29]
lncRNAs	AC010127.5, CTC-482H14.5, RP11-557C18.3, RP4-580N22.1, RP11-419K12.2, MIR4512, MIR3164, RF00019, RPS6P16, RP11-478C6.2, RP11-177A2.5, RP4-740C4.7, AC097382.5, RP11-736I24.4	BM	Merkerova 2022 [29]
tRNA/tDRs	chr6.tRNA157.ValCAC chr11.tRNA17.ValTAC chrM.tRNA12.TS1 chrX.tRNA4.ValTAC MT-TS1 chr1.tRNA35.GlyGCC chr21.tRNA2.GlyGCC chr19.tRNA9.PseudoTTT	BM	Guo 2015 [102]

BM: bone marrow; PB: peripheral blood; MNCs: mononuclear cells.

References

1. Shastri, A.; Will, B.; Steidl, U.; Verma, A. Stem and progenitor cell alterations in myelodysplastic syndromes. Blood 2017, 129, 1586–1594.
2. Cazzola, M. Myelodysplastic Syndromes. N. Engl. J. Med. 2020, 383, 1358–1374.
3. Khoury, J.D.; Solary, E.; Abla, O.; Akkari, Y.; Alaggio, R.; Apperley, J.F.; Bejar, R.; Berti, E.; Busque, L.; Chan, J.K.C.; et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022, 36, 1703–1719.
4. Greenberg, P.; Cox, C.; LeBeau, M.M.; Fenaux, P.; Morel, P.; Sanz, G.; Sanz, M.; Vallespi, T.; Hamblin, T.; Oscier, D.; et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997, 89, 2079–2088.
5. Bernard, E.; Tuechler, H.; Greenberg, P.L.; Hasserjian, R.P.; Ossa, J.E.A.; Nannya, Y.; Devlin, S.M.; Creignou, M.; Pinel, P.; Monnier, L.; et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. NEJM Evidence 2022, 1, EVIDoa2200008.
6. Fenaux, P.; Haase, D.; Santini, V.; Sanz, G.F.; Platzbecker, U.; Mey, U. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(†☆). Ann. Oncol. 2021, 32, 142–156.
7. Ogawa, S. Genetics of MDS. Blood 2019, 133, 1049–1059.

8. Hamilton, A.J.; Baulcombe, D.C. A species of small antisense RNA in posttranscriptional gene silencing in plants. Science 1999, 286, 950–952.
9. Lee, R.C.; Feinbaum, R.L.; Ambros, V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 1993, 75, 843–854.
10. Wightman, B.; Ha, I.; Ruvkun, G. Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. Cell 1993, 75, 855–862.
11. Eddy, S.R. Non-coding RNA genes and the modern RNA world. Nat. Rev. Genet. 2001, 2, 919–929.
12. Smit, S.; Widmann, J.; Knight, R. Evolutionary rates vary among rRNA structural elements. Nucleic. Acids Res. 2007, 35, 3339–3354.
13. Aravin, A.; Gaidatzis, D.; Pfeffer, S.; Lagos-Quintana, M.; Landgraf, P.; Iovino, N.; Morris, P.; Brownstein, M.J.; Kuramochi-Miyagawa, S.; Nakano, T.; et al. A novel class of small RNAs bind to MILI protein in mouse testes. Nature 2006, 442, 203–207.
14. Bachellerie, J.P.; Cavaille, J.; Huttenhofer, A. The expanding snoRNA world. Biochimie 2002, 84, 775–790.
15. Guttman, M.; Amit, I.; Garber, M.; French, C.; Lin, M.F.; Feldser, D.; Huarte, M.; Zuk, O.; Carey, B.W.; Cassady, J.P.; et al. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature 2009, 458, 223–227.
16. Zhang, P.; Wu, W.; Chen, Q.; Chen, M. Non-Coding RNAs and their Integrated Networks. J. Integr. Bioinform. 2019, 16, 20190027.
17. Yan, H.; Bu, P. Non-coding RNA in cancer. Essays Biochem. 2021, 65, 625–639.
18. Awasthi, R.; Singh, A.K.; Mishra, G.; Maurya, A.; Chellappan, D.K.; Gupta, G.; Hansbro, P.M.; Dua, K. An Overview of Circular RNAs. Adv. Exp. Med. Biol. 2018, 1087, 3–14.
19. Jiao, S.; Wu, S.; Huang, S.; Liu, M.; Gao, B. Advances in the Identification of Circular RNAs and Research Into circRNAs in Human Diseases. Front. Genet. 2021, 12, 665233.
20. Bach, D.H.; Lee, S.K.; Sood, A.K. Circular RNAs in Cancer. Mol. Ther. Nucleic. Acids 2019, 16, 118–129.
21. Guo, S.S.; Li, B.X.; Zou, D.B.; Yang, S.J.; Sheng, L.X.; Ouyang, G.F.; Mu, Q.T.; Huang, H. Tip of the iceberg: Roles of circRNAs in hematological malignancies. Am. J. Cancer Res. 2020, 10, 367–382.
22. Dostalova Merkerova, M.; Krejcik, Z.; Szikszai, K.; Kundrat, D. Circular RNAs in Hematopoiesis with a Focus on Acute Myeloid Leukemia and Myelodysplastic Syndrome. Int. J. Mol. Sci. 2020, 21, 5972.

