

REVIEW

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Role of epigenetics-microRNA axis in drug resistance of multiple myeloma

Nasrin Rastgoo^{1,2}, Jahangir Abdi^{1,2}, Jian Hou³ and Hong Chang^{1,2,3,4*}

Abstract

Despite administration of novel therapies, multiple myeloma (MM) remains incurable with resistance to drugs leading to relapse in most patients. Thus, it is critical to understand the detailed mechanisms underlying the drug resistance of MM and develop more effective therapeutic strategies. Genetic abnormalities are well known to play a central role in MM pathogenesis and therapy resistance; however, epigenetic aberrations mainly affecting the patterns of DNA methylation/histone modifications of genes (especially tumor suppressors) and miRNAs have also been shown to be involved. Importantly, while epigenetic silencing of miRNAs in MM is well documented, some epigenetic markers are known to be direct targets of miRNAs particularly the recently described “epimiRNAs”. Drugs targeting epigenetic modifiers (e.g., HDACs, EZH2) can sensitize MM-resistant cells to anti-myeloma drugs and reversibility of epigenetic changes makes these drugs promising therapeutic agents. Therefore, combination of miRNA mimics with inhibitors of epigenetic modifiers would be a more potent therapeutic strategy in MM patients in relapse or refractory to treatments. In this review, we will discuss the findings of recent investigations on epigenetics/miRNA regulatory axis in development of drug resistance in MM and highlight possible approaches for therapeutic applications of such interaction.

Keywords: Epigenetics, EZH2, MicroRNA, Myeloma, Drug resistance

Background

Multiple myeloma (MM) is a clonal expansion of plasma cells that is characterized by proliferation of malignant clones producing defective monoclonal immunoglobulins in the bone marrow. Current therapies such as proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) have improved the outcome of patients. Nevertheless, not all patients respond well to the drug, and even in responding patients usually relapse occurs. Thus, multi-drug resistance is still the major problem for the effective treatment of multiple myeloma with conventional drugs [1, 2]. Researches to decipher the molecular mechanisms underlying drug resistance (DR) of MM are keeping an unstoppable trend with miRNAs and epigenetics leading a fast-growing front. Indeed miRNAs and epigenetic markers have been identified as critical regulators of expression and function of oncogenes/tumor suppressors in cancers including MM [3]. In line with this notion, wealth

of evidence supports that epigenetic dysregulations such as aberrant DNA and histone methylation, histone deacetylation and abnormal miRNA expression are involved in the pathogenesis of MM [4–6] (listed in Table 1). This has pushed several studies in recent and past years toward assessment of epigenetic inhibitors in clinical trials of MM [7–9]. Moreover, since the epigenetic alterations are reversible, inhibition of epigenetic changes could have a promising therapeutic potential [10]. Importantly, although aberrant miRNA expression in MM due to epigenetic silencing mechanisms is well documented [11], miRNAs have also been shown to impact epigenetic modifiers in cancers [12–14] highlighting a regulatory circuit between these two regulatory systems. This concept will introduce an exciting venue to DR investigation and therapeutic targeting in MM. However, while miRNAs can play regulatory roles in drug response of MM cells [15], further studies are still required to fully elucidate whether interaction of epigenetic modulations with miRNAs contributes to DR in MM. Here to present a new mechanistic picture based on the most recent findings, we discuss epigenetic abnormalities associated with miRNAs that are involved in DR of MM.

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Table 1 Aberrant miRNAs involved in pathogenesis or drug resistance of MM

miRNAs	Dysregulation	Outcome	Refs.
miR-21	Upregulation	Inhibition of apoptosis and increase drug resistance	[74]
miR-125b	Upregulation	Reduction of cell death in dexamethasone induced MM (drug resistance)	[75]
miR-15a miR-16	Downregulation	Regulation of MM cell proliferation in vitro and in vivo Downregulated in patients with relapsed/refractory disease (drug resistance)	[76, 77]
miR-221/222	Upregulation	Inhibition of apoptosis and modulation of drug influx-efflux and ABC transporters (drug resistance)	[36]
miR-27a	Downregulation	Downregulated in MM patients with bortezomib-refractory status (drug resistance)	[46]
miR-149	Downregulation	Downregulated in glucocorticoid resistant MM cells by disturbing epigenetic landscape, leading to overexpression of MMP-9 gene which is involved in bone remodeling and tumor invasion in MM	[78]
miR-631	Downregulation	Modulates UbcH10/MDR1 pathway which is associated with the development of BTZ resistance in myeloma cells	[79]
miR-202	Downregulation	Involved on drug resistance of MM cells by targeting JNK/SAPK signaling pathway	[80]
miR-30c	Downregulation	Downregulated as a result of interaction between MM cells and bone marrow stromal cells, which in turn activation of oncogenic Wnt/ β -catenin/BCL9 pathway and promote MM cell proliferation, drug resistance and formation of MM cancer stem cells.	[81]
miR-137/197	Downregulation	Modulates MCL-1 which is dysregulated in multiple myeloma cells and overexpression of MCL-1 is associated with relapse and poor survival	[51]
miR-17-92 cluster miR-106~363 cluster	Upregulation	High level is associated with shorter overall survival	[82]
miR-148a & miR-20a	Upregulation	Shorter relapse-free survival	[83]
let-7e, miR-125a-5p, and miR-99b cluster	Upregulation	Overexpression in t(4;14) patients	[84]
miR-140-3p	Downregulation	Altered expression due to the occurrence of several allelic imbalances or loss of heterozygosity in 16q2 region	[84]
miR-32 and miR-17~92 cluster	Upregulation	Upregulated in MM patients and cell lines but not in MGUS or healthy PCs	[85]
miR-19a and 19b	Upregulation	Inhibition of IL-6 growth signaling	[85]
miR106b~25 cluster, miR-181a/b, miR-32	Upregulation	Targeting of the genes which involved in p53 regulation	[85]
miR-1/miR-133a cluster	Upregulation	Overexpressed in MM patients with t(14;16)	[86]
miR-135b and miR-146a	Downregulation	Downregulated in MM with t(4;14) and targeted the genes which are involved in IL-1 signaling pathway	[86]
miR-214	Downregulation	Positive regulation of P53 and inhibition of DNA replication	[87]
miR-29b	Downregulation	Reduction of apoptosis by upregulation of MCL1	[88]
miR-192, miR-194, miR-215	Downregulation	p53-inducible microRNAs which modulate MDM2 expression regulate IGF pathway and enhance migration of plasma cells into bone marrow	[89]

Epigenetic dysregulation and DR in MM

Although the molecular mechanisms of DR in MM are not fully understood, epigenetic abnormalities have been suggested to play an important role [16]. In fact the role of DNA methylation, histone modifications, and chromatin remodeling in MM development/progression have been well described [3–6]; however, the mechanistic role of these alterations in DR/relapse of MM has not been fully investigated. Dysregulation of DNA methylation is one of the most studied epigenetic mechanisms in DR of

different types of cancers including MM as evidenced by higher frequency of hypermethylation of some tumor suppressor genes, such as CDKN2A and CDKN2B, in relapsed than in newly diagnosed MM patients [17].

