Epigenetics and Non-Coding RNAs in Multiple Myeloma

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Multiple myeloma (MM) accounts for about 10% of hematological malignancies. It is a plasma cell malignancy that originates from the post-germinal lymphoid B-cell lineage, and is characterized by an uncontrolled clonal growth of plasma cells. The discovery of non-coding RNAs as key actors in multiple myeloma has broadened the molecular landscape of this disease, together with classical epigenetic factors such as methylation and acetylation. microRNAs and long non-coding RNAs comprise the majority of the described non-coding RNAs dysregulated in multiple myeloma, while circular RNAs are recently emerging as promising molecular targets.

CRISPR-Cas long non-coding RNA microRNA multiple myeloma non-coding RNA

1. Introduction

Multiple myeloma (MM) accounts for about 10% of hematological malignancies. It is a plasma cell malignancy that originates from the post-germinal lymphoid B-cell lineage, and is characterized by an uncontrolled clonal growth of plasma cells. It is preceded by monoclonal gammopathy of undetermined significance (MGUS) that progresses to smoldering myeloma and finally to symptomatic MM [1].

Frequently, these clones of plasma cells invade the adjacent bone and occasionally infiltrate multiple organs, causing symptoms such as hypercalcemia, renal insufficiency, anemia, and bone lesions. In the past decades, the therapeutic landscape of MM has improved with the development of targeted therapies, chemotherapeutic agents, and immunotherapy. Despite this, relapses are common [2].

2. Methylation

DNA methylation is a central epigenetic modification in cancer. It plays an important regulatory role in transcription, chromatin structure and genomic stability, X chromosome inactivation, genomic imprinting, and carcinogenesis [3]. Global hypomethylation in cancer cells was one of the first epigenetic alterations found in carcinogenesis. Moreover, certain genes are inactivated due to hypermethylation of CpG islands in regulatory regions. This process is catalyzed by DNA methyltransferases (DNMT) and involves the addition of a methyl group to the carbon 5 position of the cytosine ring in the CpG dinucleotide, generating a 5-methylcytosine (5mC) [4]. The opposite process of demethylation is mainly catalyzed by TET enzymes, which can oxidize 5mC to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC). These oxidized products can then be removed by base excision repair and substituted by cytosine in a locus-specific manner [5]. However, despite the finding of

TET2 loss-of-function mutations in some hematological malignancies, there is very few knowledge about their role in MM [6].

Methylation patterns have been shown to be different depending on the stage of MM progression. In non-malignant stages and MGUS, demethylation occurs mainly in CpG islands. At the transition from MGUS to MM, the key feature is a strong loss of methylation, associated with genome instability. In malignant stages, changes in methylation are widespread in the genome, outside of CpG islands, and affect various pathways, such as cell cycle and transcriptional activity regulators [7]. *DNMT3A* is hypermethylated and underexpressed in MM, leading to a global hypomethylation. Interestingly, DNA hypermethylation in B-cell specific enhancers seems to be a key feature of MM-staged cells. These hypermethylated regions are located in binding sites of B-cell specific transcription factors, thus leading to an impaired expression of those and, consequently, a more non-differentiated cell profile in MM cells. This hypermethylation in B-cell-specific enhancers has been found in stem cells; it is progressively eliminated in non-malignant B cells and reacquired again in MM cells [8].

Genomic studies have been performed to explain the role of promoter hypermethylation of tumor suppressor genes. Preliminary studies revealed that in MM patients, there was aberrant methylation in genes such as *SOCS-1*, p16, *CDH1*, *DAPK1*, and p73. Hypermethylation of crucial tumor modulating genes, such as *GPX3*, *RBP1*, *SPARC*, and *TGFBI* has been associated with a significantly shorter overall survival, independently of age, International Staging System (ISS) score, and adverse cytogenetics [9][10].

Moreover, several signaling pathways were found to be dysregulated in MM. STAT3 overexpression due to promoter hypermethylation was associated with an adverse prognosis and was mainly induced by IL-6 signaling [11]. DNA methyltransferase inhibitors (DNMTi), such as 5-azacytidine, were shown to revert hypermethylation and exerted synergistic anti-MM effects with bortezomib [12]. Therefore, several clinical trials have been conducted to assess DNMTi efficacy in combination with anti-MM agents, such as lenalidomide or dexamethasone [13].

3. Acetylation

Acetylation is one of the major reversible post-translational modifications that introduces an acetyl group on histone lysine residues, thus modifying the gene expression pattern. It involves a dynamic process, consisting of a balance between the activity of histone acetyltransferases (HATs) and histone deacetylases (HDACs). This balance serves as a key regulator that influences many cellular processes such as cell cycle, chromatin structure, and gene expression [4].

HATs catalyze the attachment of acetyl groups, resulting in a less condensed chromatin structure. CREB-binding protein CBP/p300 family is a HAT type A enzyme, whose mutations are often related to cancer development. It is located in the nucleus and involved in the acetylation of histones. CBP/p300 is dysregulated in hematological malignancies [14] and, in the case of MM, inhibition of CBP/p300 has been shown to induce cell death via the reduction of IRF4 expression [15]. This could open a promising therapeutic strategy but however, the majority of studies are focused on HDACs, which catalyze the amide hydrolysis of acetylated lysines. HDACs constitute a

family of 18 proteins subdivided into four classes based on homology to yeast HDACs: class I (HDAC1-3, HDAC8), class IIa (HDAC4-5, HDAC7, HDAC9), class IIb (HDAC6, HDAC10), class III (SIRT1-7), and class IV (HDAC11). Alterations in their activity have been discovered in a broad range of tumors, including MM. Their targets include histones but also non-histone proteins such as p53, Hsp90, and p65 NF-κB [16].