23. Liang, D.; Tatomer, D.C.; Luo, Z.; Wu, H.; Yang, L.; Chen, L.L.; Cherry, S.; Wilusz, J.E. The Output of Protein-Coding Genes Shifts to Circular RNAs When the Pre-mRNA Processing Machinery Is Limiting. Mol. Cell 2017, 68, 940–954.
24. Wedge, E.; Ahmadov, U.; Hansen, T.B.; Gao, Z.; Tulstrup, M.; Come, C.; Nonavinkere Srivatsan, S.; Ahmed, T.; Jespersen, J.S.; Schlotmann, B.C.; et al. Impact of U2AF1 mutations on circular RNA expression in myelodysplastic neoplasms. Leukemia 2023, 37, 1113–1125.
25. Wedge, E.; Côme, C.R.M.; Hansen, J.W.; Jespersen, J.S.; Dahl, M.; Schöllkopf, C.; Raaschou-Jensen, K.; Porse, B.; Weischenfeldt, J.; Kristensen, L.S.; et al. P751: CHARACTERIZING CIRCULAR RNA EXPRESSION IN MYELODYSPLASTIC SYNDROME. HemaSphere 2022, 6, 646–647.
26. Deng, F.; Zhang, C.; Lu, T.; Liao, E.J.; Huang, H.; Wei, S. Roles of circRNAs in hematological malignancies. Biomark Res. 2022, 10, 50.
27. Wu, W.L.; Li, S.; Zhao, G.J.; Li, N.Y.; Wang, X.Q. Identification of circular RNAs as novel biomarkers and potentially functional competing endogenous RNA network for myelodysplastic syndrome patients. Cancer Sci. 2021, 112, 1888–1898.
28. Zhou, F.; Zhang, S.; Huo, M.; Zhou, Y.; Jiang, L.; Zhou, H.; Qu, Y. The Circular RNA Circ-ANAPC7 as a Biomarker for the Risk Stratification of Myelodysplastic Syndrome. Indian J. Hematol. Blood Transfus. 2022, 39, 371–375.
29. Merkerova, M.D.; Klema, J.; Kundrat, D.; Szikszai, K.; Krejcik, Z.; Hrustincova, A.; Trsova, I.; Le, A.V.; Cermak, J.; Jonasova, A.; et al. Noncoding RNAs and Their Response Predictive Value in Azacitidine-treated Patients with Myelodysplastic Syndrome and Acute Myeloid Leukemia with Myelodysplasia-related Changes. Cancer Genom. Proteom. 2022, 19, 205–228.
30. Gao, N.; Li, Y.; Li, J.; Gao, Z.; Yang, Z.; Li, Y.; Liu, H.; Fan, T. Long Non-Coding RNAs: The Regulatory Mechanisms, Research Strategies, and Future Directions in Cancers. Front. Oncol. 2020, 10, 598817.
31. Statello, L.; Guo, C.J.; Chen, L.L.; Huarte, M. Gene regulation by long non-coding RNAs and its biological functions. Nat. Rev. Mol. Cell Biol. 2021, 22, 96–118.
32. Wagner, L.A.; Christensen, C.J.; Dunn, D.M.; Spangrude, G.J.; Georgelas, A.; Kelley, L.; Esplin, M.S.; Weiss, R.B.; Gleich, G.J. EGO, a novel, noncoding RNA gene, regulates eosinophil granule protein transcript expression. Blood 2007, 109, 5191–5198.
33. Brannan, C.I.; Dees, E.C.; Ingram, R.S.; Tilghman, S.M. The product of the H19 gene may function as an RNA. Mol. Cell. Biol. 1990, 10, 28–36.
34. Venkatraman, A.; He, X.C.; Thorvaldsen, J.L.; Sugimura, R.; Perry, J.M.; Tao, F.; Zhao, M.; Christenson, M.K.; Sanchez, R.; Yu, J.Y.; et al. Maternal imprinting at the H19-Igf2 locus maintains adult haematopoietic stem cell quiescence. Nature 2013, 500, 345–349.