In addition, DNA hypermethylation has been detected in some tumor suppressor, cell signaling, and cell adhesion molecule genes in plasma cell leukemia (PCL) cells [18]. Analyzing data from thousands of cancer cell lines and tumors showed that suppressed expression of one or more 19S proteasome subunits caused by DNA methylation led

to intrinsic proteasome inhibitor resistance [19]. Furthermore, bone marrow microenvironment-mediated global DNA hypermethylation has been suggested to be involved in DR of MM by upregulating DNA methyl transferases (DNMTs) [20]. Interestingly, it was shown that the oxidative epigenetic agent, RRx-001, inhibited DNMTs and reduced global hypermethylation leading to decrease in viability of MM cells and overcame DR. Of note, microarray screening for genes silenced by DNA methylation revealed an association between gene inactivation by DNA hypermethylation and dexamethasone resistance in MM and treating MM cells with demethylating agent 5-aza-2'-deoxycytidine restored sensitivity to dexamethasone [21]. In addition to DNA methylation, histone modification is also critical in cellular programming and dysregulation of the histone-modifying enzymes is involved in the pathogenesis of MM. Histone deacetylases (HDACs) are dysregulated in MM, and aberrant overexpression of class I HDACs is correlated with reduced overall survival of patients with MM [22]. HDAC inhibitors, including panobinostat and vorinostat, have been evaluated in the treatment of MM and recently approved by Food and Drug Administration for the treatment of relapsed and refractory MM [23]. HDAC inhibitors in combination with bortezomib (BTZ) have synergistic cytotoxic effects on MM cells by disruption of protein degradation and inhibition of the interaction of MM cells with the tumor microenvironment [24].

Furthermore, alterations in histone methyltransferases can also mediate chemotherapy resistance in MM including cell adhesion-mediated drug resistance (CAM-DR) which is a rather complex and poorly explored form of DR in MM. Kikuchi et al. demonstrated that direct adhesion to bone marrow stromal cells inactivated (phosphorylated) the histone methyltransferase enhancer of zeste homolog 2 (EZH2) which resulted in H3K27 (histone H3-Lysine 27) hypomethylation. This in turn led to sustained expression of anti-apoptotic genes such as IGF1, BCL2, and hypoxia inducible factor 1- α (HIF1A) [25]. The above study identifies stroma-induced histone hypomethylation as a mechanism of CAMDR in MM hence a tumor suppressor function of EZH2. In addition, CDK1-dependent inactivation (phosphorylation) of EZH2 and subsequent H3K27 hypomethylation also leads to resistance to tyrosine kinase inhibitors (TKIs) and cytotoxic drugs in AML [26].

On the other hand, oncogenic functions of EZH2 have also been reported by some studies. For instance, it was shown that silenced polycomb target genes were more frequent in MM and ChIP-seq profiling data revealed increased number of silenced H3K27me3 (Histone H3 lysine 27 trimethylation) target genes in MM patients at advanced stages of the disease, and the expression pattern of H3K27me3-marked genes was correlated with

poor patient survival [27, 28]. In addition, pharmacological inhibition of EZH2 reduced the expression of some MM-associated oncogenes [29], it also caused reduction of H3K27me3 level in EZH2 target genes in MM cells promoting the expression of EZH2-repressed tumor suppressor genes and subsequently blocked the cell proliferation and invasion [30, 31]. In addition to EZH2, the histone methyltransferase MMSET/WHSC1, which is overexpressed in MM patients with t(4;14), is known to be a driving factor in the pathogenesis of this MM subtype. Shah et al. showed that MMSET/WHSC1 could enhance DNA damage repair and lead to DR in MM and that depletion of MMSET enhanced the efficacy of chemotherapy, inhibited tumor growth, and extended survival in a mouse xenograft of t(4;14) KMS11 MM cells [32].

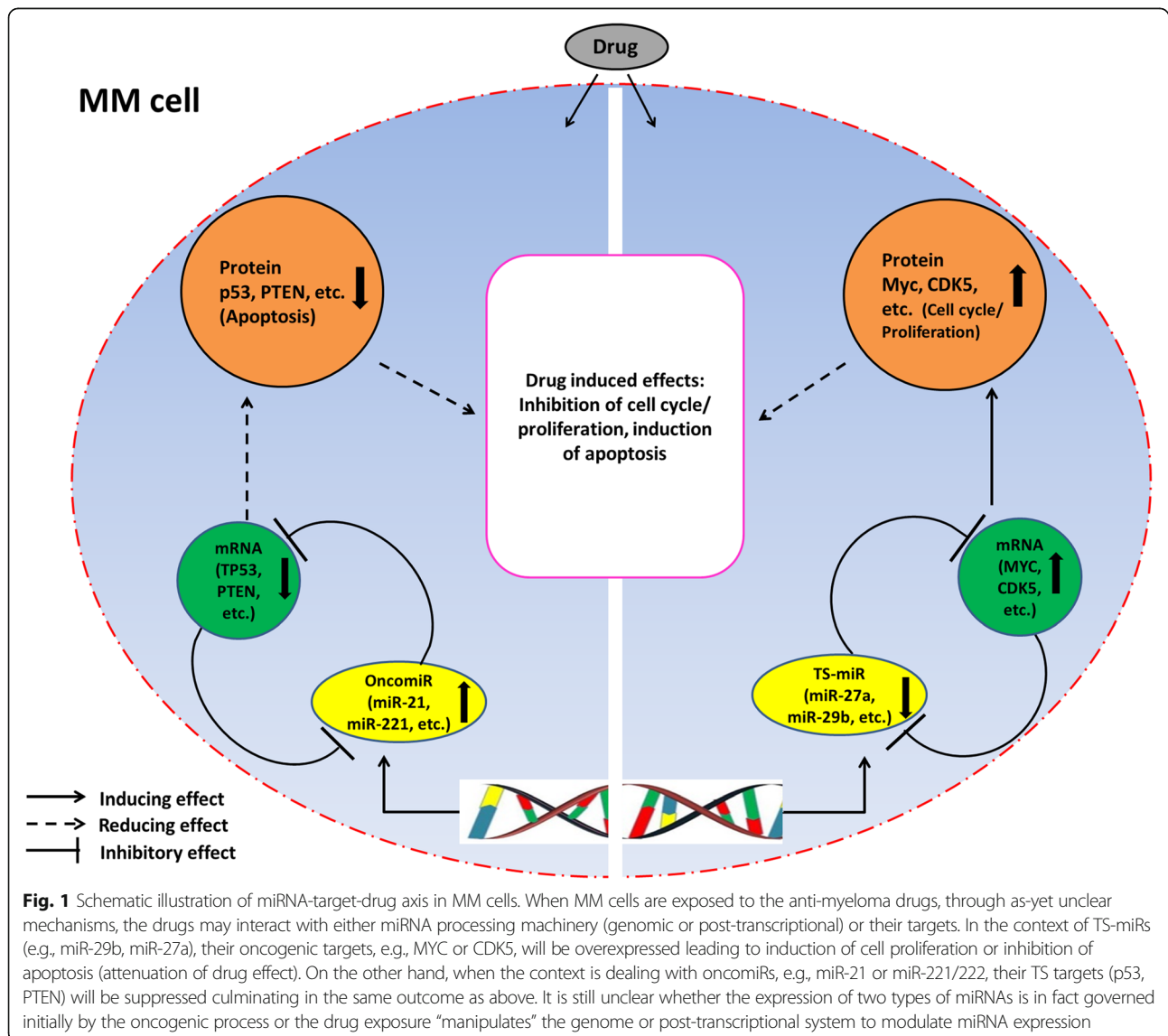
It is important to note that most studies concerning epigenetics in MM pathogenesis focused on EZH2-mediated transcription repression of target genes and it is not clear whether somatic mutations causing EZH2 gain or loss of function could also play a role in MMDR. Indeed, both types of mutations have been reported in other hematologic malignancies leading to biologic and clinical outcomes that indicate context-dependent tumor suppressor or oncogenic function of EZH2 [33]. Taken together, epigenetic mechanisms including DNA methylation and histone methylation/deacetylation play an important role in MM pathogenesis particularly DR by regulating expression of target genes with established functions in cell viability and apoptosis.

