Long non-coding RNAs in multiple myeloma (Review)

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Abstract. Multiple myeloma (MM) is one of the three major malignancies of the hematological system in middle-aged and older individuals. The incidence of MM increases with age and due to its drug resistance and high recurrence, MM seriously harms human health. Long non-coding RNAs (lncRNAs) are RNA molecules with a length of >200 nt and rarely encode proteins. Numerous studies reported that lncRNAs regulate carcinogenesis and cancer progression. MM-associated lncRNAs affect features of tumor cells, including proliferation, apoptosis, adhesion and treatment resistance. The present review aims to summarize the latest findings on the roles of lncRNAs in MM to deepen the understanding of this field and provide insight for developing specific diagnostic tools and effective treatment strategies for MM, including novel biomarkers and targeted lncRNA therapeutics.

Contents

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1. Introduction

Multiple myeloma (MM) is a type of tumor characterized by the malignant proliferation of plasma cells. Numerous plasma cells in the bone marrow proliferate and secrete monoclonal immunoglobulin or its fragment (M protein), which may lead to clinical symptoms such as anemia, renal insufficiency, bone destruction and hypercalcemia. According to global statistical reports, MM is the second most common cancer type of the hematological system (1). With the aging of the global population, the incidence of MM has increased by 126% from 1990 to 2016, causing severe health issues (1). In recent years, progress in MM treatment, such as proteasome inhibitors, immunomodulators, immunotherapy and autologous stem cell transplantation, has markedly improved patients' survival (2). However, MM is a disease that is difficult to cure. Even if the disease is controlled by treatment, MM relapse and drug resistance may eventually lead to death (3).

Following the proposal of the 'Human Genome Project' and the development of sequencing technology, 90% of the genome was discovered to be transcribed into RNA, most of which could not be translated into proteins and only 2% of which were mRNAs that contribute to protein coding (4). RNAs that do not encode proteins are called non-coding RNAs (ncRNAs). ncRNAs were considered 'waste' during transcription, but numerous studies have confirmed that they have important roles in regulating gene expression and the progression of neoplastic diseases (5). Long ncRNAs (lncRNAs), with >200 nt in length, belong to the family of ncRNAs whose function has not been fully defined.

LncRNAs are poorly conserved among species and have high tissue, cell and spatiotemporal specificities (6), making them potential tumor biomarkers. Evidence suggests that lncRNAs may either promote or suppress the progression of human neoplastic diseases (7). Although lncRNAs rarely encode proteins, they may act on nearby molecules or targets. LncRNAs in the cytoplasm bind to ribosomes, degrade and regulate mRNA, mediate regulation of RNA terminal specific structural sequences and act as bait for microRNA (miRNA/miR) and prevent miRNA

from degrading targeted mRNA (8-10). LncRNAs regulate mRNA stability and may also act as scaffoldings to regulate protein interactions (8-10). LncRNAs in the nucleus may bind to chromatin regulatory factors, transcription factors and chromatin to affect transcriptional activation, transcriptional inhibition and post-transcriptional regulation through cis- or trans-actions and regulate gene expression at the pre-transcriptional, transcriptional and post-transcriptional levels (10-12).

The present review summarizes the latest findings of lncRNAs in the pathogenesis of MM and the complex regulatory network of lncRNAs and discusses the roles of lncRNAs in diagnostic and treatment strategies for MM, laying a foundation to further the understanding of the pathogenesis of MM, the development of highly specific diagnostic and prognostic tools and effective treatment strategies.

2. LncRNAs may act as oncogenes to promote MM tumor progression

Most lncRNAs are upregulated in MM, promoting proliferation, DNA protection, adhesion, migration and invasion of MM tumor cells through various mechanisms by inhibiting apoptosis and remodeling the tumor microenvironment (TME) to facilitate the growth of tumor cells (Table I). LncRNAs with cancer-promoting effects in MM were screened and a gene regulatory network was constructed (Fig. 1), which helps understand the pathogenesis of MM.

LncRNAs promote the proliferation of MM tumor cells. MM is characterized by the malignant clonal proliferation of plasma cells (13) and most oncogenic lncRNAs promote MM cell proliferation.

LncRNAs bind to miRNAs and act as competing endogenous RNAs (ceRNAs) to regulate miRNA expression, an important molecular mechanism of the lncRNA regulatory network. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is the most widely studied lncRNA, which is upregulated in breast cancer, cervical cancer, colorectal cancer, lung cancer and other cancer types, promoting tumorigenesis (14). Silencing MALAT1 significantly inhibited MM cell proliferation (15,16). Sun *et al* (15) demonstrated that the MALAT1/miR-181a-5p/Hippo-Yes-associated protein (Hippo-YAP) pathway and silencing MALAT1 increased the expression of the targeted miR-181a-5p and activated the Hippo-YAP signaling pathway, inhibiting cell proliferation. Liu *et al* (16) reported another MALAT1/miR-188-5p pathway, in which MALAT1 negatively regulates miR-188-5p expression, promoting DNA replication and the transition from the G1 to S phase of the cell cycle. H19 imprinted maternally expressed transcript (H19) is also one of the 'hot genes' regulated by lncRNAs, which is abnormally highly expressed in oral squamous cell carcinoma, hepatocellular carcinoma, breast cancer, bladder cancer and other malignant cancers (17). Zheng *et al* (18) demonstrated that H19 silencing in tumor cells led to bromodomain containing 4 (BRD4)-mediated upregulation of proliferation-related signals, resulting in the inhibition of cell proliferation and cell cycle arrest at G1 phase and confirming the H19/miR-152-3p/BRD4 pathway. Prostate cancer-associated transcript 1 (PCAT1) promotes cell proliferation in various tumor types, such as bladder cancer, esophageal squamous cell carcinoma and lung cancer (19). Overexpression of PCAT1 by plasmid vector in MM decreased miR-129 levels and upregulated mitogen-activated protein kinase kinase kinase 7 (MAP3K7), activating the nuclear factor κB (NF-κB) pathway and leading to PCAT1/miR-129/MAP3K7/NF-κB signaling (20). Similarly, plasmacytoma variant translocation 1(PVT1) is a widely studied lncRNA (21). PVT1 is highly expressed in myeloma cells; the level of miR-203a is reduced through the targeted action of ceRNA and the PVT1/miR-203 pathway promotes cell proliferation (22). Antisense noncoding RNA in the INK4 locus (ANRIL) downregulates miR-411-3p and upregulates hypoxia-inducible factor 1α (HIF-1α), forming the ANRIL/miR-411-3p/HIF-1α pathway to promote the malignant proliferation of tumor cells and tumor stem cell-like characteristics (23). Colorectal neoplasia differentially expressed (CRNDE) negatively targets miR-451, forming a CRNDE/miR-451 pathway that promotes cell proliferation (24). Human leukocyte antigen complex P5 (HCP5) acts on miR-128-3p through a 'molecular sponge' to increase pleomorphic adenoma gene like-2 expression and activate the Wnt/β-catenin/cyclin D1 (CCND1) signaling pathway, forming the HCP5/miR-128-3p/Wnt/β-catenin/CCND1 pathway (25). Elevated transcription factor 7 (TCF7) levels may promote MM cell proliferation. Liu *et al* (26) confirmed the TCF7/miR-203/Jagged1/Notch1 pathway and Ding *et al* (27) confirmed another regulatory pathway, TCF7/miR-200c. The RNA component of mitochondrial RNA processing endoribonuclease (RMRP) may regulate cell proliferation through the RMRP/miR-34a-5p/c-Myc pathway, and c-Myc locates in the RMRP promoter region to promote RMRP transcription, forming a circular pathway (28). In addition to these 'hot spot' lncRNA studies, numerous newly discovered lncRNAs have a cancer-promoting effect in MM.MSTRG.29039.1 reduces the inhibitory effect of miR-12119 on the oncostatin M receptor (OSMR), and OSMR upregulation activates the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathway, forming the MSTRG.29039.1/miR-12119/OSMR/JAK2/STAT3 pathway (29). RP11-301G19.1 upregulates high-mobility group protein B2 (HMGB2), the target gene of miR-582-5p, promotes the phosphorylation of phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT) and activates the RP11-301G19.1/miR-582-5p/PI3K/Akt pathway (30). LINC01234 promotes MM cell proliferation through the LINC01234/miR-124-3p/growth factor receptor-bound protein 2 pathway (31). LINC00461 promotes MM cell proliferation through the LINC00461/miR-15/B-cell lymphoma 2 (Bcl-2) and LINC00461/miR-16/Bcl-2 pathways (32). In addition, there are several lncRNAs in MM that target miRNAs to regulate downstream proteins and promote cell proliferation through the 'molecular sponge' function. For instance, brain-derived neurotrophic factor-antisense (BDNF-AS)/miR-125-5p/Bcl-2 (33), urothelial cancer associated 1 (UCA1)/miR-1271-5p/hepatocyte growth factor (34), FEZ family zinc finger 1 antisense RNA 1/miR-610/AKT serine/threonine kinase 3 (35), colon cancer-associated transcript 1 (CCAT1)/miR-181a-5p/homeobox A1 (36), myocardial