35. Andrea, H.; Katarina, S.; Zdeněk, K.; Nikoleta, L.; Michaela Dostálová, M. Noncoding RNAs in Myelodysplastic Syndromes. In Recent Developments in Myelodysplastic Syndromes; Ota, F., Ed.; IntechOpen: Rijeka, Italy, 2018.
36. Wu, Z.; Gao, S.; Zhao, X.; Chen, J.; Keyvanfar, K.; Feng, X.; Kajigaya, S.; Young, N.S. Long noncoding RNAs of single hematopoietic stem and progenitor cells in healthy and dysplastic human bone marrow. Haematologica 2019, 104, 894–906.
37. Hu, W.; Yuan, B.; Flygare, J.; Lodish, H.F. Long noncoding RNA-mediated anti-apoptotic activity in murine erythroid terminal differentiation. Genes Dev. 2011, 25, 2573–2578.
38. Qiu, Y.; Xu, M.; Huang, S. Long noncoding RNAs: Emerging regulators of normal and malignant hematopoiesis. Blood 2021, 138, 2327–2336.
39. Benetatos, L.; Hatzimichael, E.; Dasoula, A.; Dranitsaris, G.; Tsiara, S.; Syrrou, M.; Georgiou, I.; Bourantas, K.L. CpG methylation analysis of the MEG3 and SNRPN imprinted genes in acute myeloid leukemia and myelodysplastic syndromes. Leuk. Res. 2010, 34, 148–153.
40. Wong, N.K.; Huang, C.L.; Islam, R.; Yip, S.P. Long non-coding RNAs in hematological malignancies: Translating basic techniques into diagnostic and therapeutic strategies. J. Hematol. Oncol. 2018, 11, 131.
41. Zhang, Z.; Liu, T.; Wang, K.; Qu, X.; Pang, Z.; Liu, S.; Liu, Q.; Du, J. Down-regulation of long non-coding RNA MEG3 indicates an unfavorable prognosis in non-small cell lung cancer: Evidence from the GEO database. Gene 2017, 630, 49–58.
42. Tian, Z.Z.; Guo, X.J.; Zhao, Y.M.; Fang, Y. Decreased expression of long non-coding RNA MEG3 acts as a potential predictor biomarker in progression and poor prognosis of osteosarcoma. Int. J. Clin. Exp. Pathol. 2015, 8, 15138–15142.
43. Zhou, Y.; Zhang, X.; Klibanski, A. MEG3 noncoding RNA: A tumor suppressor. J. Mol. Endocrinol. 2012, 48, R45–R53.
44. Wang, W.; Xie, Y.; Chen, F.; Liu, X.; Zhong, L.L.; Wang, H.Q.; Li, Q.C. LncRNA MEG3 acts a biomarker and regulates cell functions by targeting ADAR1 in colorectal cancer. World J. Gastroenterol. 2019, 25, 3972–3984.
45. Liu, Z.; Wang, P.; Yuan, S.; Wang, Y.; Cao, P.; Wen, F.; Li, H.; Zhu, L.; Liang, L.; Wang, Z.; et al. LncRNA BC200/miR-150-5p/MYB positive feedback loop promotes the malignant proliferation of myelodysplastic syndrome. Cell Death Dis. 2022, 13, 126.
46. Zhang, S.F.; Jin, L.; Chen, Y.F. Significance of LncRNA KCNQ1OT1 expression in diagnosis and prognosis judgment of myelodysplastic syndrome. Eur. Rev. Med. Pharmacol. Sci. 2020, 24, 5558–5563.