A triad of “miRNA-drug-target” shapes the drug response of MM cells

Many studies have demonstrated that miRNAs could be involved in DR of MM (listed in Table 1). It has recently been suggested that miRNAs can indirectly affect the efficacy of an anti-tumor drug depending on whether their target has negative or positive impact on the drug function [34]. This concept extends the function of miRNAs beyond what we know as stunning performers in the genome regulating expression of genes and denotes a significant role of these small molecules in DR of tumor cells [15]. However, miRNA expression pattern which would possibly be altered by the neoplastic context is the determining factor. This means downregulated miRNA (TS-miRNA) can boost or lower the efficacy of the drug, respectively, if the protein targeted by a specific miRNA promotes or dampens drug effects. The contrasting scenario will apply when the expression level of miRNAs in tumor context is high (OncomiR). MiR-221/222 and miR-21 are two known oncogenic miRNAs with high expression in MM [35–38] and other cancers [39–42]. They target the tumor suppressor PTEN and pro-apoptotic

PUMA, two proteins known to be upregulated by BTZ [43, 44]. In addition, miR-451 regulates stemness of MM side population and inhibition of this miRNA enhances anti-myeloma agents' effectiveness, through increasing cells apoptosis and reducing MDR1 (multidrug resistance 1) gene expression [45]. These miRNA-target interactions had negative impact on drug function in tumor cells, hence occurrence of DR. Notably, synthetic inhibitors of the oncomiRs miR-21 and miR221/222 have been successfully administered to preclinical models of MM yielding prominent anti-tumor effects [35–38]. MiR-27a was identified as a tumor suppressor to be downregulated in MM [46] and leukemia [47] cells and targeted the oncogenes CDK5 and P-glycoprotein, respectively, which were highly expressed in tumor cells culminating in the same outcome as above. MiR-29b is another example of TS-miRNAs

which was significantly reduced in BTZ-resistant cells as well as in cells resistant to second-generation PIs carfilzomib and ixazomib. miR-29b targeted the proteasome activator PA20 and disrupted aggresome/autophagosome formation to enhance the anti-myeloma effects of BTZ [48]. It is not surprising to expect that the target of the miRNA in this triad could also be an epigenetic modifying enzyme like EZH2 or HDACs whereby their interaction would possibly function through an established loop to sustain MM cell drug response (see below for further explanations). These statements highlight the notion that the function of an anti-myeloma drug, e.g., BTZ, or how the MM cells respond to the drug can be shaped by the pattern of miRNA-target interaction which in some cases will end in therapy resistance. The above scenario has been illustrated in Fig. 1.



Epigenetic modifications and miRNAs interplay: a scenario in the context of anti-myeloma drug

MiRNAs have a large impact on tumorigenesis by modulating expression of various oncogenes or tumor suppressors and also contribute to DR. Hence identifying the regulatory mechanisms of miRNA expression will be very helpful to understand underlying mechanisms of DR in MM and to find more effective therapeutic targets. Recent epigenetic investigations have identified promoter hypermethylation of tumor suppressor miRNAs (TS-miRNAs) in many cancer types including MM [11]. MiR-34a/b/c, miR-124-1, miR-194-2-192, miR-203, miR-152, and miR-10b-5p in MM were reported to be silenced by DNA hypermethylation [11, 49, 50]. Importantly, most target genes of these miRNAs encode for proteins involved in survival, proliferation, and DR. For instance, hypermethylation-mediated inactivation of miR-34a/b/c attenuates tumor suppressor activity of p53, as these miRNAs are known to be direct transcriptional targets and tumor-suppressive effectors downstream to p53. This in turn will lead to loss of translational repression of miR-34a/b/c targets, BCL-2, CCND1, CCNE2, CDK4, CDK6, E2F, and v-MYC.

Studies from our group [51, 52] and others [53] have identified miR-137 as a TS-miRNA whose overexpression in MM cells sensitizes them to anti-myeloma drugs. MiR-137 in MM was silenced by promoter hypermethylation which was associated with chromosomal instability (CIN) and resistance to BTZ in MM cells. AURKA, a gene coding for proteins involved in mitosis and cell proliferation, was identified as a direct target of miR-137. Ectopic expression of miR-137 sensitized the cells to BTZ by upregulating p53 and downregulating ATM/Chk2 indicating that epigenetically regulated miR-137 plays role in DR of MM cells by maintaining a proliferation or survival pathway [52].

Moreover, some oncogenes are targeted by hypermethylated miRNAs in MM and hypomethylation of miRNA genes by using DNMT inhibitors can downregulate those oncogenes and inhibit cell growth and induce apoptosis in MM cells. For example, RecQ helicases (DNA unwinding enzymes involved in the maintenance of chromosome stability) are significantly upregulated in MM and protect MM cells from melphalan and bortezomib cytotoxicity. DNMT inhibitor treatment of MM cells results in RECQ1 downregulation through miR-203 demethylation and sensitizes cells to anti-tumor drugs suggesting that epigenetic modifier could be useful for treatment of relapsed cases [54].

Resistance to drugs could also be associated with histone modifications (deacetylation, methylation) of miRNA promoters, another epigenetic mechanism regulating expression of miRNAs in cancers [14, 55, 56], although far less investigated in MM. For instance, the HDACs 1, 2, 3, and 4, DNMTs, acetylated H2B, and acetylated H3 were direct targets of several miRNAs in doxorubicin-resistant lung

cancer cell lines and were in fact in a functional interaction with these miRNAs [14]. The histone methyl transferase MMSET is overexpressed in about 15% of MM patients due to the t(4;14) translocation. MMSET overexpression induced c-MYC expression in MM cells by repressing miR-126* which targeted c-MYC, hence increase in proliferation of MM cells. It was shown that MMSET bound to miR-126* promoter which was indicated by increased H3K9 trimethylation and decreased H3 acetylation, leading to miR-126* repression [57]. Although drug response of MM cells was not explored in this setting, it may be speculated that resistance to drug could also happen due to c-MYC-mediated increased proliferation of MM cells. In support of this, cell cycle-mediated drug resistance has been suggested as a critical phenomenon impeding combined chemotherapies, which warrants development and incorporation of cell-cycle inhibitors [58].