The essential role played by HDACs in cancer and MM progression has led to the development of HDAC inhibition strategies. Pan-HDAC inhibitors seem to show stronger clinical inhibition of HDAC1, HDAC2, HDAC3, and HDAC6 than other HDACs. This suggests that their anti-tumor activity may focus on class I and class IIb HDAC inhibition [17]. Several HDAC inhibitors, such as romidespin (class I HDAC inhibitor) or panobinostat (pan-HDAC inhibitor) induce high cytotoxicity against MM cells, especially in combination with proteasome inhibitors such as bortezomib. Nevertheless, due to the wide range of targets, they also showed unfavorable side effects in clinical trials [18]. To avoid these problems, the development of selective HDAC inhibitors has become critical in MM research. To date, HDAC6 inhibitors (i.e., ricolinostat) are the ones showing encouraging results in MM treatment. HDAC6 is essential for aggresome formation, an alternative clearance pathway that is activated in response to proteasome inhibition to eliminate misfolded proteins [18]. The synergistic inhibition of proteasome and aggresome pathways leads to the accumulation of misfolded proteins, resulting in cell death [19], therefore, unveiling a promising strategy involving the combination of HDAC6 and proteasome inhibitors to tackle resistance in MM.

4. Non-Coding RNAs

Efforts in the study of the genome have classically focused on protein-coding genes that include only a small percentage of the mammalian genome. In the last years, a special emphasis has been placed on the non-protein-coding genome. The development of genomic and transcriptomic technologies has highlighted that 70% of the transcribed human genome corresponds to ncRNAs [20]. ncRNAs are divided in two groups: structural and regulatory ncRNAs. Structural ncRNAs include transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs). These ncRNAs are part of the machinery involved in protein synthesis. Regulatory ncRNAs are divided depending on their size: microRNAs (miRNAs) and PIWI-interacting RNAs (piRNAs) are less than 200 nucleotides long, while long non-coding RNAs (lncRNAs) comprise the biggest. Another type of ncRNAs are circular RNAs (circRNAs), which mainly function as miRNA sponges [21].

4.1. microRNAs

miRNAs are 19 to 25 base-pair-long ncRNA molecules that trigger the translational repression, and sometimes degradation, of target messenger RNAs (mRNAs) with complementary sequences. Alterations in miRNAs have raised special interest in cancer research, including MM (**Table 1**). miRNAs constitute one of the central and most-studied post-transcriptional regulator components affecting myelomagenesis, MM progression, development, and prognosis. miRNAs can be classified into tumor-suppressive miRNAs, when they target an oncogenic gene, or oncogenic miRNAs, when they target a tumor suppressor gene, and they are tissue-specific.

Activity/Pathway Affected	miRNA	Status [1]	Target	References
Enhances PI3K/Akt pathway	miR-20a	↑	*EGR2*, *PTEN*	[22][23]
	miR-21	↑	*PIAS3*	[24]
	miR-25-3p	↑	*PTEN*	[25]
	miR-221/222	↑	*PUMA*, *PTEN*, *CDKN1B*, p27	[26]
	miR-410	↑	*KLF10*	[27]
Enhances mTOR pathway	miR-19b	↑	*TSC1*	[28][29]
	miR-135b, miR-642a	↑	*DEPTOR*	[30]
Related to a hypoxia phenotype	miR-210	↑	*DIMT1*	[31][32]
	miR-1305	↑	*MDM2*, *IGF1*, *FGF2*	[33]
Disrupts PRC2 activity	miR-124	↑	*EZH2*	[34]
Modulates microenvironment	miR-146a	↑	Not described	[35]
	miR-155	↑	Not described	[36]
Promotes proliferation, circulating miRNAs	miR-17-92	↑	*BIM*	[28]

Activity/Pathway Affected	miRNA	Status [1]	Target	References
Circulating miRNA	miR-221/222	↑		[26]
	miR-1	↑	Not described	[37]
	miR-133a/b	↑	Not described	[37]
	miR-135b	↑	*HIF1A*	[38][39]
	miR-146b	↑	Not described	[40]
	miR-181a	↑	*BCL2L11*	[41][42]
	miR-214	↓	*CD276*	[43]
	miR-125b	↓	*IL6R*, *STAT3*, *MALAT1*	[44][45]
	miR-331-3p	↓	*IL6R*	[46]
Represses JAK/STAT pathway	miR-375	↓	*PDPK1*	[47]
	miR-451	↓	*IL6R*	[48]
	let-7b-5p	↓	*IGF1R*	[49]
Regulates cyclin activity	miR-26a	↓	*CDK6*	[50]
	miR-28-5p	↓	*CCND1*	[51]