Table I. Molecular mechanisms of multiple myeloma-associated lncRNAs.

LncRNA	Author, year	Direction of differential expression	ceRNA target	Downstream regulatory targets	Function	(Refs.)
MALAT1	Sun, 2019	Up-regulated	miR-181a-5p	Hippo/YAP	Proliferation, adherence	(15)
	Liu, 2021	Up-regulated	miR-188-5p	n.a.	Proliferation, DNA replication	(16)
	Hu, 2018	Up-regulated	n.a.	PARP1, LIG3	Apoptosis, DNA repair, drug resistance	(52)
	Gao, 2017	Up-regulated	n.a.	HMGB1/Beclin-1, HMGB1/LC3B	Apoptosis	(56)
	Liu, 2020	Up-regulated	miR-1271-5p	SOX13	Invasion, glycolysis	(60)
	Amodio, 2018	Up-regulated	n.a.	NRF1/2	Apoptosis	(126)
H19	Zheng, 2020	Up-regulated	miR-152-3p	BRD4	Proliferation, cell cycle	(18)
	Sun, 2017	Up-regulated	n.a.	NF-κB, IL-8	Proliferation, colony formation	(38)
	Pan, 2019	Up-regulated	miR-29b-3p	MCL1	Drug resistance, apoptosis	(117)
PCAT1	Shen, 2020	Up-regulated	miR-129	MAP3K7/NF-κB	Proliferation	(20)
	Shen, 2019	Up-regulated	n.a.	p38, JNK/MAPK	Proliferation, drug resistance	(39)
PVT1	Yang, 2018	Up-regulated	miR-203a	n.a.	Proliferation	(22)
	Handa, 2020	Up-regulated	n.a.	MYC	Proliferation	(40)
ANRIL	Wang, 2020	Up-regulated	miR-411-3p	HIF-1α	Proliferation, stem cell-like properties of tumors	(23)
	Yang, 2021	Up-regulated	n.a.	EZH2/PTEN/AKT	Drug resistance	(100)
CRNDE	Meng, 2017	Up-regulated	miR-451	n.a.	Proliferation	(24)
	David, 2021	Up-regulated	n.a.	IL-6/STAT, RAS, MAPK, PI3K/AKT	Drug resistance	(121)
HCP5	Liu, 2021	Up-regulated	miR-128-3p	PLAGL2/Wnt/β-catenin/CCND1	Proliferation	(25)
TCF7	Liu, 2021	Up-regulated	miR-203	Jagged1/Notch1	Proliferation	(26)
	Ding, 2021	Up-regulated	miR-200c	n.a.	Proliferation	(27)
RMRP	Xiao, 2019	Up-regulated	miR-34a-5p	c-Myc	Proliferation	(28)
MSTRG.29039.1	Liu, 2021	Up-regulated	miR-12119	OSMR/JAK2/STAT3	Proliferation	(29)
RP11-301G19.1	Wang, 2022	Up-regulated	miR-582-5p	HMGB2/PI3K/AKT	Proliferation, cell cycle	(30)
LINC01234	Chen, 2019	Up-regulated	miR-124-3p	GRB2	Proliferation, cell cycle	(31)
LINC00461	Deng, 2019	Up-regulated	miR-15/16	Bcl2	Proliferation	(32)
BDNF-AS	Chu, 2022	Up-regulated	miR-125-5p	Bcl2	Proliferation	(33)
UCA1	Yang, 2019	Up-regulated	miR-1271-5p	HGF	Proliferation	(34)
FEZF1-AS1	Li, 2018	Up-regulated	miR-610	AKT3	Proliferation, cell cycle	(35)
CCAT1	Chen, 2018	Up-regulated	miR-181a-5p	HOXA1	Proliferation, cell cycle	(36)
MIAT	Fu, 2019	Up-regulated	miR-29b	MCL1, Sp1	Proliferation, drug resistance	(37)
ST3GAL6-AS1	Ronchetti, 2020	Up-regulated	n.a.	MAPK, ubiquitination protein	Proliferation	(41)
	Shen, 2021	Up-regulated	n.a.	hnRNPA2B1/ST3GAL6	Adherence, migration, invasion	(63)
NEAT1	Geng, 2018	Up-regulated	n.a.	Wnt/β-catenin	Proliferation, migration, invasion	(42)
	Taiana, 2020	Up-regulated	n.a.	RAD51B, CHK1, CHK2, RPA32, BRCA1	Apoptosis, DNA repair	(55)

Table I. Continued.

LncRNA	Author, year	Direction of differential expression	ceRNA target	Downstream regulatory targets	Function	(Refs.)
	Gao, 2020	Up-regulated	miR-214	B7-H3	Remodeling the TME	(66)
	Che, 2021	Up-regulated	miR-29b-3p	Sp1	Drug resistance	(118)
	Wu, 2018	Up-regulated	miR-193a	MCL1	Drug resistance	(120)
HOTAIR	Zhu, 2019	Up-regulated	n.a.	NF-κB	Proliferation	(43)
	Guan, 2019	Up-regulated	n.a.	JAK2/STAT3	Drug resistance	(107)
LUCAT1	Liu, 2020	Up-regulated	n.a.	TGF-β	Proliferation, cell cycle	(44)
AL928768.3	Shen, 2022	Up-regulated	n.a.	CDK2, CCND1, p21	Proliferation, cell cycle	(45)
HOXB-AS1	Chen, 2020	Up-regulated	n.a.	FUT4-Wnt-β-catenin	Proliferation	(46)
LBX2-AS1	Jia, 2021	Up-regulated	n.a.	LBX2	Proliferation	(47)
SNHG16	Yang, 2020	Up-regulated	miR-342-3p	Caspase3, caspase9, Foxa3a, Bax, Bcl2, CCND1, PI3K-AKT	Apoptosis, cell cycle	(57)
SOX2OT	Yu, 2020	Up-regulated	miR-144-3p	c-MET	Tumor progression	(61)
LINC01606	He, 2021	Up-regulated	miR-579-3p	n.a.	Migration, invasion	(62)
LOC606724	Wang, 2022	Up-regulated	n.a.	eIF4E, c-Myc	Remodeling the TME	(67)
PDIA3P	Yang, 2018	Up-regulated	n.a.	c-Myc, G6PD	Drug resistance	(116)
LINC01003	Wu, 2021	Down-regulated	miR-33a-5p	PIM1	Proliferation, adherence	(68)
OIP5-AS1	Yang, 2017	Down-regulated	miR-410	PTEN/PI3K/AKT/KLF10	Cell cycle	(69)
	Wang, 2020	Down-regulated	miR-27a-3p	TSC1	Apoptosis, migration, invasion	(70)
DANCR	Wu, 2021	Down-regulated	miR-135b-5p	KLF9	Migration, invasion	(71)
IRAIN	Jiang, 2019	Down-regulated	miR-125b	n.a.	Proliferation	(72)
XLOC-013703	Pu, 2019	Down-regulated	n.a.	IL-6/NF-κB	Apoptosis, cell cycle	(73)
BM742401	Li, 2020	Down-regulated	n.a.	n.a.	Homing, migration	(74)
PRAL	Xiao, 2018	Down-regulated	miR-210	BMP2	Drug resistance	(79)