47. Huang, H.H.; Chen, F.Y.; Chou, W.C.; Hou, H.A.; Ko, B.S.; Lin, C.T.; Tang, J.L.; Li, C.C.; Yao, M.; Tsay, W.; et al. Long non-coding RNA HOXB-AS3 promotes myeloid cell proliferation and its higher expression is an adverse prognostic marker in patients with acute myeloid leukemia and myelodysplastic syndrome. BMC Cancer 2019, 19, 617.
48. Symeonidis, A.; Chatzilygeroudi, T.; Chondrou, V.; Sgourou, A. Contingent Synergistic Interactions between Non-Coding RNAs and DNA-Modifying Enzymes in Myelodysplastic Syndromes. Int. J. Mol. Sci. 2022, 23, 16069.
49. Zhao, X.; Yin, H.; Li, N.; Zhu, Y.; Shen, W.; Qian, S.; He, G.; Li, J.; Wang, X. An Integrated Regulatory Network Based on Comprehensive Analysis of mRNA Expression, Gene Methylation and Expression of Long Non-coding RNAs (lncRNAs) in Myelodysplastic Syndromes. Front. Oncol. 2019, 9, 200.
50. Szikszai, K.; Krejcik, Z.; Klema, J.; Loudova, N.; Hrustincova, A.; Belickova, M.; Hruba, M.; Vesela, J.; Stranecky, V.; Kundrat, D.; et al. LncRNA Profiling Reveals That the Deregulation of H19, WT1-AS, TCL6, and LEF1-AS1 Is Associated with Higher-Risk Myelodysplastic Syndrome. Cancers 2020, 12, 2726.
51. Yao, C.-Y.; Chen, C.-H.; Huang, H.-H.; Hou, H.-A.; Lin, C.-C.; Tseng, M.-H.; Kao, C.-J.; Lu, T.-P.; Chou, W.-C.; Tien, H.-F. A 4-lncRNA scoring system for prognostication of adult myelodysplastic syndromes. Blood Adv. 2017, 1, 1505–1516.
52. Ozata, D.M.; Gainetdinov, I.; Zoch, A.; O'Carroll, D.; Zamore, P.D. PIWI-interacting RNAs: Small RNAs with big functions. Nat. Rev. Genet. 2019, 20, 89–108.
53. Klattenhoff, C.; Theurkauf, W. Biogenesis and germline functions of piRNAs. Development 2008, 135, 3–9.
54. Yuan, C.; Qin, H.; Ponnusamy, M.; Chen, Y.; Lin, Z. PIWI-interacting RNA in cancer: Molecular mechanisms and possible clinical implications (Review). Oncol. Rep. 2021, 46, 1–16.
55. Chen, S.; Ben, S.; Xin, J.; Li, S.; Zheng, R.; Wang, H.; Fan, L.; Du, M.; Zhang, Z.; Wang, M. The biogenesis and biological function of PIWI-interacting RNA in cancer. J. Hematol. Oncol. 2021, 14, 93.
56. Genzor, P.; Cordts, S.C.; Bokil, N.V.; Haase, A.D. Aberrant expression of select piRNA-pathway genes does not reactivate piRNA silencing in cancer cells. Proc. Natl. Acad. Sci. USA 2019, 116, 11111–11112.
57. Beck, D.; Ayers, S.; Wen, J.; Brandl, M.B.; Pham, T.D.; Webb, P.; Chang, C.C.; Zhou, X. Integrative analysis of next generation sequencing for small non-coding RNAs and transcriptional regulation in Myelodysplastic Syndromes. BMC Med. Genom. 2011, 4, 19.
58. Merkerova, M.D.; Krejcik, Z. Transposable elements and Piwi-interacting RNAs in hemato-oncology with a focus on myelodysplastic syndrome (Review). Int. J. Oncol. 2021, 59, 105.