Activity/Pathway Affected	miRNA	Status [1]	Target	References
	miR-30a-3p	↓	*MAF*	[52]
	miR-338-3p	↓	*CDK4*	[53]
	miR-340-5p	↓	*CCND1*, *NRAS*	[54]
	miR-196a/b	↓	*CCND2*	[37]
Regulates proliferation	miR-22	↓	*c-Myc*	[55]
	miR-29a	↓	*c-Myc*	[56]
	miR-34a	↓	*BCL2*, *CDK6*, *NOTCH1*, *c-Myc*, *MET*, *IL6R*	[45][57][58]
	miR-193a	↓	*MCL1*	[59]
	miR-497	↓	*BCL2*	[60]
	miR-767-5p	↓	*MAPK4*	[61]
	miR-874-3p	↓	*HDAC1*	[62]
	miR-1180	↓	*YAP*	[63]
Prevents angiogenesis	miR-15a/16	↓	*BCL2*, *VEGF*, *IL17*	[64]

References

Activity/Pathway Affected	miRNA	Status [1]	Target	References
Regulates acetylation	miR-29b	⬇	*HDAC4*, *MCL1*	[65]
Regulates transcriptional activity	miR-509-5p	⬇	*FOXP1*	[66]
	miR-1271-5p	⬇	*SOX13*, *HGF*	[67][68]
Prevents hypoxia phenotype	miR-199a-5p	⬇	*HIF1A*, *VEGFA*	[69]
Prevents osteolytic activity	miR-342	⬇	*RUNX2*	[70]
	miR-363	⬇	*RUNX2*	[70]

[1] Arrow up indicates overexpression of the miRNA, and arrow down indicates underexpression of the miRNA.

miRNAs may act in clusters, where a group of miRNAs have their expression regulated concomitantly. One of the largest clusters involved in MM is miR-17-92, a six-member polycistronic cluster encoding for six individual miRNAs: miR-17, miR-18a, miR-19a, miR-19b, miR-20a, and miR-92a. Some of these miRNAs are known for regulating the PTEN/PI3K/Akt pathway (**Figure 1**). This cluster was demonstrated to take part in controlling cell proliferation, differentiation, and apoptosis, as it was positively regulated by c-Myc, which conferred to this cluster a key role in MM tumorigenesis [28]. Several studies have empirically proven, using functional assays, that *BIM* is the direct target of miR-17-92. This was confirmed in MM cells with upregulated miR-17-92 that showed an increased expression of anti-apoptotic Bcl-2 [28][71]. Despite their coordinated role, some of the miRNAs belonging to this cluster also had specific functions. Interestingly, miR-20a was highly expressed in bone marrow samples of MM patients when compared to healthy donors. The introduction of a synthetic substitutive miR-20a (mimic-based approach) showed an increased growth rate and decreased apoptosis in the U266 MM cell line, and a promoted tumor growth in a SCID/NOD mouse xenograft model [22]. *PTEN* was shown to be a downstream target of miR-20a, pointing out the PTEN/PI3K/Akt pathway as altered by miR-20a [23]. miR-19b specifically targeted the tumor-suppressive co-chaperone TSC1 and activated the mTOR pathway, which promoted cancer stem cell (CSC) proliferation [29].

8. Agirre, X.; Castellano, G.; Pascual, M.; Heath, S.; Kulis, M.; Segura, V.; Bergmann, A.; Esteve, A.; Merkel, A.; Raineri, E.; et al. Whole-epigenome analysis in multiple myeloma reveals DNA hypermethylation of B cell-specific enhancers. Genome Res. 2015, 25, 478–487.
9. Kaiser, M.F.; Johnson, D.C.; Wu, P.; Walker, B.A.; Brioli, A.; Mirabella, F.; Wardell, C.P.; Melchor, L.; Davies, F.E.; Morgan, G.J. Global methylation analysis identifies prognostically important epigenetically inactivated tumor suppressor genes in multiple myeloma. Blood 2013, 122, 219–226.
10. Martínez-Baños, D.; Sánchez-Hernández, B.; Jimenez, G.; Barrera-Lumbreras, G.; Barrales-Benítez, O. Global methylation and promoter-specific methylation of the P16, SOCS-1, E-cadherin, P73 and SHP-1 genes and their expression in patients with multiple myeloma during active disease and remission. Exp. Ther. Med. 2017, 13, 2442–2450.
11. Chong, P.S.Y.; Ching, W.-J.; de Mel, S. STAT3: A promising therapeutic target in multiple myeloma. Cancers 2019, 11, 731.
12. Kiziltepe, T.; Hideshima, T.; Catley, L.; Raje, N.; Yasui, H.; Shiraishi, N.; Okawa, Y.; Ikeda, H.; Vallet, S.; Pozzi, S.; et al. 5-azacytidine, a DNA methyltransferase inhibitor, induces ATR-mediated DNA double-strand break responses, apoptosis and synergistic cytotoxicity with doxorubicin and bortezomib against multiple myeloma cells. Mol. Cancer Ther. 2007, 6, 1718–1727.