The chromatin remodeling enzyme EZH2 is probably the most attractive epigenetic modifier in cancers [33, 59, 60] which has been shown to induce DR in tumor cells by silencing miRNAs and establishing a functional mutual interaction with miRNAs [13]. EZH2 has also been shown to interact with transcription factors which are targets of tumor suppressor miRNAs, such as MYC in lymphomas [61] and in MM [29]. Alzrigat et al. demonstrated that pharmacologic inhibition of EZH2 in MM cell lines and primary cells suppressed transcription factors with oncogenic activity in MM including IRF-4, XBP-1, PRDM1/BLIMP-1, and c-MYC. In parallel, EZH2 inhibition reactivated the expression of TS-miRNAs, miR-125a-3p, and miR-320c, which were also targets of EZH2 and H3K27m3 [29]. Additionally, miR-138 that targets EZH2 is suppressed in drug-resistant phenotypes of MM cells, restoration of this miRNA using EZH2 silencing or pharmacologic inhibition reverses DR and sensitizes MM cells to drug-induced toxic effects (our unpublished data). These observations provide evidence that the epigenetic modifier EZH2 contributes significantly to MM cell proliferation and DR by targeting TS-miRNAs. Figure 2 illustrates the miRNA/epigenetic modifier enzyme interactions which are involved in MMDR.

It is interesting to note that a group of miRNAs, termed “epi-miRNAs”, has been reported to reciprocally modulate epigenetic regulators, suggesting the existence of a regulatory circuit between miRNAs and epigenetic modifiers [62]. The best example in MM is miR-29b which was shown to specifically target HDAC4 in a mutually functional loop [63, 64]. Silencing/inhibition of HDAC4 triggered apoptosis, enhanced drug (bortezomib and dexamethasone)-induced cell death, and upregulated miR-29b in MM cells (by promoter hyperacetylation). On the contrary, overexpression or inhibition of miR-29b, respectively, antagonized or potentiated the anti-myeloma effects of the pan-HDAC inhibitor SAHA

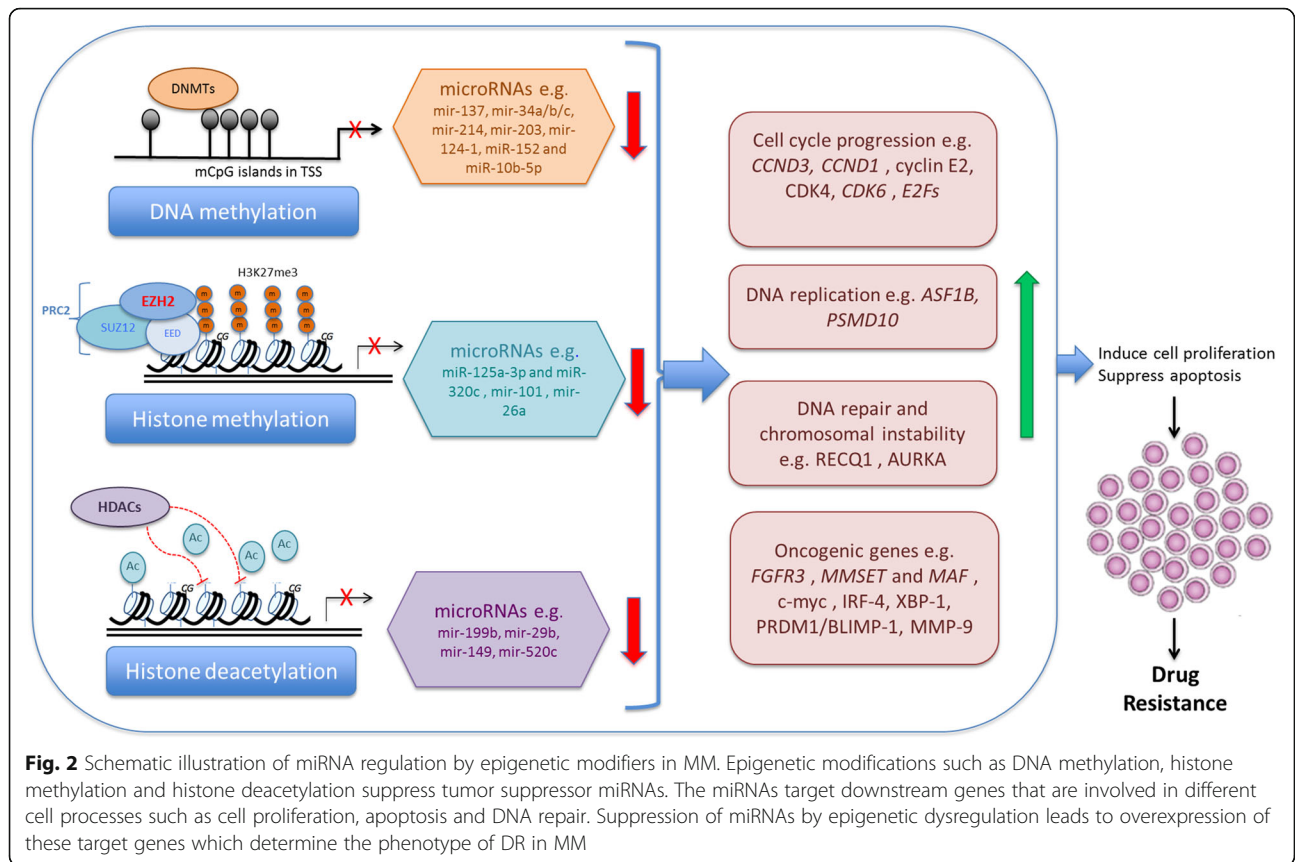


Table 2 Summary of key epigenetic modifiers found in MM and their miRNA targets

Sample source	Epigenetic modifiers	miRNAs targeted	Targets/pathways modulated by miRNA	Functional outcomes	Refs.
MM cell lines (NCI-H929, U266, KMS11, OPM2, RPMI8226, MM1.5) and MM primary samples	DNA methylation (DNMTs)	miR-137	AURKA/p-ATM, p-Chk2	Induction of drug resistance to bortezomib and epirubicin, chromosomal instability	[52]
MM cell lines (MM1S, H929, OPM-2, JJN3, and RPMI 2886)	DNA methylation (DNMTs)	miR-214	PSMD10 & ASF1B/p53-MDM2	A significant enrichment for DNA replication and induction of cell proliferation, and as a consequence also in cell survival	[87]
MM cell lines (NCI-H929 and U-266, KMS-12-PE, LP-1, OPM-2) and MM primary samples	DNA methylation (DNMTs)	miR-124-1	CDK6	Induction of cell proliferation	[50]
MM cell lines (KMS11, SKMM1, and NCI-H929) and PCL and MM primary samples	HDACs	miR-29b	Mcl1/SP1 and HDAC4	Induction of cell growth by upregulation of pro-survival proteins (MCL-1 and SP1)	[63]
MM cell lines (MM.1S, LP1, H929, and JJN3)	HDACs	miR-9-5p	IGF2BP3/CD44	CD44 overexpression, a glycoprotein that has been associated with lenalidomide and dexamethasone resistance in myeloma	[90]
MM cell lines (INA-6, LP-1, L363, KMS-11) and MM primary samples	EZH2	miR-125a-3p & miR-320c	RF-4, XBP-1, BLIMP-1, c-MYC	Upregulation of oncogenes and inhibit apoptosis	[29]
MM cell lines RPMI8226 and U266	EZH2	miR-101	E-cadherin, MMP9, c-Myc, cyclin D3, CDK4, and CDK6	Induction of cell proliferation and inhibit apoptosis	[91]

confirming that HDAC4-miR-29b axis modulates the effects of anti-myeloma drugs. The key epigenetic modifiers found in MM and their miRNA targets are summarized in Table 2.