59. Hrustincova, A.; Krejcik, Z.; Kundrat, D.; Szikszai, K.; Belickova, M.; Pecherkova, P.; Klema, J.; Vesela, J.; Hruba, M.; Cermak, J.; et al. Circulating Small Noncoding RNAs Have Specific Expression Patterns in Plasma and Extracellular Vesicles in Myelodysplastic Syndromes and Are Predictive of Patient Outcome. Cells 2020, 9, 794.
60. Sloan, K.E.; Warda, A.S.; Sharma, S.; Entian, K.D.; Lafontaine, D.L.J.; Bohnsack, M.T. Tuning the ribosome: The influence of rRNA modification on eukaryotic ribosome biogenesis and function. RNA Biol. 2017, 14, 1138–1152.
61. Baßler, J.; Hurt, E. Eukaryotic Ribosome Assembly. Annu. Rev. Biochem. 2019, 88, 281–306.
62. Elhamamsy, A.R.; Metge, B.J.; Alsheikh, H.A.; Shevde, L.A.; Samant, R.S. Ribosome Biogenesis: A Central Player in Cancer Metastasis and Therapeutic Resistance. Cancer Res. 2022, 82, 2344–2353.
63. Moss, T.; Langlois, F.; Gagnon-Kugler, T.; Stefanovsky, V. A housekeeper with power of attorney: The rRNA genes in ribosome biogenesis. Cell. Mol. Life Sci. 2007, 64, 29–49.
64. Bielczyk-Maczyńska, E.; Lam Hung, L.; Ferreira, L.; Fleischmann, T.; Weis, F.; Fernández-Pevida, A.; Harvey, S.A.; Wali, N.; Warren, A.J.; Barroso, I.; et al. The Ribosome Biogenesis Protein Nol9 Is Essential for Definitive Hematopoiesis and Pancreas Morphogenesis in Zebrafish. PLoS Genet. 2015, 11, e1005677.
65. Tummala, H.; Walne, A.J.; Williams, M.; Bockett, N.; Collopy, L.; Cardoso, S.; Ellison, A.; Wynn, R.; Leblanc, T.; Fitzgibbon, J.; et al. DNAJC21 Mutations Link a Cancer-Prone Bone Marrow Failure Syndrome to Corruption in 60S Ribosome Subunit Maturation. Am. J. Hum. Genet. 2016, 99, 115–124.
66. Penzo, M.; Montanaro, L. Turning Uridines around: Role of rRNA Pseudouridylation in Ribosome Biogenesis and Ribosomal Function. Biomolecules 2018, 8, 38.
67. Narla, A.; Ebert, B.L. Ribosomopathies: Human disorders of ribosome dysfunction. Blood 2010, 115, 3196–3205.
68. Cheah, J.J.C.; Hahn, C.N.; Hiwase, D.K.; Scott, H.S.; Brown, A.L. Myeloid neoplasms with germline DDX41 mutation. Int. J. Hematol. 2017, 106, 163–174.
69. Akef, A.; McGraw, K.; Cappell, S.D.; Larson, D.R. Ribosome biogenesis is a downstream effector of the oncogenic U2AF1-S34F mutation. PLoS Biol. 2020, 18, e3000920.
70. Raval, A.; Sridhar, K.J.; Patel, S.; Turnbull, B.B.; Greenberg, P.L.; Mitchell, B.S. Reduced rRNA expression and increased rDNA promoter methylation in CD34+ cells of patients with myelodysplastic syndromes. Blood 2012, 120, 4812–4818.
71. Raval, A.; Pollyea, D.A.; Shridhar, K.J.; Patel, S.; Greenberg, P.L.; Mitchell, B.S. Ribosomal RNA Expression In CD34+ Hematopoietic Progenitor Cells Inversely Correlates with Ribosomal DNA

Methylation In Myelodysplastic Syndromes. Blood 2010, 116, 1682.