13. U.S National Institutes of Health-ClinicalTrials.Gov. Available online: www.clinicaltrials.gov (accessed on 1 September 2020).
14. Dutta, R.; Tiu, B.; Sakamoto, K.M. CBP/p300 acetyltransferase activity in hematologic malignancies. Mol. Genet. Metab. 2016, 119, 37–43.
15. Zhu, Y.X.; Shi, C.-X.; Bruins, L.A.; Wang, R.; Riggs, B.L.; Porter, B.; Ahmann, J.M.; de Campos, C.B.; Braggio, E.; Bergsagel, P.L.; et al. Identification of lenalidomide resistance pathways in myeloma and targeted resensitization using cereblon replacement, inhibition of STAT3 or targeting of IRF4. Blood Cancer J. 2019, 9, 19.
16. Falkenberg, K.J.; Johnstone, R.W. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat. Rev. Drug Discov. 2014, 13, 673–691.
17. Bradner, J.E.; West, N.; Grachan, M.L.; Greenberg, E.F.; Haggarty, S.J.; Warnow, T.; Mazitschek, R. Chemical phylogenetics of histone deacetylases. Nat. Chem. Biol. 2010, 6, 238–243.
18. Imai, Y.; Hirano, M.; Kobayashi, M.; Futami, M.; Tojo, A. HDAC inhibitors exert anti-myeloma effects through multiple modes of action. Cancers 2019, 11, 475.
19. Hideshima, T.; Bradner, J.E.; Wong, J.; Chauhan, D.; Richardson, P.; Schreiber, S.L.; Anderson, K.C. Small-molecule inhibition of proteasome and aggresome function induces synergistic antitumor activity in multiple myeloma. Proc. Natl. Acad. Sci. USA 2005, 102, 8567–8572.
20. Gupta, S.C.; Tripathi, Y.N. Potential of long non-coding RNAs in cancer patients: From biomarkers to therapeutic targets. Int. J. Cancer 2017, 140, 1955–1967.
21. Su, M.; Xiao, Y.; Ma, J.; Tang, Y.; Tian, B.; Zhang, Y.; Li, X.; Wu, Z.; Yang, D.; Zhou, Y.; et al. Circular RNAs in cancer: Emerging functions in hallmarks, stemness, resistance and roles as potential biomarkers. Mol. Cancer 2019, 18, 90.
22. Wang, T.; Tao, W.; Zhang, L.; Li, S. Oncogenic role of microRNA-20a in human multiple myeloma. Onco Targets Ther. 2017, 10, 4465–4474.
23. Jiang, Y.; Chang, H.; Chen, G. Effects of microRNA-20a on the proliferation, migration and apoptosis of multiple myeloma via the PTEN/PI3K/AKT signaling pathway. Oncol. Lett. 2018, 15, 10001–10007.
24. Xiong, Q.; Zhong, Q.; Zhang, J.; Yang, M.; Li, C.; Zheng, P.; Bi, L.-J.; Ge, F. Identification of novel miR-21 target proteins in multiple myeloma cells by quantitative proteomics. J. Proteome Res. 2012, 11, 2078–2090.
25. Zi, Y.; Zhang, Y.; Wu, Y.; Zhang, L.; Yang, R.; Huang, Y. Downregulation of microRNA-25-3p inhibits the proliferation and promotes the apoptosis of multiple myeloma cells via targeting the PTEN/PI3K/AKT signaling pathway. Int. J. Mol. Med. 2021, 47, 8.