TME, tumor microenvironment; lncRNA, long non-coding RNA; miRNA/miR, microRNA; ceRNA, competing endogenous RNA; n.a., no information available; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; H19, H19 imprinted maternally expressed transcript; PCAT1, prostate cancer-associated transcript 1; PVT1, plasmacytoma variant translocation 1; ANRIL, antisense noncoding RNA in the INK4 locus; CRNDE, colorectal neoplasia differentially expressed; HCP5, human leukocyte antigen complex P5; TCF7, transcription factor 7; RMRP, RNA component of mitochondrial RNA processing endoribonuclease; BDNF-AS, brain-derived neurotrophic factor-antisense; UCA1, urothelial cancer associated 1; FEZF1-AS1, FEZ family zinc finger 1 antisense RNA 1; CCAT1, colon cancer-associated transcript 1; MIAT, myocardial infarction associated transcript; ST3GAL6-AS1, ST3 β-galactoside α-2,3-sialyltransferase 6-antisense RNA1; NEAT1, nuclear enriched abundant transcript 1; HOTAIR, HOX transcript antisense RNA; LUCAT1, lung cancer-associated transcript 1; HOXB-AS1, HOXB cluster antisense RNA 1; SNHG16, small nucleolar RNA host gene 16; SOX2OT, SOX2 overlapping transcript; PDIA3P, protein disulfide isomerase family A member 3 pseudogene 1; OIP5-AS1, Opa-interacting protein 5-antisense RNA 1; DANCR, differentiation antagonizing non-protein coding RNA; IRAIN, insulin-like growth factor receptor antisense imprinted non-protein coding RNA; PRAL, p53 regulation associated lncRNA.

infarction-associated transcript (MIAT)/miR-29b/myeloid cell leukemia-1 (MCL1) and MIAT/miR-29b/Sp1 transcription factor (Sp1) (37).

In addition to targeting miRNAs, lncRNAs may directly mediate protein expression or activate signaling pathways, thus promoting myeloma cell proliferation. H19 directly

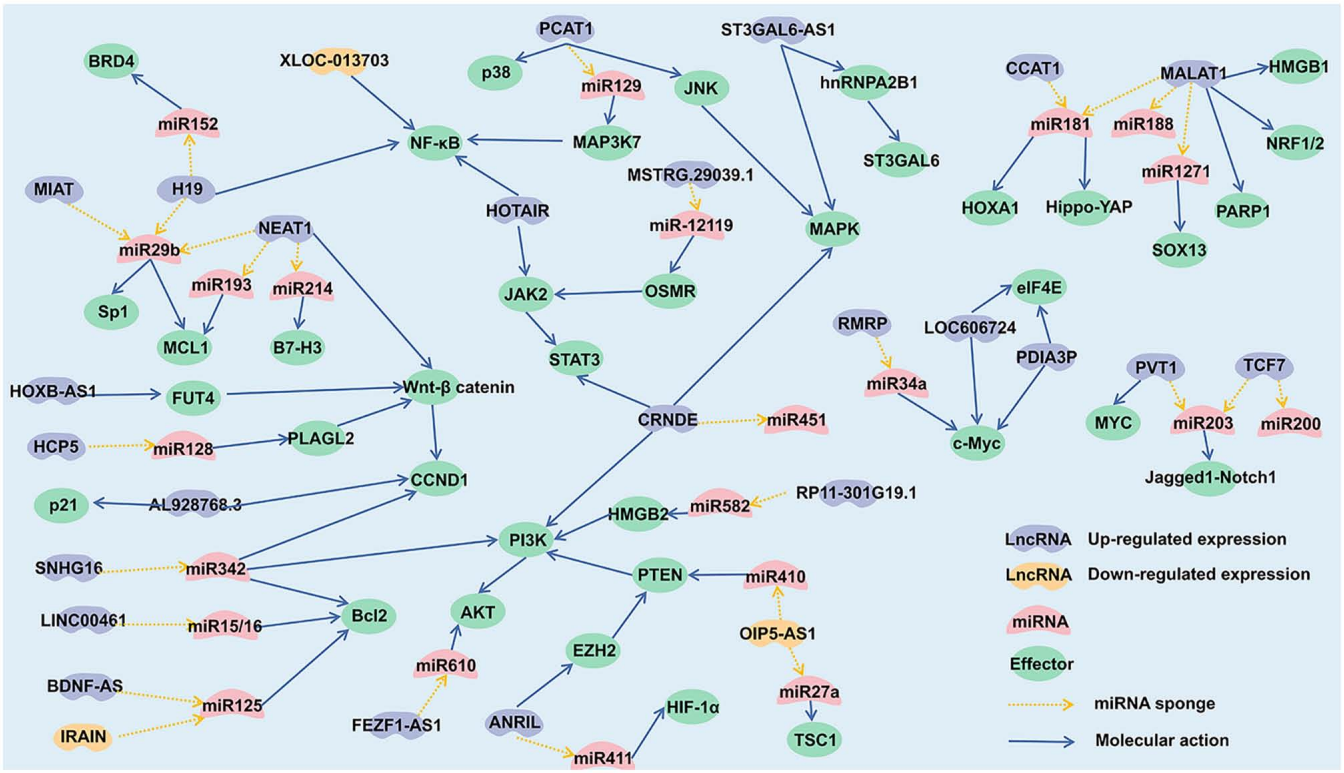

Figure 1. Molecular regulatory networks of multiple myeloma-associated lncRNAs. LncRNA, long non-coding RNA; miRNA, microRNA.

activates the NF-κB signaling pathway and upregulates the secretion of the downstream cytokine IL-8, thus promoting cell proliferation and colony formation (38). PCAT1 directly activates the p38 and c-Jun N-terminal kinase (JNK)/mitogen-activated protein kinase (MAPK) signaling pathways, promoting the proliferation and survival of MM cells (39). PVT1 regulates MYC expression at the transcriptional level, and both PVT1 and MYC genes are regulated by BRD4 (40). Ronchetti *et al* (41) reported that ST3 β-galactoside α-2,3-sialyltransferase 6-antisense RNA1 (ST3GAL6-AS1) silencing decreased MAPK phosphorylation and ubiquitination, thereby inhibiting cell proliferation. Geng *et al* (42) demonstrated that nuclear enriched abundant transcript 1 (NEAT1) overexpression increased the expression of proteins related to the Wnt/β-catenin signaling pathway, suggesting that NEAT1 is able to mediate the Wnt/β-catenin signaling pathway to regulate cell proliferation. Similarly, HOX transcript antisense RNA (HOTAIR) was indicated to activate the NF-κB signaling pathway in myeloma cells (43), and lung cancer-associated transcript 1 (LUCAT1) activated the transforming growth factor-β signaling pathway (44). AL928768.3, which directly acts on cyclin-dependent kinase 2 and CCND1, reduces cyclin suppressor gene p21 to avoid cell cycle arrest in G0/G1 phase, which is conducive to cell proliferation (45). LncRNAs may also enhance mRNA stability and promote the proliferation of myeloma cells by improving the expression of target genes. Chen *et al* (46) reported that HOXB cluster antisense RNA 1 was able to enhance the interaction between ELAV-like RNA binding protein 1 and fucosyltransferase 4 (FUT4) proteins, promote the stability of FUT4 mRNA and thus activate the Wnt-β-catenin signaling pathway. Ladybird homeobox 2 (LBX2)-AS1 improved the stability of LBX2 mRNA and increased its expression of LBX2, thus promoting myeloma progression (47).