72. Lambert, M.; Benmoussa, A.; Provost, P. Small Non-Coding RNAs Derived From Eukaryotic Ribosomal RNA. Noncoding RNA 2019, 5, 16.
73. Cherlin, T.; Magee, R.; Jing, Y.; Pliatsika, V.; Loher, P.; Rigoutsos, I. Ribosomal RNA fragmentation into short RNAs (rRFs) is modulated in a sex- and population of origin-specific manner. BMC Biol. 2020, 18, 38.
74. Morais, P.; Adachi, H.; Yu, Y.T. Spliceosomal snRNA Epitranscriptomics. Front. Genet. 2021, 12, 652129.
75. Huang, Z.H.; Du, Y.P.; Wen, J.T.; Lu, B.F.; Zhao, Y. snoRNAs: Functions and mechanisms in biological processes, and roles in tumor pathophysiology. Cell Death Discov. 2022, 8, 259.
76. Wajahat, M.; Bracken, C.P.; Orang, A. Emerging Functions for snoRNAs and snoRNA-Derived Fragments. Int. J. Mol. Sci. 2021, 22, 10193.
77. Dong, J.; Wang, H.; Zhang, Z.; Yang, L.; Qian, X.; Qian, W.; Han, Y.; Huang, H.; Qian, P. Small but strong: Pivotal roles and potential applications of snoRNAs in hematopoietic malignancies. Front. Oncol. 2022, 12, 939465.
78. Calvo Sánchez, J.; Köhn, M. Small but Mighty-The Emerging Role of snoRNAs in Hematological Malignancies. Noncoding RNA 2021, 7, 68.
79. Challakkara, M.F.; Chhabra, R. snoRNAs in hematopoiesis and blood malignancies: A comprehensive review. J. Cell. Physiol. 2023, 238, 1207–1225.
80. Chlon, T.M.; Stepanchick, E.; Hershberger, C.E.; Daniels, N.J.; Hueneman, K.M.; Kuenzi Davis, A.; Choi, K.; Zheng, Y.; Gurnari, C.; Haferlach, T.; et al. Germline DDX41 mutations cause ineffective hematopoiesis and myelodysplasia. Cell Stem Cell 2021, 28, 1966–1981.
81. Michel, C.I.; Holley, C.L.; Scruggs, B.S.; Sidhu, R.; Brookheart, R.T.; Listenberger, L.L.; Behlke, M.A.; Ory, D.S.; Schaffer, J.E. Small nucleolar RNAs U32a, U33, and U35a are critical mediators of metabolic stress. Cell Metab. 2011, 14, 33–44.
82. Gañán-Gómez, I.; Wei, Y.; Yang, H.; Pierce, S.; Bueso-Ramos, C.; Calin, G.; Boyano-Adánez Mdel, C.; García-Manero, G. Overexpression of miR-125a in myelodysplastic syndrome CD34+ cells modulates NF-κB activation and enhances erythroid differentiation arrest. PLoS ONE 2014, 9, e93404.
83. Ma, Y.; Qiao, T.; Meng, Y. Increased expression of miR-22 corresponds to the high-risk subtypes of myelodysplastic syndromes and lower OS rate. Leuk. Lymphoma 2020, 61, 1763–1765.
84. Wen, J.; Huang, Y.; Li, H.; Zhang, X.; Cheng, P.; Deng, D.; Peng, Z.; Luo, J.; Zhao, W.; Lai, Y.; et al. Over-expression of miR-196b-5p is significantly associated with the progression of myelodysplastic syndrome. Int. J. Hematol. 2017, 105, 777–783.

85. Kirimura, S.; Kurata, M.; Nakagawa, Y.; Onishi, I.; Abe-Suzuki, S.; Abe, S.; Yamamoto, K.; Kitagawa, M. Role of microRNA-29b in myelodysplastic syndromes during transformation to overt leukaemia. Pathology 2016, 48, 233–241.

86. Wan, C.; Wen, J.; Liang, X.; Xie, Q.; Wu, W.; Wu, M.; Liu, Z. Identification of miR-320 family members as potential diagnostic and prognostic biomarkers in myelodysplastic syndromes. Sci. Rep. 2021, 11, 183.

87. Choi, J.S.; Nam, M.H.; Yoon, S.Y.; Kang, S.H. MicroRNA-194-5p could serve as a diagnostic and prognostic biomarker in myelodysplastic syndromes. Leuk. Res. 2015, 39, 763–768.

88. Kang, S.H.; Choi, J.S. MicroRNA-661 upregulation in myelodysplastic syndromes induces apoptosis through p53 activation and associates with decreased overall survival. Leuk. Lymphoma 2019, 60, 2779–2786.

89. Choi, Y.; Hur, E.H.; Moon, J.H.; Goo, B.K.; Choi, D.R.; Lee, J.H. Expression and prognostic significance of microRNAs in Korean patients with myelodysplastic syndrome. Korean J. Intern. Med. 2019, 34, 390–400.

90. Liang, X.; Shi, Z.; Huang, X.; Wan, C.; Zhu, S.; Wu, M.; Li, Z.; Tang, Z.; Li, J.; Zhao, W.; et al. MiR-181a-2-3p as a potential diagnostic and prognostic marker for myelodysplastic syndrome. Hematology 2022, 27, 1246–1252.

91. Kontandreopoulou, C.-N.; Syriopoulou, S.; Diamantopoulos, P.T.; Giannakopoulou, N.; Vlachopoulou, D.; Katsiampoura, P.; Stafylidis, C.; Dimou, M.; Galanopoulos, A.; Papageorgiou, S.; et al. Micrornas Analysis in Patients with Myelodysplastic Syndrome. Possible Implications in Risk Stratification. Blood 2022, 140, 6958–6959.

92. Dostalova Merkerova, M.; Hrustincova, A.; Krejcik, Z.; Votavova, H.; Ratajova, E.; Cermak, J.; Belickova, M. Microarray profiling defines circulating microRNAs associated with myelodysplastic syndromes. Neoplasma 2017, 64, 571–578.