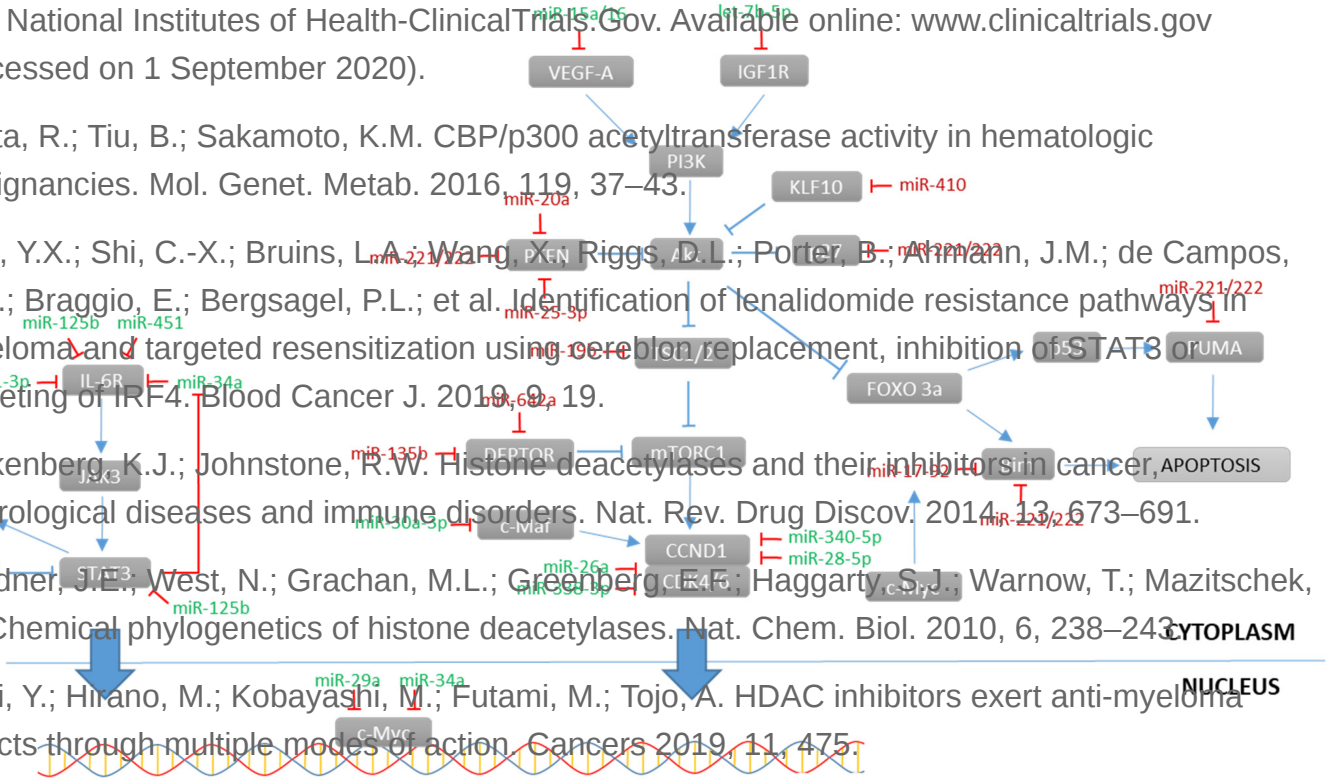

Figure 1. Overview of the main signaling pathways altered by miRNAs in MM cells. Oncogenic miRNAs (red) are overexpressed, and tumor-suppressive miRNAs (green) are underexpressed in MM cells.

4.2. Long Non-Coding RNAs

lncRNAs include ncRNAs whose transcripts are longer than 200 nucleotides. Their classification is performed depending on their localization (**Figure 2**). Nowadays, there is an incomplete understanding of the mechanism of action of lncRNAs, but it is widely accepted that they play an important role in cancer [20].

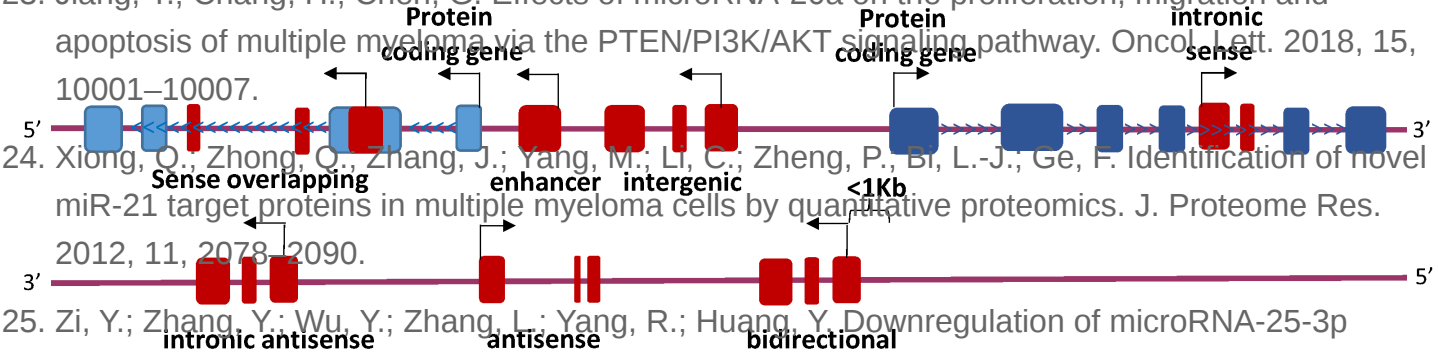

Figure 2. lncRNA classification attending to their localization. The enhancer, intronic, and intergenic lncRNAs contain their own promoters that are distinct from protein coding gene. Bidirectional lncRNAs share promoter with a

26. Song, J.; Guo, Y.; Chen, J.; Li, X.; Zhao, Y.; Yang, K.; Zhao, X.; Chen, Y.; Fan, C.; Yuan, W. Potential value of miR-221/222 as diagnostic, prognostic, and therapeutic biomarkers for diseases. Front. Immunol. 2017, 8, 56.
27. Yang, N.; Chen, J.; Zhang, H.; Wang, X.; Yao, H.; Peng, Y.; Zhang, W. LncRNA OIP5-AS1 loss-induced microRNA-410 accumulation regulates cell proliferation and apoptosis by targeting KLF10 via activating PTEN/PI3K/AKT-pathway in multiple myeloma. Cell Death Dis. 2017, 8, e2975.

In MM, dysregulated lncRNAs affect various aspects of the disease (**Table 2**). Several of them act as competing endogenous RNAs (ceRNAs), having miRNAs as targets and acting as miRNA sponges (**Table 3**) [72].

Table 2. lncRNAs that are dysregulated in MM.

lncRNA	Status [1]	Target	Activity/Pathway Affected	References
ANGPLT1-3	↑	miR-30a-3p	ceRNA	[52]
BM742401	↓	Not described	Inhibit myeloma cell migration, biomarker	[73]
CRNDE	↑	miR-451	ceRNA	[48][74]
DARS-AS1	↑	*RBM39*	Enhances mTOR pathway, hypoxia phenotype	[75]
H19	↑	miR-29b	ceRNA, biomarker	[76]
HOTAIR	↑	Not described	Enhances JAK/STAT pathway	[77]
MALAT1	↑	*HMGB1*, miR-509-5p, miR-1271	Contributes to genomic stability, ceRNA, biomarker	[66][67][78][79]
MEG3	↓	miR-181a	Promotes osteogenic differentiation, biomarker, ceRNA	[80]
MIAT	↑	miR-29b	Inducible by bortezomib, ceRNA, biomarker	[81]
NEAT1	↑	miR-214,	Downregulates genes involved in DNA repair, enhances Wnt/β-catenin pathway, ceRNA	[43][59][82][83]

lncRNA	Status [1]	Target	Activity/Pathway Affected	References
		miR-193a		
NR_046683	↑	Not described	Biomarker	[84]
OPI5-AS1	↑	miR-410	ceRNA	[27]
PDIA3P	↑	*c-Myc*	Regulates proliferation	[85]
RUNX2-AS1	↑	*RUNX2* pre-mRNA	Promotes osteogenesis	[86]
SMILO	↑	Not described	Regulates proliferation	[87]
SNHG16	↑	miR-342	ceRNA	[88]
UCA1	↑	miR-1271-5p, miR-331-3p	ceRNA	[54][68]
XLOC_013703	↓	*IKKA*	Represses NF-κB pathway	[89]