Taken all together, in the setting of MM cells, the mutual interaction between miRNAs and epigenetic markers plays an important role in regulation of drug response of MM cells.

Clinical application of epigenetic inhibitors in combination with miRNAs in MM

Strategies for clinical application of epigenetic inhibitors including DNMT, HDAC, and HAT inhibitors in MM therapy have been reviewed elsewhere [65, 66]. Generally, these inhibitors have been administered in combination regimens in MM. For instance, EZH2 inhibitors have been applied to clinical trials in lymphoma and are suggested as promising therapeutic strategy in MM in combination with IMiDs [8] and proteasome inhibitors [67]. Kikuchi et al. showed that HDACs were critical targets of BTZ and knockdown of HDAC1 enhanced BTZ-induced apoptosis, whereas HDAC1 overexpression conferred resistance to BTZ in MM cells, suggesting that combination of BTZ and HDAC inhibitors could be a more efficient treatment strategy for MM [68]. Indeed, HDAC inhibitors have also been applied to clinical therapies of MM in combination with IMiDs or proteasome inhibitors [69, 70]. While miRNA mimics have been tested in many pre-clinical studies in MM, obstacles to apply these agents to MM clinical trials still persist [71]. Efficient delivery of nucleic acids into tumor tissues and their uptake specifically by the tumor cells have been stressed to be the challenging issues. On the other hand, considering an established functional interaction between miRNAs and epigenetic regulators, which regulates MM cell drug responses, combination of miRNA mimics with inhibitors of these modifiers could be a more potent therapeutic strategy in MM patients in relapse or refractory to treatments.

Conclusions

Current era of MM therapy is witnessing the significant progress of strategies and approaches aiming mostly at overcoming the DR. While most novel treatments including proteasome inhibitors especially in combination modalities have proved to increase the survival of patients, MM still remains to be drug resistant and most patients relapse or become refractory. Studies have demonstrated that miRNA may be applied for the targeted delivery of personalized medicine to improve the outcome of MM patients [72]. Furthermore, the number of studies focusing on pre-clinical applications of miRNAs in MM is increasing; however, concerns and obstacles to these approaches in terms of translation to clinic still

persist [71]. Epigenetics is perhaps taking an exciting and promising position at the frontier of MMDR mechanisms. Taking advantage of epigenetic regulation of miRNAs, future studies should attempt to examine therapeutic application of epigenetic markers to restore TS-miRNAs in MM pre-clinical models. This strategy will especially be promising when MM cases with resistance to HDAC inhibitors are dealt with [73].

In conclusion, epigenetics-miRNA axis plays a crucial role in MM pathogenesis and could provide potential therapeutic targets. However; due to limited studies, further in-depth studies in this regard are required to open a novel and exiting venue to understand the underlying mechanism of DR in MM, which tends to be the outstanding obstacle to MM therapy.

Abbreviations

AML: Acute myeloid leukemia; AURKA: Aurora kinase A; BCL-2: B cell lymphoma 2; BTZ: Bortezomib; CAM-DR: Cell adhesion-mediated drug resistance; CCND1: Cyclin D1; CCNE2: Cyclin E2; CDK4,5,6: Cyclin-dependent kinase 4,5,6; CDKN2A,B: Cyclin-dependent kinase inhibitor 2 A,B; ChIP-seq: Chromatin immunoprecipitation followed by sequencing; CIN: Chromosomal instability; DNMT: DNA methyl transferase; DR: Drug resistance; EZH2: Enhancer of zeste homolog 2; HAT: Histone acetyl transferase; HDAC: Histone deacetylase; HIF1A: Hypoxia inducible factor 1- α ; IFR4: Interferon regulatory factor 4; IGF1: Insulin growth factor 1; IMiDs: Immunomodulatory drugs; MDR1: Multidrug resistance 1; MM: Multiple myeloma; MMDR: Multiple myeloma drug resistance; MMSET/WHSC1: Multiple myeloma SET domain/Wolf-Hirschhorn syndrome candidate 1; PCL: Plasma cell leukemia; PI: Proteasome inhibitor; PRDM1/BLIMP1: PR domain zinc finger protein 1/B lymphocyte inducer of maturation program 1; PTEN: Phosphatase and tensin homolog; PUMA: P53 upregulated modulator of apoptosis; TKI: Tyrosine kinase inhibitor; TS-miRNA: Tumor suppressor micro-RNA

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Availability of data and materials

Please contact author for data requests.

Authors' contributions

NR and JA drafted the manuscript. JH participated in the design of the study. HC conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

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Ethics approval and consent to participate