93. Zuo, Z.; Maiti, S.; Hu, S.; Loghavi, S.; Calin, G.A.; Garcia-Manero, G.; Kantarjian, H.M.; Medeiros, L.J.; Cooper, L.J.; Bueso-Ramos, C.E. Plasma circulating-microRNA profiles are useful for assessing prognosis in patients with cytogenetically normal myelodysplastic syndromes. Mod. Pathol. 2015, 28, 373–382.

94. Guo, Y.; Strickland, S.A.; Mohan, S.; Li, S.; Bosompem, A.; Vickers, K.C.; Zhao, S.; Sheng, Q.; Kim, A.S. MicroRNAs and tRNA-derived fragments predict the transformation of myelodysplastic syndromes to acute myeloid leukemia. Leuk. Lymphoma 2017, 58, 2144–2155.

95. Berg, M.D.; Brandl, C.J. Transfer RNAs: Diversity in form and function. RNA Biol. 2021, 18, 316–339.

96. Avcilar-Kucukgoze, I.; Kashina, A. Hijacking tRNAs From Translation: Regulatory Functions of tRNAs in Mammalian Cell Physiology. Front. Mol. Biosci. 2020, 7, 610617.

97. Weng, Q.; Wang, Y.; Xie, Y.; Yu, X.; Zhang, S.; Ge, J.; Li, Z.; Ye, G.; Guo, J. Extracellular vesicles-associated tRNA-derived fragments (tRFs): Biogenesis, biological functions, and their role as potential biomarkers in human diseases. J. Mol. Med. 2022, 100, 679–695.
98. Lee, Y.S.; Shibata, Y.; Malhotra, A.; Dutta, A. A novel class of small RNAs: tRNA-derived RNA fragments (tRFs). Genes Dev. 2009, 23, 2639–2649.
99. Mei, Y.; Yong, J.; Liu, H.; Shi, Y.; Meinkoth, J.; Dreyfuss, G.; Yang, X. tRNA binds to cytochrome c and inhibits caspase activation. Mol. Cell 2010, 37, 668–678.
100. Liberante, F.G.; Lappin, K.; Barros, E.M.; Vohhodina, J.; Grebien, F.; Savage, K.I.; Mills, K.I. Altered splicing and cytoplasmic levels of tRNA synthetases in SF3B1-mutant myelodysplastic syndromes as a therapeutic vulnerability. Sci. Rep. 2019, 9, 2678.
101. Gattermann, N.; Wulfert, M.; Junge, B.; Germing, U.; Haas, R.; Hofhaus, G. Ineffective hematopoiesis linked with a mitochondrial tRNA mutation (G3242A) in a patient with myelodysplastic syndrome. Blood 2004, 103, 1499–1502.
102. Guo, Y.; Bosompem, A.; Mohan, S.; Erdogan, B.; Ye, F.; Vickers, K.C.; Sheng, Q.; Zhao, S.; Li, C.I.; Su, P.F.; et al. Transfer RNA detection by small RNA deep sequencing and disease association with myelodysplastic syndromes. BMC Genom. 2015, 16, 727.
103. Guzzi, N.; Muthukumar, S.; Cieśla, M.; Todisco, G.; Ngoc, P.C.T.; Madej, M.; Munita, R.; Fazio, S.; Ekström, S.; Mortera-Blanco, T.; et al. Pseudouridine-modified tRNA fragments repress aberrant protein synthesis and predict leukaemic progression in myelodysplastic syndrome. Nat. Cell Biol. 2022, 24, 299–306.
104. Guzzi, N.; Cieśla, M.; Ngoc, P.C.T.; Lang, S.; Arora, S.; Dimitriou, M.; Pimková, K.; Sommarin, M.N.E.; Munita, R.; Lubas, M.; et al. Pseudouridylation of tRNA-Derived Fragments Steers Translational Control in Stem Cells. Cell 2018, 173, 1204–1216.
105. Magee, R.; Rigoutsos, I. On the expanding roles of tRNA fragments in modulating cell behavior. Nucleic. Acids Res. 2020, 48, 9433–9448.
106. Dana, H.; Chalbatani, G.M.; Mahmoodzadeh, H.; Karimloo, R.; Rezaiean, O.; Moradzadeh, A.; Mehmandoost, N.; Moazzen, F.; Mazraeh, A.; Marmari, V.; et al. Molecular Mechanisms and Biological Functions of siRNA. Int. J. Biomed. Sci. 2017, 13, 48–57.
107. Friedrich, M.; Aigner, A. Therapeutic siRNA: State-of-the-Art and Future Perspectives. BioDrugs 2022, 36, 549–571.
108. Carthew, R.W.; Sontheimer, E.J. Origins and Mechanisms of miRNAs and siRNAs. Cell 2009, 136, 642–655.
109. Sloand, E.M.; Pfannes, L.; Chen, G.; Shah, S.; Solomou, E.E.; Barrett, J.; Young, N.S. CD34 cells from patients with trisomy 8 myelodysplastic syndrome (MDS) express early apoptotic markers

but avoid programmed cell death by up-regulation of antiapoptotic proteins. Blood 2007, 109, 2399–2405.