[1]

lncRNA	miRNA	Gene	References
ANGPLT1-3	miR-30a-3p	*MAF*	[52]
CRNDE	miR-451	*IL6R*	[48][74]
H19	miR-29b	*HDAC4* and *MCL1*	[65][76]
MALAT1	miR-509-5p	*FOXP1*	[66]

lncRNA	miRNA	Gene	References
	miR-1271-5p	*SOX13*	[67]
MEG3	miR-181a	*BCL2L11*	[80]
MIAT	miR-29b	*HDAC4* and *MCL1*	[65][81]
NEAT1	miR-214	*CD276*	[43]
	miR-193a	*MCL1*	[59]
OPI5-AS1	miR-410	*KLF10*	[27]
PRAL	miR-210	*DIMT1*	[31][32]
SNHG16	miR-342	*RUNX2*	[88]
UCA1	miR-331-3p	*IL6R*	[54]
	miR-1271-5p	*SOX13* and *HGF*	[68]

The impact of ncRNA dysregulation in MM goes beyond the well-studied miRNAs and lncRNAs. piRNAs constitute a very recent family of 24-31 nucleotide RNAs that can be abnormally expressed in various cancers. piRNA-823 is the only described example of its kind involved in MM pathogenesis so far [90]. Its overexpression was associated with a poor prognosis, suggesting that its detection could be part of a suitable risk stratification strategy. The oncogenic action of piRNA-823 seemed to be mediated through de novo methylation, as its overexpression was associated with DNMT3A/3B expression levels in primary MM cells [91]. Moreover, levels of piRNA-823 were higher in extracellular vesicles shed by MM cells, suggesting that this may promote proliferation, angiogenesis, and invasion in endothelial cells [90]. These findings reinforce the importance of cellular communication between MM cells and the microenvironment, also via piRNAs.

snoRNAs are also relevant in cancer development. Beyond their canonical function in rRNA processing, mRNA splicing, and editing, as well as stress responses, they are involved in pathological processes such as cell transformation, tumorigenesis, and metastasis. The most important finding about snoRNAs in MM involved ACA11, an orphan box H/ACA snoRNA encoded within an intron of MMSET [92]. ACA11 was found to be localized into

59. Wu, Y.; Wang, H. LncRNA NEAT1 promotes doxorubicin resistance in multiple myeloma by targeting miR-193a/MCL1 pathway. J. Biochem. Mol. Toxicol. 2018, 32, e22068.
60. Tian, F.; Zhan, Y.; Zhu, W.; Li, J.; Tang, M.; Chen, X.; Jiang, J. microRNA-497 inhibits multiple myeloma growth and increases susceptibility to bortezomib by targeting Bcl-2. Int. J. Mol. Med. 2019, 43, 1058–1066.
61. Feng, Y.; Zhang, L.; Wu, J.; Khadka, B.; Fang, Z.; Gu, J.; Tang, B.; Xiao, R.; Pan, G.; Liu, J. CircRNA circ_0000190 inhibits the progression of multiple myeloma through modulating miR-767-5p/MAPK4 pathway. J. Exp. Clin. Cancer Res. 2019, 38, 54.
62. Tian, F.-Q.; Chen, Z.-R.; Zhu, W.; Tang, M.-Q.; Li, J.-H.; Zhang, X.-C.; Jiang, J.; Cheng, X.-H. Inhibition of hsa_circ_0003489 shifts balance from autophagy to apoptosis and sensitizes multiple myeloma cells to bortezomib via miR-874-3p/HDAC1 axis. J. Gene Med. 2021, 23, e3329.
63. Chen, F.; Wang, X.; Fu, S.; Wang, S.; Fu, Y.; Zhang, J.; Liu, Z. circular RNA circ-CDYL sponges miR-1180 to elevate yes-associated protein in multiple myeloma. Exp. Biol. Med. 2020, 245, 925–932.
64. Li, Y.; Zhang, B.; Li, W.; Wang, L.; Yan, Z.; Li, H.; Yao, Y.; Yao, R.; Xu, K.; Li, Z. miR-15a/16 regulates the growth of myeloma cells, angiogenesis and antitumor immunity by inhibiting Bcl-2, VEGF-A and IL-17 expression in multiple myeloma. Leuk. Res. 2016, 49, 73–79.
65. Kwon, J.J.; Factora, T.D.; Dey, S.; Kota, J. A systematic review of miR-29 in cancer. Mol. Ther.-Oncolytics 2019, 12, 173–194.
66. Gu, J.; Xiao, X.; Yang, S. Linc-RNA-MALAT1 acts as an oncogene in multiple myeloma through sponging miR-509-5p to modulate FOXP1 expression. Oncotarget 2017, 8, 101984–101998.
67. Liu, N.; Feng, S.; Li, H.; Chen, X.; Bai, S.; Liu, Y. Long non-coding RNA MALAT1 facilitates the tumorigenesis, invasion and glycolysis of multiple myeloma via miR-1271-5p/SOX13 axis. J. Cancer Res. Clin. Oncol. 2020, 146, 367–379.
68. Yang, Y.; Chen, L. Downregulation of lncRNA UCA1 facilitates apoptosis and reduces proliferation in multiple myeloma via regulation of the miR-1271-5p/HGF axis. J. Chin. Med. Assoc. 2019, 82, 699–709.
69. Raimondi, L.; Amodio, N.; Di Martino, M.T.; Altomare, E.; Leotta, M.; Caracciolo, D.; Gulla, A.; Neri, A.; Taverna, S.; D'Aquila, P.; et al. Targeting of multiple myeloma-related angiogenesis by miR-199a-5p mimics: In vitro and In Vivo anti-tumor activity. Oncotarget 2014, 5, 3039–3054.
70. Gowda, P.S.; Wildman, B.J.; Trotter, T.N.; Xu, X.; Hao, X.; Hassan, M.Q.; Yang, Y. Runx2 suppression by miR-342 and miR-363 inhibits multiple myeloma progression. Mol. Cancer Res. 2018, 16, 1138–1148.