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References

- Mahindra A, Laubach J, Rajee N, Munshi N, Richardson PG, Anderson K. Latest advances and current challenges in the treatment of multiple myeloma. *Nat Rev Clin Oncol*. 2012;9(3):135–43.
- Joao C, Costa C, Coelho I, Vergueiro MJ, Ferreira M, da Silva MG. Long-term survival in multiple myeloma. *Clin Case Rep*. 2014;2(5):173–9.
- Bianchi G, Munshi NC. Pathogenesis beyond the cancer clone(s) in multiple myeloma. *Blood*. 2015;125(20):3049–58.
- Sharma A, Heuck CJ, Fazzari MJ, Mehta J, Singhal S, Grealley JM, et al. DNA methylation alterations in multiple myeloma as a model for epigenetic changes in cancer. *Wiley Interdiscip Rev Syst Biol Med*. 2010;2(6):654–69.
- Chapman MA, Lawrence MS, Keats JJ, Cibulskis K, Sougnez C, Schinzel AC, et al. Initial genome sequencing and analysis of multiple myeloma. *Nature*. 2011;471(7339):467–72.
- Dimopoulos K, Gimsing P, Gronbaek K. Aberrant microRNA expression in multiple myeloma. *Eur J Haematol*. 2013;91(2):95–105.
- Yap TA, Johnson PWM, Winter J, Leonard J, Giulino-Roth L, Horner T, Radswillas K, Carver J, Dhar A. A phase I, open-label study of GSK2816126, an enhancer of zeste homolog 2 (EZH2) inhibitor, in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (tFL), other non-Hodgkin's lymphomas (NHL), multiple myeloma (MM) and solid tumor. *J Clin Oncol*. 2016;34(suppl 15):TPS2595-TPS2595.
- Laurie Herviou AK, Boireau S, Robert N, Requirand G, Vincent L, Seckinger A, Goldschmidt H, Hose D, Cavalli G, Moreaux J. Targeting EZH2 in multiple myeloma could be promising for a subgroup of MM patients in combination with IMiDs. *Blood*. 2016;128:311.
- Richardson P, Mitsiades C, Colson K, Reilly E, McBride L, Chiao J, et al. Phase I trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) in patients with advanced multiple myeloma. *Leuk Lymphoma*. 2008;49(3):502–7.
- Tompkins JD, Hall C, Chen VC, Li AX, Wu X, Hsu D, et al. Epigenetic stability, adaptability, and reversibility in human embryonic stem cells. *Proc Natl Acad Sci U S A*. 2012;109(31):12544–9.
- Wong KY, Huang X, Chim CS. DNA methylation of microRNA genes in multiple myeloma. *Carcinogenesis*. 2012;33(9):1629–38.
- Ahmad A, Ginnebaugh KR, Yin S, Bollig-Fischer A, Reddy KB, Sarkar FH. Functional role of miR-10b in tamoxifen resistance of ER-positive breast cancer cells through down-regulation of HDAC4. *BMC Cancer*. 2015;15:540.
- Zhang Q, Padi SK, Tindall DJ, Guo B. Polycomb protein EZH2 suppresses apoptosis by silencing the proapoptotic miR-31. *Cell Death Dis*. 2014;5:e1486.
- El-Awady RA, Hersi F, Al-Tunajji H, Saleh EM, Abdel-Wahab AH, Al Homssi A, et al. Epigenetics and miRNA as predictive markers and targets for lung cancer chemotherapy. *Cancer Biol Ther*. 2015;16(7):1056–70.
- Abdi J, Jian H, Chang H. Role of micro-RNAs in drug resistance of multiple myeloma. *Oncotarget*. 2016;7(37):60723–35.
- Nikesitch N, Ling SC. Molecular mechanisms in multiple myeloma drug resistance. *J Clin Pathol*. 2016;69(2):97–101.
- Heuck CH, Mehta J, Tariman J, Pulliam N, Yu Y, Bhagat T, Nischal S, Meagher R, Hu CY, Verma A, Singhal SB. Epigenomic profiling of multiple myeloma shows widespread stage specific alterations in DNA methylation that occur early during myelomagenesis. *Blood*. 2010;116:784.
- Walker BA, Wardell CP, Chiecchio L, Smith EM, Boyd KD, Neri A, et al. Aberrant global methylation patterns affect the molecular pathogenesis and prognosis of multiple myeloma. *Blood*. 2011;117(2):553–62.
- Tsvetkov P, Sokol E, Jin D, Brune Z, Thiru P, Ghandi M, et al. Suppression of 19S proteasome subunits marks emergence of an altered cell state in diverse cancers. *Proc Natl Acad Sci U S A*. 2017;114(2):382–7.
- Das DS, Ray A, Das A, Song Y, Tian Z, Oronsky B, et al. A novel hypoxia-selective epigenetic agent RRx-001 triggers apoptosis and overcomes drug resistance in multiple myeloma cells. *Leukemia*. 2016;30(11):2187–97.
- Nojima M, Maruyama R, Yasui H, Suzuki H, Maruyama Y, Tarasawa I, et al. Genomic screening for genes silenced by DNA methylation revealed an association between RASD1 inactivation and dexamethasone resistance in multiple myeloma. *Clin Cancer Res*. 2009;15(13):4356–64.
- Mithraprabhu S, Kalf A, Chow A, Khong T, Spencer A. Dysregulated Class I histone deacetylases are indicators of poor prognosis in multiple myeloma. *Epigenetics*. 2014;9(11):1511–20.
- Affif S, Michael A, Azimi M, Rodriguez M, Lendvai N, Landgren O. Role of histone deacetylase inhibitors in relapsed refractory multiple myeloma: a focus on vorinostat and panobinostat. *Pharmacotherapy*. 2015;35(12):1173–88.
- Hideshima T, Richardson PG, Anderson KC. Mechanism of action of proteasome inhibitors and deacetylase inhibitors and the biological basis of synergy in multiple myeloma. *Mol Cancer Ther*. 2011;10(11):2034–42.
- Kikuchi J, Koyama D, Wada T, Izumi T, Hofgaard PO, Bogen B, et al. Phosphorylation-mediated EZH2 inactivation promotes drug resistance in multiple myeloma. *J Clin Invest*. 2015;125(12):4375–90.
- Gollner S, Oellerich T, Agrawal-Singh S, Schenk T, Klein HU, Rohde C, et al. Loss of the histone methyltransferase EZH2 induces resistance to multiple drugs in acute myeloid leukemia. *Nat Med*. 2017;23(1):69–78.
- Kalushkova A, Fryknas M, Lemaire M, Fristedt C, Agarwal P, Eriksson M, et al. Polycomb target genes are silenced in multiple myeloma. *PLoS One*. 2010;5(7):e11483.
- Agarwal P, Alzrigat M, Parraga AA, Enroth S, Singh U, Ungerstedt J, et al. Genome-wide profiling of histone H3 lysine 27 and lysine 4 trimethylation in multiple myeloma reveals the importance of Polycomb gene targeting and highlights EZH2 as a potential therapeutic target. *Oncotarget*. 2016;7(6):6809–23.
- Alzrigat M, Parraga AA, Agarwal P, Zureigat H, Osterborg A, Nahi H, et al. EZH2 inhibition in multiple myeloma downregulates myeloma associated oncogenes and upregulates microRNAs with potential tumor suppressor functions. *Oncotarget*. 2017;8(6):10213–24.
- Hernando H, Gelato KA, Lesche R, Beckmann G, Koehr S, Otto S, et al. EZH2 inhibition blocks multiple myeloma cell growth through upregulation of epithelial tumor suppressor genes. *Mol Cancer Ther*. 2016;15(2):287–98.
- Zeng D, Liu M, Pan J. Blocking EZH2 methyltransferase activity by GSK126 decreases stem cell-like myeloma cells. *Oncotarget*. 2017;8(2):3396–411.
- Shah MY, Martinez-Garcia E, Phillip JM, Chambliss AB, Popovic R, Ezponda T, et al. MMSET/WHSC1 enhances DNA damage repair leading to an increase in resistance to chemotherapeutic agents. *Oncogene*. 2016;35(45):5905–15.
- Herviou L, Cavalli G, Cartron G, Klein B, Moreaux J. EZH2 in normal hematopoiesis and hematological malignancies. *Oncotarget*. 2016;7(3):2284–96.
- Rukov JL, Wilentzik R, Jaffe I, Vinther J, Shomron N. PharmacomiR: linking microRNAs and drug effects. *Brief Bioinform*. 2014;15(4):648–59.
- Di Martino MT, Gulla A, Cantafio ME, Lionetti M, Leone E, Amodio N, et al. In vitro and in vivo anti-tumor activity of miR-221/222 inhibitors in multiple myeloma. *Oncotarget*. 2013;4(2):242–55.
- Gulla A, Di Martino MT, Gallo Cantafio ME, Morelli E, Amodio N, Botta C, et al. A 13 mer LNA-i-miR-221 inhibitor restores drug sensitivity in melphalan-refractory multiple myeloma cells. *Clin Cancer Res*. 2016;22(5):1222–33.
- Zhao JJ, Chu ZB, Hu Y, Lin J, Wang Z, Jiang M, et al. Targeting the miR-221-222/PUMA/BAK/BAX pathway abrogates dexamethasone resistance in multiple myeloma. *Cancer Res*. 2015;75(20):4384–97.
- Leone E, Morelli E, Di Martino MT, Amodio N, Foresta U, Gulla A, et al. Targeting miR-21 inhibits in vitro and in vivo multiple myeloma cell growth. *Clin Cancer Res*. 2013;19(8):2096–106.
- Sarkar S, Dubaybo H, Ali S, Goncalves P, Kollepara SL, Sethi S, et al. Down-regulation of miR-221 inhibits proliferation of pancreatic cancer cells through up-regulation of PTEN, p27(kip1), p57(kip2), and PUMA. *Am J Cancer Res*. 2013;3(5):465–77.
- Bai H, Wei J, Deng C, Yang X, Wang C, Xu R. MicroRNA-21 regulates the sensitivity of diffuse large B-cell lymphoma cells to the CHOP chemotherapy regimen. *Int J Hematol*. 2013;97(2):223–31.
- Gong C, Yao Y, Wang Y, Liu B, Wu W, Chen J, et al. Up-regulation of miR-21 mediates resistance to trastuzumab therapy for breast cancer. *J Biol Chem*. 2011;286(21):19127–37.
- Wei X, Wang W, Wang L, Zhang Y, Zhang X, Chen M, et al. MicroRNA-21 induces 5-fluorouracil resistance in human pancreatic cancer cells by regulating PTEN and PDCD4. *Cancer Med*. 2016;5(4):693–702.
- Hu J, Van Valckenborgh E, Xu D, Menu E, De Raevae H, De Bruyne E, et al. Synergistic induction of apoptosis in multiple myeloma cells by bortezomib