LncRNAs inhibit apoptosis of MM cells. During normal cell proliferation, the G1/S checkpoint of the cell cycle actively recognizes the integrity of DNA replication. If DNA damage occurs, the cell cycle stops at the G1 phase and the cell becomes unable to enter the S phase to start the DNA repair process (48). If the damage is so severe that it outpaces the cell's ability to repair DNA, apoptosis is triggered in the cell (49). Due to the lack of 'functional' p53, the key regulator of the G1/S checkpoint, the cell cycle of tumor cells is accelerated to rapidly enter the S phase, but DNA damage, such as DNA double-strand break (DSB), single strand break (SSB) and interchain crosslinking may have toxic effects on cells (50). Recent studies indicated that tumor cells enhance their DNA repair ability to avoid apoptosis (51). LncRNAs in myeloma cells may act as oncogenes to mediate the DNA repair process, thus having a role in DNA protection and anti-apoptosis. As a protein scaffold, MALAT1 directly binds poly (ADP-ribose) polymerase 1 (PARP1) to form functional complexes, and it indirectly binds DNA ligase 3 (LIG3) to enhance the alternative non-homologous end joining DNA repair pathway (52,53). PARP1 is a protein closely related to DSB and SSB in the process of DNA repair, which may catalyze PAR and induce apoptosis. MALAT1 binding to PARP1 may reduce PAR signaling and inhibit the release of PARP1, thus reducing cell apoptosis (54). NEAT1 mediates a variety of DNA repair mechanisms, including the homologous recombination signaling pathway, mismatch repair and nucleotide resection repair. NEAT1 silencing downregulated DNA repair-related genes, such as RAD51 recombinase paralog B, checkpoint

kinase 1 (CHK1), CHK2, 32-kDa subunit of human RPA and breast cancer gene 1, and it significantly inhibited the DNA repair ability of myeloma cells (55).

LncRNAs in MM cells may also directly regulate miRNA or protein expression and inhibit tumor cell apoptosis. MALAT1 decreases HMGB1 ubiquitination, inhibits the degradation of HMGB1 after its translation and promotes the expression of Beclin-1 and microtubule associated protein 1 light chain 3 β proteins, thus inhibiting apoptosis (56). Through the effect of ceRNA, small nucleolar RNA host gene 16 (SNHG16) regulates the expression of miR-342-3p, downregulates the levels of caspase 3, caspase 9, forkhead transcription factor O subfamily member 3a and Bax, and upregulates the levels of Bcl-2, CCND1, PI3K and AKT, promoting the transition of the cell cycle from the G1 phase to the S phase (57).

LncRNAs enhance the adhesion, invasion and energy metabolism of MM cells. The adhesion and invasion ability of tumor cells endows the process of tumor metastasis and promotes the development of tumors (58). Rapid and abnormal proliferation of tumor cells requires a large amount of energy metabolism. Normal cells are mainly powered by the oxidative phosphorylation of ATP; however, there is widespread hypoxia in tumor tissues, which cannot effectively carry out the oxidative phosphorylation process. Therefore, the energy supply of tumor cells may occur in an anaerobic environment, and the energy metabolism proceeds through glycolysis via the glucose-pyruvate-lactic acid pathway (59). Studies have indicated that MM-associated lncRNAs may enhance the adhesion, invasion and glycolytic abilities of tumor cells. MALAT1 forms the MALAT1/miR-1271-5p/SRY-box transcription factor 13 (SOX13) pathway, promoting MM cell invasion and glycolysis (60). SOX2 overlapping transcript (SOX2OT) forms the SOX2OT/miR-144-3p/c-MET pathway and promotes MM progression (61). LINC01606 forms part of the LINC01606/miR-579-3p pathway, promoting the migration and invasion of myeloma cells (62). ST3GAL6-AS1 recruits heterogeneous nuclear ribonucleoprotein A2/B1 protein, inhibits the degradation of ST3GAL6 mRNA, upregulates ST3GAL6 protein, and promotes cell adhesion, migration and invasion (63).

LncRNAs reshape the TME in MM cells. The TME is an environment for the survival of tumor cells, containing fibroblasts, immune cells, endothelial cells, adipocytes, neurons and other non-neoplastic cells, as well as the components of the extracellular matrix, such as chemokines, cytokines and exosomes (64). The TME is an important regulatory factor in tumor angiogenesis, continuous proliferation, migration, invasion and immune escape. Various cytokines and exosomes reshape the TME and maintain an environment conducive to tumor growth. Cells in the TME are also stimulated by cytokines and undergo phenotypic changes, further promoting tumor development (65). MM-associated lncRNAs participate in the remodeling of the TME. For instance, NEAT1 regulates B7-H3 by mediating the expression of miR-214 through a 'molecular sponge' effect. B7-H3 activates the JAK2-STAT3 signaling pathway to regulate macrophage polarization in the TME. NEAT1 promotes the polarization of M2-type tumor-associated macrophages through the NEAT1/miR-214/B7-H3 pathway (66). LncRNAs in the TME may also affect MM cells. Wang *et al* (67) reported that adipocytes in the TME secrete exosomes enriched with LOC606724 and SNHG1, and apoptosis of MM cells is significantly inhibited after phagocytosis of exosomes. LOC606724 may act as a 'molecular scaffold' to connect eukaryotic translation initiation factor 4E (eIF4E) and c-Myc. eIF4E is a key factor in protein translation and LOC606724 may promote the synthesis of c-Myc mediated by eIF4E.

3. LncRNAs may act as tumor suppressor genes to inhibit MM tumor progression

Although studies have indicated that most lncRNAs promote cancer occurrence and development, certain lncRNAs function as tumor suppressor genes and their expression is downregulated in MM (Table I; Fig. 1). MM-related tumor suppressor lncRNAs inhibit tumor cell proliferation and migration through ceRNA and promote apoptosis. LINC01003 inhibits tumor cell adhesion and proliferation through the LINC01003/miR-33a-5p/Pim-1 proto-oncogene, serine/threonine kinase pathway (68). Studies have indicated that Opa-interacting protein 5-antisense RNA 1 (OIP5-AS1) may have a role in cancer inhibition through multiple regulatory pathways, and the OIP5-AS1/miR-410/phosphatase and tensin homolog (PTEN)/PI3K/AKT pathway regulates the expression of downstream KLF transcription factor 10 (KLF10) to arrest cell cycle progression (69). The OIP5-AS1/miR-27a-3p/tuberous sclerosis 1 pathway inhibits tumor cell migration and invasion and promotes apoptosis (70). Differentiation antagonizing non-protein coding RNA (DANCR) forms the DANCR/miR-135b-5p/KLF9 pathway, which reduces tumor cell viability, migration and invasion (71). Insulin-like growth factor receptor antisense imprinted non-protein coding RNA (IRAIN) forms the IRAIN/miR-125b pathway to inhibit tumor cell proliferation and promote apoptosis (72). LncRNAs may also directly regulate signaling pathways in tumor cells. XLOC-013703 reduces the secretion of interleukin 6 (IL-6) and inhibits the activation of the NF-κB signaling pathway, thus causing cell cycle arrest and accelerating apoptosis (73). The low expression of MM-associated lncRNAs in tumor tissues may be related to hypermethylation of the promoter region. Li *et al* (74) demonstrated that BM742401 inhibits the homing and migration of MM cells but does not affect cell proliferation or apoptosis. The failure of BM742401's anti-cancer function is due to the hypermethylation of its promoter region. A demethylation agent promoted BM742401 expression and restored its anti-tumor effect.

4. LncRNAs are closely related to MM tumor progression and patient prognosis

Both oncogenic and tumor suppressor lncRNAs have a key role in the incidence and development of MM, suggesting that lncRNA expression is closely related to MM progression and the prognosis of patients (Table II). The expression of cancer-promoting lncRNAs was significantly higher in the intermediate and late stages of MM than in the early stage; lncRNA expression was positively associated with the level of tumor pathogenicity factors and negatively associated with

Table II. Association between multiple myeloma-associated lncRNAs and clinicopathological factors.