5. Conclusions

Recent findings on epigenetic and ncRNA alterations involved in MM have suggested their importance in the development and progression of the disease. A considerable amount of these dysregulations affects crucial pathways implicated in the cell cycle, proliferation, genomic stability, angiogenesis, and hypoxia. Besides, the identification of ncRNA biomarkers suggests their potential use as efficient diagnosis and prognosis tools. However, more research is still required. The emergence of techniques such as CRISPR-Cas opens the way for possibilities to develop new treatments and improve the outcome of MM patients.

71. Inomata, M.; Tagawa, H.; Guo, Y.-M.; Kameoka, Y.; Takahashi, N.; Sawada, K. microRNA-17-92 down-regulates expression of distinct targets in different B-cell lymphoma subtypes. Blood 2009, 113, 396–402.
72. Qi, X.; Zhang, D.-H.; Wu, N.; Xiao, J.-H.; Wang, X.; Ma, W. ceRNA in cancer: Possible functions and clinical implications. J. Med. Genet. 2015, 52, 710–718.
73. Li, Z.; Kumar, S.; Jin, D.-Y.; Calin, G.A.; Chng, W.-J.; Siu, K.-L.; Poon, M.W.; Chim, C.S. Epigenetic silencing of long non-coding RNA BM742401 in multiple myeloma: Impact on prognosis and myeloma dissemination. Cancer Cell Int. 2020, 20, 403.
74. Meng, Y.-B.; He, X.; Huang, Y.-F.; Wu, Q.-N.; Zhou, Y.-C.; Hao, D.-J. Long noncoding RNA CRNDE promotes multiple myeloma cell growth by suppressing miR-451. Oncol. Res. 2017, 25, 1207–1214.
75. Tong, J.; Xu, X.; Zhang, Z.; Ma, C.; Xiang, R.; Liu, J.; Xu, W.; Wu, C.; Li, J.; Zhan, F.; et al. Hypoxia-induced long non-coding RNA DARS-AS1 regulates RBM39 stability to promote myeloma malignancy. Haematologica 2020, 105, 1630–1640.
76. Pan, Y.; Zhang, Y.; Liu, W.; Huang, Y.; Shen, X.; Jing, R.; Pu, J.; Wang, X.; Ju, S.; Cong, H.; et al. LncRNA H19 overexpression induces bortezomib resistance in multiple myeloma by targeting MCL-1 via miR-29b-3p. Cell Death Dis. 2019, 10, 106.
77. Guan, R.; Wang, W.; Fu, B.; Pang, Y.; Lou, Y.; Li, H. Increased lncRNA HOTAIR expression promotes the chemoresistance of multiple myeloma to dexamethasone by regulating cell viability and apoptosis by mediating the JAK2/STAT3 signaling pathway. Mol. Med. Rep. 2019, 20, 3917–3923.
78. Hu, Y.; Lin, J.; Fang, H.; Fang, J.; Li, C.; Chen, W.; Liu, S.; Ondrejka, S.; Gong, Z.; Reu, F.; et al. Targeting the MALAT1/PARP1/LIG3 complex induces DNA damage and apoptosis in multiple myeloma. Leukemia 2018, 32, 2250–2262.
79. Handa, H.; Kuroda, Y.; Kimura, K.; Masuda, Y.; Hattori, H.; Alkebsi, L.; Matsumoto, M.; Kasamatsu, T.; Kobayashi, N.; Tahara, K.-I.; et al. Long non-coding RNA MALAT1 is an inducible stress response gene associated with extramedullary spread and poor prognosis of multiple myeloma. Br. J. Haematol. 2017, 179, 449–460.
80. Benetatos, L.; Dasoula, A.; Hatzimichael, E.; Georgiou, I.; Syrrou, M.; Bourantas, K.L. Promoter hypermethylation of the MEG3 (DLK1/MEG3) imprinted gene in multiple myeloma. Clin. Lymphoma Myeloma 2008, 8, 171–175.
81. Fu, Y.; Liu, X.; Zhang, F.; Jiang, S.; Liu, J.; Luo, Y. Bortezomib-inducible long non-coding RNA myocardial infarction associated transcript is an oncogene in multiple myeloma that suppresses miR-29b. Cell Death Dis. 2019, 10, 319.