- and hypoxia-activated prodrug TH-302, in vivo and in vitro. *Mol Cancer Ther.* 2013;12(9):1763–73.
44. Fujita T, Doihara H, Washio K, Kawasaki K, Takabatake D, Takahashi H, et al. Proteasome inhibitor bortezomib increases PTEN expression and enhances trastuzumab-induced growth inhibition in trastuzumab-resistant cells. *Anticancer Drugs.* 2006;17(4):455–62.
 45. Du J, Liu S, He J, Liu X, Qu Y, Yan W, et al. MicroRNA-451 regulates stemness of side population cells via PI3K/Akt/mTOR signaling pathway in multiple myeloma. *Oncotarget.* 2015;6(17):14993–5007.
 46. Ballabio E, Armesto M, Breeze CE, Manterola L, Arestin M, Tramonti D, et al. Bortezomib action in multiple myeloma: microRNA-mediated synergy (and miR-27a/CDK5 driven sensitivity)? *Blood Cancer J.* 2012;2:e83.
 47. Feng DD, Zhang H, Zhang P, Zheng YS, Zhang XJ, Han BW, et al. Down-regulated miR-331-5p and miR-27a are associated with chemotherapy resistance and relapse in leukaemia. *J Cell Mol Med.* 2011;15(10):2164–75.
 48. Jagannathan S, Vad N, Vallabhapurapu S, Anderson KC, Driscoll JJ. MiR-29b replacement inhibits proteasomes and disrupts aggresome + autophagosome formation to enhance the antimyeloma benefit of bortezomib. *Leukemia.* 2015;29(3):727–38.
 49. Zhang W, Wang YE, Zhang Y, Leleu X, Reagan M, Mishima Y, et al. Global epigenetic regulation of microRNAs in multiple myeloma. *PLoS One.* 2014; 9(10):e110973.
 50. Wong KY, So CC, Loong F, Chung LP, Lam WW, Liang R, et al. Epigenetic inactivation of the miR-124-1 in haematological malignancies. *PLoS One.* 2011;6(4):e19027.
 51. Yang Y, Li F, Saha MN, Abdi J, Qiu L, Chang H. miR-137 and miR-197 induce apoptosis and suppress tumorigenicity by targeting MCL-1 in multiple myeloma. *Clin Cancer Res.* 2015;21(10):2399–411.
 52. Qin Y, Zhang S, Deng S, An G, Qin X, Li F, et al. Epigenetic silencing of miR-137 induces drug resistance and chromosomal instability by targeting AURKA in multiple myeloma. *Leukemia.* 2017;31(5):1123–35.
 53. Zhang B, Ma L, Wei J, Hu J, Zhao Z, Wang Y, et al. miR-137 suppresses the phosphorylation of AKT and improves the dexamethasone sensitivity in multiple myeloma cells via targeting MITF. *Curr Cancer Drug Targets.* 2016; 16(9):807–17.
 54. Viziteu E, Klein B, Basbous J, Lin YL, Hirtz C, Gourzones C, et al. RECQ1 helicase is involved in replication stress survival and drug resistance in multiple myeloma. *Leukemia.* 2017.
 55. Kim Y, Kim H, Park D, Jeoung D. miR-335 targets SIAH2 and confers sensitivity to anti-cancer drugs by increasing the expression of HDAC3. *Mol Cells.* 2015;38(6):562–72.
 56. Swierczynski S, Kliesser E, Illig R, Alinger-Scharinger B, Kiesslich T, Neureiter D. Histone deacetylation meets miRNA: epigenetics and post-transcriptional regulation in cancer and chronic diseases. *Expert Opin Biol Ther.* 2015; 15(5):651–64.
 57. Min DJ, Ezponda T, Kim MK, Will CM, Martinez-Garcia E, Popovic R, et al. MMSET stimulates myeloma cell growth through microRNA-mediated modulation of c-MYC. *Leukemia.* 2013;27(3):686–94.
 58. Shah MA, Schwartz GK. Cell cycle-mediated drug resistance: an emerging concept in cancer therapy. *Clin Cancer Res.* 2001;7(8):2168–81.
 59. Kim KH, Roberts CW. Targeting EZH2 in cancer. *Nat Med.* 2016;22(2):128–34.
 60. Simon JA, Lange CA. Roles of the EZH2 histone methyltransferase in cancer epigenetics. *Mutat Res.* 2008;647(1-2):21–9.
 61. Zhao X, Lwin T, Zhang X, Huang A, Wang J, Marquez VE, et al. Disruption of the MYC-miRNA-EZH2 loop to suppress aggressive B-cell lymphoma survival and clonogenicity. *Leukemia.* 2013;27(12):2341–50.
 62. Iorio MV, Piovano C, Croce CM. Interplay between microRNAs and the epigenetic machinery: an intricate network. *Biochim Biophys Acta.* 2010; 1799(10-12):694–701.
 63. Amodio N, Stamato MA, Gulla AM, Morelli E, Romeo E, Raimondi L, et al. Therapeutic targeting of miR-29b/HDAC4 epigenetic loop in multiple myeloma. *Mol Cancer Ther.* 2016;15(6):1364–75.
 64. Amodio N, Rossi M, Raimondi L, Pitari MR, Botta C, Tagliaferri P, et al. miR-29: a family of epi-miRNAs with therapeutic implications in hematologic malignancies. *Oncotarget.* 2015;6(15):12837–61.
 65. Issa ME, Takhsha FS, Chirumamilla CS, Perez-Novo C, Vanden Berghe W, Cuendet M. Epigenetic strategies to reverse drug resistance in heterogeneous multiple myeloma. *Clin Epigenetics.* 2017;9:17.
 66. Tandon N, Ramakrishnan V, Kumar SK. Clinical use and applications of histone deacetylase inhibitors in multiple myeloma. *Clin Pharmacol.* 2016;8:35–44.
 67. Ola Rizq NM, Koide S, Ma A, Jin J, Iseki T, Nakaseko C, Iwama A. EZH2 inhibition and the combination with proteasome inhibition are novel potential strategies for the treatment of multiple myeloma. *Blood.* 2014;124:2094.
 68. Kikuchi J, Wada T, Shimizu R, Izumi T, Akutsu M, Mitsunaga K, et al. Histone deacetylases are critical targets of bortezomib-induced cytotoxicity in multiple myeloma. *Blood.* 2010;116(3):406–17.