LncRNA	Author, year	Expression	Pathological indicators	Clinical manifestations and cytogenetics	Prognosis	(Refs.)
ST3GAL6-AS1	Shen, 2021 Shen, 2018	Up-regulated	DS, ISS, R-ISS, infiltration of plasma cells	n.a.	n.a.	(63,76)
H19	Zheng, 2020 Sun, 2017 Pan, 2018	Up-regulated	DS, ISS	Bone disease	OS	(18,38,77)
TUG1	Yin, 2019	Up-regulated	DS, ISS, R-ISS, β_2-MG, albumin, globulin	n.a.	n.a.	(78)
BDNF-AS	Chu, 2022	Up-regulated	DS, ISS	n.a.	OS	(33)
MIAT	Fu, 2019	Up-regulated	DS, ISS, IgH, IgL	Overall cytogenetic risk	OS	(37)
ANRIL	Yin, 2021 Yang, 2021	Up-regulated	ISS, β_2-MG	n.a.	OS, PFS, CR	(85,100)
MSTRG.29039.1	Liu, 2021	Up-regulated	ISS, β_2-MG, LDH, infiltration of plasma cells	n.a.	n.a.	(29)
NEAT1	Gao, 2020 Yu, 2020	Up-regulated	ISS, β_2-MG, LDH	n.a.	OS, PFS, CR, ORR	(66,86)
HCP5	Liu, 2021	Up-regulated	ISS	n.a.	PFS	(25)
UCA1	Sedlarikova, 2017	Up-regulated	ISS, albumin, IgM	t(4;14), Del(13q14), 1q21 amplification	OS	(87)
PCAT1	Zhao, 2021	Up-regulated	ISS, R-ISS, β_2-MG, LDH	Bone disease, Del(17p)	OS, PFS	(88)
TCF7	Liu, 2021 Ding, 2021	Up-regulated	ISS, β_2-MG	t(14;16)	OS, EFS, CR	(26,27)
NR-046683	Dong, 2019	Up-regulated	ISS, β_2-MG	n.a.	PFS	(89)
AL928768.3	Shen, 2022	Up-regulated	ISS	n.a.	n.a.	(45)
LUCAT1	Liu,2020	Up-regulated	ISS	n.a.	OS	(44)
ANGPTL1-3	Zhou, 2022	Up-regulated	ISS, R-ISS	Del(17p), t(4;14)	PFS, CR	(90)
CCAT1	Chen, 2018	Up-regulated	ISS	n.a.	OS	(36)
CCAT2	Xu, 2020	Up-regulated	ISS, β_2-MG	Kidney disease	n.a.	(91)
PRINS	Sedlarikova, 2018	Up-regulated	Infiltration of plasma cells	t(4;14)	n.a.	(95)
RMRP	Xiao, 2019	Up-regulated	n.a.	n.a.	OS, DFS	(28)
HCP5	Liu, 2021	Up-regulated	n.a.	n.a.	OS	(25)
CRNDE	Meng, 2017	Up-regulated	n.a.	n.a.	OS	(24)
LINC01606	He, 2021	Up-regulated	n.a.	n.a.	OS	(62)
LINC00461	Deng, 2019	Up-regulated	n.a.	n.a.	OS	(32)
LOC606724	Wang, 2022	Up-regulated	n.a.	n.a.	OS, CR	(67)
SNHG1	Wang, 2022	Up-regulated	n.a.	n.a.	OS, CR	(67)
OIP5-AS1	Wang, 2020	Down-regulated	ISS, IMWG risk stratification	n.a.	OS	(70)
XLOC-013703	Pu, 2019	Down-regulated	DS, R-ISS, β_2-MG	n.a.	n.a.	(73)
PRAL	Xiao, 2018	Down-regulated	DS, ISS	n.a.	OS, DFS	(79)
BM742401	Li, 2020	Down-regulated	n.a.	n.a.	OS	(74)

LncRNA, long non-coding RNA; DS, Durie-Salmon staging; ISS, International Staging System; R-ISS, Revised International Staging System; β2-MG, β2 microglobulin; LDH, Lactate dehydrogenase; IMWG, International Myeloma Working Group; OS, overall survival; DFS, disease-free survival; CR, complete remission; ORR, overall remission rate; EFS, event-free survival; PFS, progression-free survival; n.a., no information available; ST3GAL6-AS1, ST3 β-galactoside α-2,3-sialyltransferase 6-antisense RNA1; H19, H19 imprinted maternally expressed transcript; TUG1, taurine-up regulated gene 1; BDNF-AS, brain-derived neurotrophic factor-antisense; MIAT, myocardial infarction associated transcript; ANRIL, antisense noncoding RNA in the INK4 locus; NEAT1, nuclear enriched abundant transcript 1; HCP5, human leukocyte antigen complex P5; UCA1, urothelial cancer associated 1; PCAT1, prostate cancer-associated transcript 1; TCF7, transcription factor 7; LUCAT1, lung cancer-associated transcript 1; CCAT1, colon cancer-associated transcript 1; CCAT2, colon cancer associated transcript 2; PRINS, psoriasis susceptibility-related RNA gene induced by stress; RMRP, RNA component of mitochondrial RNA processing endoribonuclease; HCP5, human leukocyte antigen complex P5; CRNDE, colorectal neoplasia differentially expressed; SNHG16, small nucleolar RNA host gene 16; OIP5-AS1, opa-interacting protein 5-antisense RNA 1; PRAL, p53 regulation associated lncRNA.

the survival time of patients and complete remission (CR). However, tumor suppressor lncRNAs have the opposite effects.

LncRNAs are associated with pathological indicators of MM. Owing to the variety of clinical manifestations of MM and its numerous variants, there are currently multiple diagnostic criteria and staging systems for MM. Durie-Salmon staging (DS staging) was the first MM staging system and is most widely used (75). ST3GAL6-AS1 (76), H19 (77), taurine-upregulated gene1 (TUG1) (78), p53 regulation associated lncRNA (PRAL) (79), BDNF-AS (33), XLOC-013703 (73) and MIAT (37) were associated with the DS stage of MM. Subsequent studies have indicated that β2 microglobulin (β2-MG) may affect MM malignancy and patient prognosis and become a reliable predictor of the survival time of patients with MM (80,81). Albumin may mediate IL-6 expression and affect MM cell proliferation and tumor malignancy, and serum albumin is an important prognostic factor for MM (82,83). In 2005, the International Myeloma Foundation proposed a new International Staging System (ISS) based on β2-MG and albumin levels (84). Previous studies have confirmed that most MM-related lncRNAs are associated with ISS staging. Examples for this are ANRIL (85), ST3GAL6-AS1 (63), MSTRG.29039.1 (29), H19 (77), NEAT1 (86), HCP5 (25), UCA1 (87), PCAT1 (88), PRAL (79), TCF7 (26), NR-046683 (89), AL928768.3 (45), BDNF-AS (33), LUCAT1 (44), OIP5-AS1 (70), angiopoietin-like (ANGPTL)1-3 (90), MIAT (37), CCAT1 (36), CCAT2 (91) and TUG1 (78). Other studies have found that ANRIL (85), MSTRG.29039.1 (29), NEAT1 (86), TUG1 (78), PCAT1 (88), TCF7 (26), NR-046683 (89), CCAT2 (91) and XLOC-013703 (73) were correlated with serum β2-MG levels in patients with MM. Furthermore, UCA1 (87) and TUG1 (78) were associated with serum albumin levels in patients with MM. Lactate dehydrogenase (LDH) is not a characteristic indicator of MM, but elevated LDH indicates a significantly poor prognosis (92,93). MSTRG.29039.1 (29), NEAT1 (86) and PCAT1 (88) are associated with serum LDH levels. In 2015, the International Myeloma Working Group (IMWG) published the Revised International Staging System (R-ISS) based on LDH levels (94). Studies have confirmed that ST3GAL6-AS1 (76), PCAT1 (88), ANGPTL1-3 (90), XLOC-013703 (73) and TUG1 (78) are related to the R-ISS stage. In addition, OIP5-AS1 is related to the risk stratification proposed by IMWG (70). ST3GAL6-AS1 (76), MSTRG.29039.1 (29) and PRINS (95) were related to the infiltration level of plasma cells. TUG1 expression is associated with serum globulin levels (78), UCA1 with serum IgM (87) and MIAT with serum IgH and IgL (37).