110. Madan, V.; Kanojia, D.; Li, J.; Okamoto, R.; Sato-Otsubo, A.; Kohlmann, A.; Sanada, M.; Grossmann, V.; Sundaresan, J.; Shiraishi, Y.; et al. Aberrant splicing of U12-type introns is the hallmark of ZRSR2 mutant myelodysplastic syndrome. Nat. Commun. 2015, 6, 6042.
111. Mackin, S.J.; O'Neill, K.M.; Walsh, C.P. Comparison of DNMT1 inhibitors by methylome profiling identifies unique signature of 5-aza-2'deoxycytidine. Epigenomics 2018, 10, 1085–1101.
112. Wang, Y.; Kellner, J.; Liu, L.; Zhou, D. Inhibition of p38 mitogen-activated protein kinase promotes ex vivo hematopoietic stem cell expansion. Stem Cells Dev. 2011, 20, 1143–1152.
113. Venner, C.P.; Woltosz, J.W.; Nevill, T.J.; Deeg, H.J.; Caceres, G.; Platzbecker, U.; Scott, B.L.; Sokol, L.; Sung, S.; List, A.F.; et al. Correlation of clinical response and response duration with miR-145 induction by lenalidomide in CD34(+) cells from patients with del(5q) myelodysplastic syndrome. Haematologica 2013, 98, 409–413.
114. Oliva, E.N.; Cuzzola, M.; Aloe Spiriti, M.A.; Poloni, A.; Laganà, C.; Rigolino, C.; Morabito, F.; Galimberti, S.; Ghio, R.; Cortelezzi, A.; et al. Biological activity of lenalidomide in myelodysplastic syndromes with del5q: Results of gene expression profiling from a multicenter phase II study. Ann. Hematol. 2013, 92, 25–32.
115. Merkerova, M.D.; Krejcik, Z.; Belickova, M.; Hrustincova, A.; Klema, J.; Stara, E.; Zemanova, Z.; Michalova, K.; Cermak, J.; Jonasova, A. Genome-wide miRNA profiling in myelodysplastic syndrome with del(5q) treated with lenalidomide. Eur. J. Haematol. 2015, 95, 35–43.
116. Krejcik, Z.; Belickova, M.; Hrustincova, A.; Votavova, H.; Jonasova, A.; Cermak, J.; Dyr, J.E.; Merkerova, M.D. MicroRNA profiles as predictive markers of response to azacitidine therapy in myelodysplastic syndromes and acute myeloid leukemia. Cancer Biomark. 2018, 22, 101–110.
117. Wang, H.; Zhang, T.T.; Jin, S.; Liu, H.; Zhang, X.; Ruan, C.G.; Wu, D.P.; Han, Y.; Wang, X.Q. Pyrosequencing quantified methylation level of miR-124 predicts shorter survival for patients with myelodysplastic syndrome. Clin. Epigenetics 2017, 9, 91.
118. Kim, Y.; Cheong, J.W.; Kim, Y.K.; Eom, J.I.; Jeung, H.K.; Kim, S.J.; Hwang, D.; Kim, J.S.; Kim, H.J.; Min, Y.H. Serum microRNA-21 as a potential biomarker for response to hypomethylating agents in myelodysplastic syndromes. PLoS ONE 2014, 9, e86933.
119. Mongiorgi, S.; De Stefano, A.; Ratti, S.; Indio, V.; Astolfi, A.; Casalin, I.; Pellagatti, A.; Paolini, S.; Parisi, S.; Cavo, M.; et al. A miRNA screening identifies miR-192-5p as associated with response to azacitidine and lenalidomide therapy in myelodysplastic syndromes. Clin. Epigenetics 2023, 15, 27.
120. Li, H.; Xie, C.; Lu, Y.; Chang, K.; Guan, F.; Li, X. Exosomal miR92a Promotes Cytarabine Resistance in Myelodysplastic Syndromes by Activating Wnt/β-catenin Signal Pathway.

Biomolecules 2022, 12, 1448.

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