 69. Hideshima T, Cottini F, Ohguchi H, Jakubikova J, Gorgun G, Mimura N, et al. Rational combination treatment with histone deacetylase inhibitors and immunomodulatory drugs in multiple myeloma. *Blood Cancer J.* 2015;5:e312.
 70. Kaufman JL, Fabre C, Lonial S, Richardson PG. Histone deacetylase inhibitors in multiple myeloma: rationale and evidence for their use in combination therapy. *Clin Lymphoma Myeloma Leuk.* 2013;13(4):370–6.
 71. Tagliaferri P, Rossi M, Di Martino MT, Amodio N, Leone E, Gulla A, et al. Promises and challenges of MicroRNA-based treatment of multiple myeloma. *Curr Cancer Drug Targets.* 2012;12(7):838–46.
 72. Ahmad N, Haider S, Jagannathan S, Anaissie E, Driscoll JJ. MicroRNA therapeutics for the clinical management of multiple myeloma. *Leukemia.* 2014;28(4):732–8.
 73. Mithraprabhu S, Khong T, Spencer A. Overcoming inherent resistance to histone deacetylase inhibitors in multiple myeloma cells by targeting pathways integral to the actin cytoskeleton. *Cell Death Dis.* 2014;5:e1134.
 74. Wang X, Li C, Ju S, Wang Y, Wang H, Zhong R. Myeloma cell adhesion to bone marrow stromal cells confers drug resistance by microRNA-21 up-regulation. *Leuk Lymphoma.* 2011;52(10):1991–8.
 75. Murray MY, Rushworth SA, Zaitseva L, Bowles KM, Macewan DJ. Attenuation of dexamethasone-induced cell death in multiple myeloma is mediated by miR-125b expression. *Cell Cycle.* 2013;12(13):2144–53.
 76. Roccaro AM, Sacco A, Thompson B, Leleu X, Azab AK, Azab F, et al. MicroRNAs 15a and 16 regulate tumor proliferation in multiple myeloma. *Blood.* 2009;113(26):6669–80.
 77. Hao M, Zhang L, An G, Sui W, Yu Z, Zou D, et al. Suppressing miRNA-15a/-16 expression by interleukin-6 enhances drug-resistance in myeloma cells. *J Hematol Oncol.* 2011;4:37.
 78. Hentati-Kallel M, Le Jan S, Bernard P, Antonicelli F, Trussardi-Regnier A. Histone deacetylases meet microRNA-associated MMP-9 expression regulation in glucocorticoid-sensitive and -resistant cell lines. *Int J Oncol.* 2017;50(2):717–26.
 79. Xi H, Li L, Du J, An R, Fan R, Lu J, et al. hsa-miR-631 resensitizes bortezomib-resistant multiple myeloma cell lines by inhibiting UbcH10. *Oncol Rep.* 2017; 37(2):961–8.
 80. Shen X, Guo Y, Qi J, Shi W, Wu X, Ni H, et al. Study on the association between miRNA-202 expression and drug sensitivity in multiple myeloma cells. *Pathol Oncol Res.* 2016;22(3):531–9.
 81. Zhao JJ, Lin J, Zhu D, Wang X, Brooks D, Chen M, et al. miR-30-5p functions as a tumor suppressor and novel therapeutic tool by targeting the oncogenic Wnt/beta-catenin/BCL9 pathway. *Cancer Res.* 2014;74(6):1801–13.
 82. Wu P, Agnelli L, Walker BA, Todoerti K, Lionetti M, Johnson DC, et al. Improved risk stratification in myeloma using a microRNA-based classifier. *Br J Haematol.* 2013;162(3):348–59.
 83. Huang JJ, Yu J, Li JY, Liu YT, Zhong RQ. Circulating microRNA expression is associated with genetic subtype and survival of multiple myeloma. *Med Oncol.* 2012;29(4):2402–8.
 84. Lionetti M, Biasiolo M, Agnelli L, Todoerti K, Mosca L, Fabris S, et al. Identification of microRNA expression patterns and definition of a microRNA/mRNA regulatory network in distinct molecular groups of multiple myeloma. *Blood.* 2009;114(25):e20–6.
 85. Pichiorri F, Suh SS, Ladetto M, Kuehl M, Palumbo T, Drandi D, et al. MicroRNAs regulate critical genes associated with multiple myeloma pathogenesis. *Proc Natl Acad Sci U S A.* 2008;105(35):12885–90.
 86. Gutierrez NC, Sarasquete ME, Misiewicz-Krzeminska I, Delgado M, De Las Rivas J, Ticona FV, et al. Deregulation of microRNA expression in the different genetic subtypes of multiple myeloma and correlation with gene expression profiling. *Leukemia.* 2010;24(3):629–37.
 87. Misiewicz-Krzeminska I, Sarasquete ME, Quwaider D, Krzeminski P, Ticona FV, Paino T, et al. Restoration of microRNA-214 expression reduces growth of myeloma cells through positive regulation of P53 and inhibition of DNA replication. *Haematologica.* 2013;98(4):640–8.
 88. Zhang YK, Wang H, Leng Y, Li ZL, Yang YF, Xiao FJ, et al. Overexpression of microRNA-29b induces apoptosis of multiple myeloma cells through down regulating Mcl-1. *Biochem Biophys Res Commun.* 2011;414(1):233–9.
 89. Pichiorri F, Suh SS, Rocci A, De Luca L, Taccioli C, Santhanam R, et al. Downregulation of p53-inducible microRNAs 192, 194, and 215 impairs the

p53/MDM2 autoregulatory loop in multiple myeloma development. *Cancer Cell*. 2010;18(4):367–81.

90. Canella A, Cordero Nieves H, Sborov DW, Cascione L, Radomska HS, Smith E, et al. HDAC inhibitor AR-42 decreases CD44 expression and sensitizes myeloma cells to lenalidomide. *Oncotarget*. 2015;6(31):31134–50.
91. Wu C, Ruan T, Liu W, Zhu X, Pan J, Lu W, et al. Effect and mechanism of curcumin on EZH2 - miR-101 regulatory feedback loop in multiple myeloma. *Curr Pharm Des*. 2017.

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