LncRNAs associated with the clinical manifestations of MM. Deregulated proliferation and extensive infiltration of malignant plasma cells in the bone marrow may cause bone issues, such as bone pain and pathological fractures. About two out of three patients with MM seek treatment for a bone disease as their first symptom (96). H19 (18) and PCAT1 (88) were associated with MM-related bone diseases. The accumulation of monoclonal immunoglobulin secreted by malignant plasma cells may seriously interfere with renal tubular function, resulting in renal damage manifestations such as renal dysfunction, proteinuria and hematuria, as well as increased serum creatinine and urea nitrogen (97). CCAT2 is associated with MM-associated kidney disease (91).

LncRNAs are associated with cytogenetic abnormalities of MM. The IMWG proposed that cytogenetic abnormalities worsen the prognosis of patients with MM and suggests that Del(17p), t(4;14), t(14;16), as well as other factors, should be included as reference factors in the diagnosis of MM and cytogenetic abnormalities maybe detected using fluorescence *in situ* hybridization technology for risk stratification (98). It was reported that Del(17p) is related to PCAT1 (88) and ANGPTL1-3 (90); t(4;14) is related to UCA1 (87), ANGPTL1-3 (90) and psoriasis susceptibility-related RNA gene induced by stress (PRINS) (95); UCA1 is also associated with Del(13q14) and 1q21 amplification (87); t(14;16) is related to TCF7 (27); and MIAT is associated with overall cytogenetic risk (37).

LncRNAs are associated with the prognosis of patients with MM. The overall survival (OS) rate of patients with MM has improved since 1970, but the prognosis is still not ideal due to the high recurrence and drug resistance of MM (99). Therefore, a new method of risk stratification is required to accurately assess the prognosis. MM-associated lncRNAs are associated with tumor progression and may be potential indicators of disease and prognosis. Elevated expression of 'cancer-promoting lncRNAs' is associated with poor prognosis and short survival. Studies suggested that ANRIL (100), LOC606724 (67), SNHG1 (67), H19 (38), NEAT1 (66), HCP5 (25), UCA1 (87), PCAT1 (88), PRAL (79), TCF7 (27), BM742401 (74), BDNF-AS (33), CRNDE (24), LINC01606 (62), LUCAT1 (44), LINC00461 (32), OIP5-AS1 (70), CCAT1 (36), MIAT (37) and RMRP (28) were associated with OS in patients with MM. In addition, certain lncRNAs are associated with other survival indicators. For instance, PRAL (79) and RMRP (28) were correlated with disease-free survival, ANRIL (85), NEAT1 (66), HCP5 (25), PCAT1 (88), NR-046683 (89) and ANGPTL1-3 (90) with progression-free survival and TCF7 with event-free survival (27). For hematological malignancies, including MM, treatment response is directly correlated with the survival time of patients. During treatment, to prolong survival, CR is considered the basic condition for effective treatment (101,102). Detection of the expression levels of MM-related lncRNAs to assess CR in patients may help to estimate the prognosis. High expression of cancer-promoting lncRNAs, such as ANRIL (85), LOC606724 (67), SNHG1 (67), NEAT1 (86), TCF7 (26) and ANGPTL1-3 (90), may predict low CR rates. NEAT1 was negatively correlated with the overall response rate (86).

5. LncRNAs are potential markers for diagnosing liquid biopsies in patients with MM

At present, liquid biopsy is a popular research field for cancer diagnosis. It may diagnose the disease without invasive surgery or examination and effectively reduce patients' pain and economic burden (103). Bone marrow aspiration is a traditional examination method for MM diagnosis. However, for patients with MM who require an early differential diagnosis and regular examination during treatment, bone marrow

Table III. Diagnostic value of MM-associated lncRNAs in liquid biopsy.

LncRNA	Author, year	Number of cases	Expression	Sensitivity, %	Specificity, %	AUC	(Refs.)
TUG1	Yin, 2019	110 MM patients/98 healthy controls	Up-regulated	65.5	94.9	0.792	(78)
PCAT1	Shen, 2017	60 MM patients/48 healthy controls	Up-regulated	71.7	93.8	0.892	(106)
H19	Pan, 2018	80 MM patients/67 healthy controls	Up-regulated	77.5	88.1	0.888	(77)
HOTAIR	Guan, 2019	118 MM patients/78 healthy controls	Up-regulated	70.1	79.9	0.798	(107)
LINC01606	He, 2021	72 MM patients/68 healthy controls	Up-regulated	85.3	72.4	0.862	(62)
PRINS	Sedlarikova, 2018	50 MM patients/30 healthy controls	Up-regulated	80.8	76.9	0.753	(95)
LBX2-AS1	Jia, 2021	60 MM patients/60 healthy controls	Up-regulated	n.a.	n.a.	0.753	(47)
XLOC-013703	Pu, 2019	107 MM patients/60 healthy controls	Down-regulated	89.7	90.9	0.940	(73)

AUC, area under curve; MM, multiple myeloma; n.a., no information available.

aspiration is an invasive examination that may cause great pain and have low repeatability. Furthermore, MM is a multi-focal disease with significant spatial heterogeneity and extramedullary disease, and the results of bone marrow aspiration may be biased (104,105). MM-associated lncRNAs are abnormally expressed in the peripheral blood of patients, and compared with conventional clinical indicators, their sensitivity and specificity are similar or even better, exhibiting specific biomarker characteristics, and they may thus be potential diagnostic indicators for MM (Table III).

β2-MG and globulin are commonly used to diagnose MM. A study reported that the serum TUG1 levels in patients with MM were significantly higher than those in healthy individuals, with better sensitivity and specificity (65.5 and 94.9%, respectively), and even better than β2-MG (65.5 and 79.6%, respectively) and globulin (54.5 and 69.4%, respectively) (78). To study the stability of lncRNAs in serum, after the first detection of TUG1 levels, the authors placed the serum samples at room temperature for 24 h or repeatedly froze and thawed them 10 times, and TUG1 was measured. The results indicated no significant changes in the TUG1 levels from the two measurements, unaffected by harsh conditions. It has been suggested that lncRNAs in the serum have good stability. Shen *et al* (106) reported that the sensitivity of serum PCAT1 (71.7%) was higher than that of the common MM indices, β2-MG (48.3%), LDH (15.0%), κ light chain (25.0%) and λ light chain (28.3%), with similar specificity. The sensitivity and specificity of β2-MG combined with PCAT1 were 85 and 88%, respectively. Studies also suggested that the sensitivity and specificity of serum H19 (77), HOTAIR (107), LINC01606 (62) and XLOC-013703 (73) were 77.5 and 88.1%, 70.1 and 79.9%, 85.3 and 72.4%, and 89.7 and 90.9%, respectively. LBX2-AS1 was reported to be an effective diagnostic marker for MM (47). In addition to free lncRNAs in serum, lncRNAs in serum exosomes are potential diagnostic markers. Exosomes are biological vesicles that encapsulate tumor derivatives and have roles in information exchange and substance transfer. The peripheral molecular membrane endows exosomes with high stability and is not easily damaged by interference from the external environment (108). LncRNAs wrapped in exosomes maybe detected and applied. Sedlarikova *et al* (95) reported that PRINS in peripheral blood exosomes of patients with MM was significantly increased, and the sensitivity and specificity for the diagnosis of MM were 80.8 and 76.9%, respectively.