82. Taiana, E.; Favasuli, V.; Ronchetti, D.; Todoerti, K.; Pelizzoni, F.; Manzoni, M.; Barbieri, M.; Fabris, S.; Silvestris, I.; Cantafio, M.E.G.; et al. Long non-coding RNA NEAT1 targeting impairs the DNA repair machinery and triggers anti-tumor activity in multiple myeloma. Leukemia 2020, 34, 234–244.
83. Geng, W.; Guo, X.; Zhang, L.; Ma, Y.; Wang, L.; Liu, Z.; Ji, H.; Xiong, Y. Resveratrol inhibits proliferation, migration and invasion of multiple myeloma cells via NEAT1-mediated Wnt/beta-catenin signaling pathway. Biomed. Pharmacother. 2018, 107, 484–494.
84. Dong, H.; Jiang, S.; Fu, Y.; Luo, Y.; Gui, R.; Liu, J. Upregulation of lncRNA NR_046683 serves as a prognostic biomarker and potential drug target for multiple myeloma. Front. Pharmacol. 2019, 10, 45.
85. Yang, X.; Ye, H.; He, M.; Zhou, X.; Sun, N.; Guo, W.; Lin, X.; Huang, H.; Lin, Y.; Yao, R.; et al. LncRNA PDIA3P interacts with c-Myc to regulate cell proliferation via induction of pentose phosphate pathway in multiple myeloma. Biochem. Biophys. Res. Commun. 2018, 498, 207–213.
86. Li, B.; Xu, H.; Han, H.; Song, S.; Zhang, X.; Ouyang, L.; Qian, C.; Hong, Y.; Qiu, Y.; Zhou, W.; et al. Exosome-mediated transfer of lncRUNX2-AS1 from multiple myeloma cells to MSCs contributes to osteogenesis. Oncogene 2018, 37, 5508–5519.
87. Carrasco-Leon, A.; Ezponda, T.; Meydan, C.; Valcarcel, L.V.; Ordoñez, R.; Kulis, M.; Garate, L.; Miranda, E.; Segura, V.; Guruceaga, E.; et al. Characterization of complete lncRNAs transcriptome reveals the functional and clinical impact of lncRNAs in multiple myeloma. Leukemia 2021, 35, 1438–1450.
88. Yang, X.; Huang, H.; Wang, X.; Liu, H.; Liu, H.; Lin, Z. Knockdown of lncRNA SNHG16 suppresses multiple myeloma cell proliferation by sponging miR-342-3p. Cancer Cell Int. 2020, 20, 38.
89. Pu, J.; Huang, H.; Su, J.; Yuan, J.; Cong, H.; Wang, X.; Ju, S. Decreased expression of long noncoding RNA XLOC_013703 promotes cell growth via NF-kappaB pathway in multiple myeloma. IUBMB Life 2019, 71, 1240–1251.
90. Li, B.; Hong, J.; Hong, M.; Wang, Y.; Yu, T.; Zang, S.; Wu, Q. piRNA-823 delivered by multiple myeloma-derived extracellular vesicles promoted tumorigenesis through re-educating endothelial cells in the tumor environment. Oncogene 2019, 38, 5227–5238.
91. Yan, H.; Wu, Q.-L.; Sun, C.-Y.; Ai, L.-S.; Deng, J.; Zhang, L.; Chen, L.; Chu, Z.-B.; Tang, B.; Wang, K.; et al. piRNA-823 contributes to tumorigenesis by regulating de novo DNA methylation and angiogenesis in multiple myeloma. Leukemia 2015, 29, 196–206.
92. Taulli, R.; Pandolfi, P.P. “Snorkeling” for missing players in cancer. J. Clin. Investig. 2012, 122, 2765–2768.

93. Chu, L.; Su, M.Y.; Maggi, L.B., Jr.; Lu, L.; Mullins, C.; Crosby, S.; Huang, G.; Chng, W.J.; Vij, R.; Tomasson, M.H. Multiple myeloma-associated chromosomal translocation activates orphan snoRNA ACA11 to suppress oxidative stress. J. Clin. Investig. 2012, 122, 2793–2806.
94. Oliveira, V.; Mahajan, N.; Bates, M.L.; Tripathi, C.; Kim, K.Q.; Zaher, H.S.; Maggi, L.B., Jr.; Tomasson, M.H. The snoRNA target of t(4;14) in multiple myeloma regulates ribosome biogenesis. FASEB BioAdvances 2019, 1, 404–414.
95. Zhou, Y.; Goodenbour, J.M.; Godley, L.A.; Wickrema, A.; Pan, T. High levels of tRNA abundance and alteration of tRNA charging by bortezomib in multiple myeloma. Biochem. Biophys. Res. Commun. 2009, 385, 160–164.
96. Zhou, F.; Wang, D.; Wei, W.; Chen, H.; Shi, H.; Zhou, N.; Wu, L.; Peng, R. Comprehensive profiling of circular RNA expressions reveals potential diagnostic and prognostic biomarkers in multiple myeloma. BMC Cancer 2020, 20, 40.
97. Gao, M.; Li, C.; Xiao, H.; Dong, H.; Jiang, S.; Fu, Y.; Gong, L. hsa_circ_0007841: A novel potential biomarker and drug resistance for multiple myeloma. Front. Oncol. 2019, 9, 1261.