6. LncRNAs regulate drug resistance in MM cells

The continuous development of new anti-MM drugs in the past 20 years has significantly improved the prognosis of patients and the average survival time has been extended from 3-4 years to 7-8 years (109,110). There is currently no cure for MM and initial anti-MM treatment is active and effective. However, relapse inevitably occurs over time and after each relapse, MM becomes more aggressive and resistant to the initial treatment regimen, leading to recurrent/refractory MM (111). Understanding the underlying mechanisms of MM resistance is essential for studying the pathogenesis of relapsed/refractory MM and developing more effective treatment strategies.

MM secretes proteins in large quantities, which relies on proteasomal degradation of misfolded and aggregated proteins. When the function of the proteasome is inhibited, the excessive accumulation of proteins in MM cells may trigger apoptosis, so proteasome inhibitors are used as the first-line standard therapy for MM (112,113). Bortezomib, a new-generation proteasome inhibitor, is the first drug approved by the US Food and Drug Administration (FDA) to treat relapsed/refractory MM, marking a breakthrough in anti-MM therapy (114). Bortezomib inhibits the activation of anti-apoptotic proteins downstream of the NF-κB signaling pathway and prevents the degradation of pro-apoptotic proteins, thus accelerating apoptosis in MM cells (115). Studies have indicated that MM-related lncRNAs regulate the resistance of MM cells to bortezomib, resulting in drug resistance. ANRIL interacts with the enhancer of zeste 2 polycomb repressive complex 2 subunit in the MM cell nucleus to regulate the post-translational modification of the downstream target PTEN, resulting in epigenetic silencing of the PTEN promoter region binding to H3K27me3, thus increasing the phosphorylation of AKT and the resistance of

MM cells to bortezomib, and reducing bortezomib-induced apoptosis (100). PCAT1 directly targets the downstream p38 and JNK-MAPK signaling pathways, reducing the sensitivity of MM cells to bortezomib (39). By interacting with the oncogene c-Myc, protein disulfide isomerase family A member 3 pseudogene 1 regulates the transactivation activity of c-Myc and binds to the promoter of glucose 6-phosphate dehydrogenase (G6PD) to increase G6PD expression, thereby increasing pentose phosphate pathway (PPP) flux. PPP produces NADPH in MM cells to enhance bortezomib resistance (116). MM-associated lncRNAs also regulate the expression of miRNAs through the classical 'molecular sponge' action, thus making cells resistant to bortezomib. H19 targets miR-29b-3p to promote the expression of MCL1, which inhibits apoptosis, leading to drug resistance (117). NEAT1 forms the NEAT1/miR-29b-3p/Sp1 pathway to enhance drug resistance of MM cells, and Sp1, as a transcription factor, targets the promoter region binding to NEAT1 to induce the transcription of NEAT1, eventually forming a feedback pathway (118). MIAT forms the MIAT/miR-29b pathway to enhance bortezomib resistance in MM cells (37). As a tumor suppressor lncRNA, PRAL was downregulated in MM cells and the PRAL/miR-210/bone morphogenetic protein 2 (BMP2) pathway was used to mediate the upregulation of BMP2 by targeting miR-210 to enhance the therapeutic effect of bortezomib on MM cells (79).

In addition to increasing bortezomib resistance, MM-associated lncRNAs may mediate resistance to other drugs. Dexamethasone is the most widely used glucocorticoid in MM therapy and may degrade poly (ADP) nucleotides, reduce the mitochondrial transmembrane potential and induce MM cell apoptosis (119). NEAT1 promotes MCL1 expression through the NEAT1/miR-193a/MCL1 pathway and the resistance of MM cells to dexamethasone (120). CRNDE activates the IL-6 signaling pathway, enhances the activity of downstream STAT, RAS, MAPK and PI3K/AKT pathways, and prevents dexamethasone-induced apoptosis in MM cells, resulting in drug resistance and disease recurrence (121). HOTAIR activates the JAK2/STAT3 signaling pathway and enhances the resistance to dexamethasone in MM cells (107). Hu *et al* (52) reported that MALAT1 was increased in bortezomib-, mefalam- and adriamycin-resistant cell lines, and silencing MALAT1 rendered drug-resistant cell lines sensitive to the corresponding drugs, suggesting that MALAT1 regulates the resistance of MM cells to bortezomib, mefalam and adriamycin.

7. LncRNAs may be a new treatment target for MM

Currently, the focus of drug research for MM treatment involves small chemicals and biomacromolecules (122). However, the non-targeting of small chemical molecules and the difficulty of biomacromolecules penetrating cell membranes limit their potential applications (123). Conventional therapy for tumors frequently has a temporary therapeutic effect, followed by a reduced response because it targets disease-related proteins rather than transcribed genes (124). In contrast, nucleic acid therapy may achieve sustained therapeutic effects and even cure disease by introducing, inhibiting, replacing and editing the relevant DNA or RNA. Therefore, nucleic acid therapy may be used as an alternative or complementary therapy to chemotherapy (125). Most nucleic acid treatments in clinical trials are performed in four ways: Antisense oligonucleotides (ASO), short interfering RNA, lipid nanoparticles and adeno-associated virus carriers. ASO is the application of a short oligonucleotide-binding target RNA, causing RNase H-dependent RNA degradation. Several ASO drugs have been approved by the FDA for the treatment of spinal muscular atrophy, cytomegalovirus retinitis and muscular dystrophy (124).

Previous studies have indicated that MM-related lncRNAs are crucial for tumorigenesis and development. Nucleic acid therapy may degrade 'cancer-promoting lncRNAs' or enhance the effect of 'cancer-suppressing lncRNAs', providing a new direction for anti-MM therapy. Amodio *et al* (126) demonstrated that MALAT1 was an intracellular lncRNA with significantly high expression in MM cells, which promoted proteasomal degradation of damaged and misfolded proteins and inhibited apoptosis through upregulation of the proteasome transcription activator NF-E2 related factor-1/2 (NRF1/2), and NRF1 binds to the promoter of MALAT1 to form a counter-activated feedback pathway. After LNA gapmeR-ASO was applied to target MALAT1 degradation, H3K27Me3 shifted from the promoter region of Kelch-like ECH-associated protein 1 (KEAP1) to reduce KEAP1 methylation. Increased KEAP1 expression reduced NRF1/2 and proteasome levels, promoting apoptosis. In the above study, LNA gapmeR-ASO not only tolerated nucleases and had a good target affinity, but also showed no toxicity which proved that LNA gapmeR-ASO was an ideal nucleic acid therapy route. LNA gapmeR-ASO targeting MALAT1 enhanced the sensitivity of MM cells to bortezomib, suggesting that they may be used alone to induce apoptosis or in conjunction with bortezomib in MM treatment. Hu *et al* (52) reported that MALAT1 promotes DNA repair and anti-apoptosis through the MALAT1/PARP1/LIG3 pathway, and silencing MALAT1 enhanced the toxic effect of bortezomib on MM cells. To further investigate ASO targeting MALAT1 in MM treatment, they combined ASO and MALAT1 with the nanomaterial single-wall carbon nanotube (SWCNT) to enhance targeting affinity and drug stability. After injection of SWCNT-ASO-MALAT1 into the mouse model of MM, the drug concentrated near the tumor, reducing the tumor burden and significantly prolonging the survival of the mice, suggesting that SWCNT-ASO targeting MALAT1 may effectively inhibit tumor growth *in vivo* without significant toxicity.

8. Bioinformatics assisting lncRNA research

With the innovation of gene chips and high-throughput sequencing technology, lncRNA research has been continuously improved. The application of sequencing databases and network tools combined with bioinformatics methods is the current trend in medical research (127). The conventional bioinformatics approach for lncRNA research involves first obtaining the whole-genome transcripts. Second, filter conditions are set to screen for transcripts

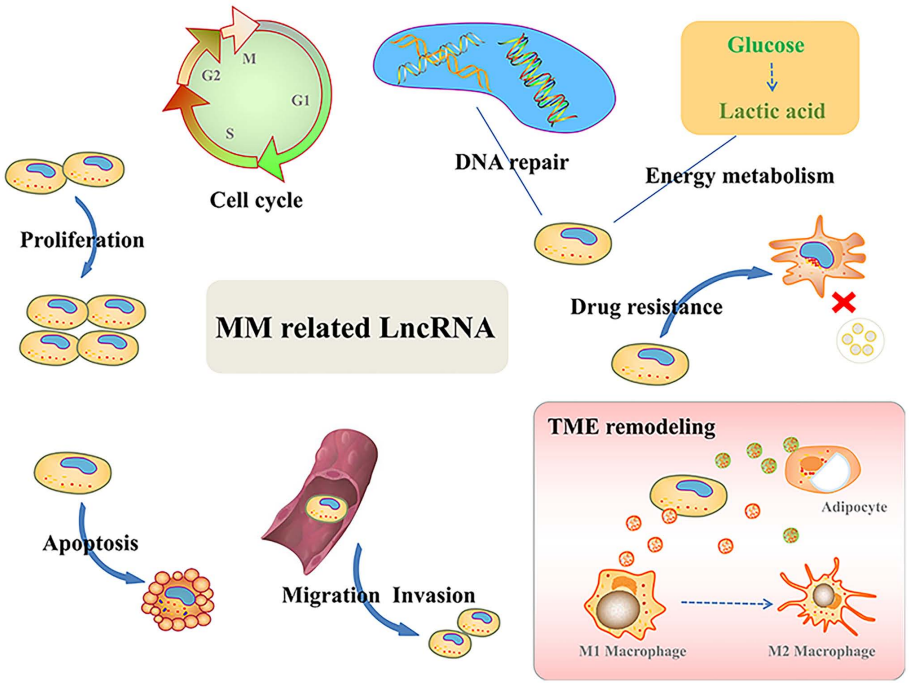

Figure 2. Roles of MM-associated lncRNAs in tumors. LncRNA, long non-coding RNA; TME, tumor microenvironment; MM, multiple myeloma.

that do not encode proteins. The expression levels of protein-coding genes and lncRNAs are obtained from RNA sequencing, and lncRNA quantity is analyzed by calculation. Finally, the functions of lncRNAs are predicted based on the co-expression networks between lncRNAs and protein-coding genes, the interactions between lncRNAs and RNAs, and the interactions between lncRNAs and proteins (128-130). With the development of lncRNA research, a large amount of experimental data has continued to emerge. Bioinformatics and mathematical algorithms are applied to effectively store experimental information in the databases, which are continuously maintained and updated, which is helpful for researchers to directly use the databases for experimental designs and avoid starting from the transcriptome sequencing analysis for each study, thereby effectively saving time and cost.

This section briefly describes the lncRNA-related databases that are widely used at present. The LNCipedia database integrates the information of several human lncRNA databases, including LncRNAdb, Broad Institute, Ensembl and Gencode, and provides the sequence, annotation, structure and miRNA combination information of lncRNAs. It currently contains 127,802 transcripts and 56,946 genes (131). The LNCBook database launched a new version (LNCBook 2.0) in June 2022, providing information on lncRNA expression, sequence alignment, classification, coding ability prediction, methylation, variation, lncRNA-miRNA interactions and lncRNA-protein interactions (132). It is one of the most abundant databases that provides human lncRNA information. The LncSEA database provides detailed information on >50,000 human lncRNAs, including expression, methylation, disease relationships, tumor markers, subcellular localization and transcription factors (133). The LncExpDB database is not limited to diseases and it covers multiple biological components, such as normal tissues, normal cell lines, tumor cell lines, organ development, cell differentiation and exosomes; 101,293 lncRNAs have been included, including the annotation and predictive function (134). The deepBase database was updated with the deepBase 3.0 version in January 2021, providing information on lncRNA expression, evolution, function prediction, prognosis and other information on tissues, cancers and exosomes (135). The TANRIC database integrates lncRNA information in tissues and cell lines from The Cancer Genome Atlas and Cancer Cell Line Encyclopedia databases, providing lncRNA annotation, expression, clinical indicators and prognosis information (136). The LnCAR database is based on 52,300 samples from 10 types of cancer in the Gene Expression Omnibus database, providing differential expression of lncRNAs, clinical indicators and prognosis information (137). The LncRNADisease 2.0 database focuses on association analysis between lncRNAs and diseases, providing 205,959 association scores (138). The LncMAP database provides regulatory networks among lncRNAs, transcription factors and genes in >20 types of tumors (139). The lncRNA SNP database focuses on single nucleotide polymorphism information in human and mouse lncRNAs (140). The Lnc2Meth database focuses on the association analysis of lncRNAs and DNA methylation in human diseases (141).

Most studies use bioinformatics to initially screen target lncRNAs and predict their functions for studying MM-related lncRNAs, which is then verified by *in vitro* and *in vivo* experiments. Due to the lack of validation, only a small number of studies have been solely based on bioinformatics data analysis. Todoerti *et al* (142) screened the data of patients with MM with molecular aberrations and clinical information from public databases and indicated that MIAT was positively correlated with cytogenetic indicators t(4;14), del(1p), del(13q) and hyperdiploidy, and high MIAT expression suggested poor OS. In MM pathogenesis, genes

encoding ribosome, immune response, mitotic spindle, apoptosis and p53 pathway are upregulated in cases with high MIAT expression. By contrast, DNA repair-related genes and MYC target genes are downregulated. Regarding drug resistance, MIAT expression increased in MM cells with drug resistance, or MM relapsed after bortezomib treatment. Todoerti *et al* (142) conducted a comprehensive study of MIAT but did not perform any experimental verification. Zhou *et al* (143) downloaded a large amount of gene expression data and clinical information of patients with MM from the GEO database and identified 59 lncRNAs associated with OS; four of them were independent risk factors for predicting OS, RP4-803J11.2 and RP1-43E13.2 were upregulated, and ZFY-AS1 and RP11-553L6.5 downregulated. Functional enrichment analysis suggested that RP4-803J11.2, RPP1-43E13.2, ZFY-AS1 and RP11-553L6.5 were involved in the cell cycle, chromatin modification, DNA replication, microtubule process, DNA repair and RNA processing in MM.

9. Summary and outlook

In recent years, researchers have identified numerous lncRNAs abnormally expressed in tumors, making lncRNAs a research hotspot. The present review discussed recent studies on MM-associated lncRNAs, emphasizing their roles in tumor development (Fig. 2). MM-associated lncRNAs change the biological features of tumor cells, such as proliferation, apoptosis, adhesion, invasion, energy metabolism, therapeutic resistance and TME reshaping. LncRNAs are closely related to pathological indicators and prognosis of MM and are potential biomarkers and reference molecules for disease risk stratification. Regarding the molecular mechanisms, lncRNAs exert their effects through ceRNA interactions, binding proteins and transcription factors, acting as 'molecular scaffolds', mRNA stabilizers, mediating cell signaling pathways, epigenetic gene regulation and other pathways. By determining the specific regulatory mechanisms of lncRNAs, targeted therapies for MM using nucleic acids may avoid frequent drug resistance and disease relapse.

However, in the face of tens of thousands of lncRNAs and the complex and huge molecular regulatory networks behind them, the current understanding of lncRNAs remains incomplete. There is insufficient evidence for lncRNA as a mature tumor diagnostic marker, which requires to be further explored in large-sample studies and with multi-disease stratification. A single lncRNA cannot drive the biological functions of tumor cells and the same signaling pathway does not function alone. It is necessary to further explore the synergistic effects of multiple lncRNAs, signaling pathways and acting proteins, and to enrich and expand the molecular regulatory networks of lncRNAs, which will deepen our understanding of the pathogenesis of MM. The present study provides a solid foundation and new insight for developing novel biomarkers and targeted lncRNA therapeutics.

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Availability of data and materials

Data sharing is not applicable.

Authors' contributions

CY wrote the manuscript. YL, JS and SW drew the figures. YH performed the literature review. KC and MS designed the study and approved the final version of the manuscript for publication. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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