INTRODUCTION

Multiple myeloma (MM) is characterized by the malignant proliferation of plasma cells in the bone marrow microenvironment, accompanied by organ dysfunctions, including anemia, hypercalcemia, renal insufficiency, and osteolytic bone disease. Recent advances in molecular and genetic research have contributed to identifying the association between the clinical behavior of MM patients and the biological features of myeloma cells, leading to eventually individualize treatment. It is well known that the epigenetic abnormalities and dysregulation of miRNA expression are associated with the development and prognosis of MM. Gao X et al found that MM patients with high levels of miRNA-15a, miRNA-16-1, miRNA-17, miRNA-20a, and miRNA-92-1 always led to poor prognosis and a shorter progression-free survival duration. In addition, miRNA-15a and miRNA-16 can regulate the proliferation and growth of MM cells by inhibiting AKT serine/threonine protein kinase (AKT3), ribosomal protein S6, MAP kinases, and the NF-kappaB activator MAP3KIP3. Furthermore, miRNA expression profiles can also be applied to the risk stratification of MM. Nonetheless, our understanding of MM biology remains limited to explain the genesis and evolution of this disease.

The human genome project revealed that at least 90% of the human genome was actively transcribed to RNA, but less than 2% of RNA-encoded proteins. The dysregulation of miRNAs has been reported to virtually occur in all types of cancers, including MM. Recent studies have provided evidence that long non-coding RNAs (lncRNAs) are also involved in tumor initiation, metastasis, and drug resistance. LncRNAs, with a length of over 200 nucleotides, have little or no capacity for protein synthesis. These have been shown to regulate gene expression at the transcriptional, post-transcriptional, and epigenetic levels and are implicated in diverse biological functions, including development, proliferation, differentiation, and apoptosis.

LncRNAs have been observed to regulate complex cellular progresses and vital signal transduction pathways that are commonly deregulated in cancer. Moreover, accumulating evidence suggests that lncRNAs have multiple functions in normal and malignant hematopoiesis. For example, the dysregulation of IncRNA BGL3 has been observed in chronic myeloid leukemia, and it was described...
to act as a tumor suppressor. For their function in carcinogenesis, related mechanisms can be classified based on their influence on the chromatin state and methylation, the stability of proteins and complexes, or the ability to act as a sponge for miRNA inhibition.

The present review primarily focused on some mechanisms of lncRNAs in MM to help in providing a good understanding of their roles in MM.

2 | MECHANISMS OF LncRNAs IN MM

2.1 | MALAT1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), an 8.5-Kb IncRNA (7 kb in mice) located on chromosome 11 (11q13.1), consists of two exons and is one of the few biologically well-studied lncRNAs, and it has been reported to involve the regulation of gene expressions and the regulation of alternative splicing and cell cycle. MALAT1 misregulation has been shown to play a role in the development of several solid tumors, including lung, colorectal, bladder, and laryngeal cancers.

A previous study revealed that MALAT1 was overexpressed in newly diagnosed patients, when compared with post-treatment patients, and its expression in newly diagnosed MM patients was not associated with the concentration of plasma cells in the bone marrow. It was observed that patients with a greater decrease in MALAT1 after initial treatment had a significantly prolonged progression-free survival (PFS) duration, while patients with smaller MALAT1 changes after treatment had a significantly higher risk of early progression. This means that MALAT1 expression may serve as a molecular predictor for patients. Furthermore, MALAT1 expression was markedly higher in extramedullary myeloma (EMM), when compared to intramedullary myeloma cells. It was also found that MALAT1 expression level was positively correlated with the mRNA levels of HSP90, which has been reported to be induced by bortezomib, and contributes to drug resistance. This phenomenon indicates that MALAT1 is upregulated as a stress response.

Further studies have revealed that in mesenchymal stem cells (MSCs) from patients with MM, MALAT1 could recruit the transcription factor Sp1 on the latent TGF-β-binding protein 3 (LTBP3) promoter. Furthermore, in the formation of a stable complex among MALAT1, the LTBP3 promoter and Sp1 were able to increase the expression of the LTBP3 gene. In addition, LTBP3 regulates the bioavailability of TGF-β, especially in the bone. TGF-β plays a role in MM cell growth or resistance to apoptosis, which induces the secretion of IL-6 and vascular endothelial growth factor (VEGF).

In addition, using RNA interference, cyclin D1 and cyclin E are downregulated in MALAT1-silenced MM cells, which lead to the inhibition of the proliferation of MM cells through cell cycle arrest at the G1 phase. Furthermore, the knockdown of MALAT1 induces apoptosis in MM cells through an endogenous apoptotic pathway by downregulating Bcl-2 and upregulating Bax. On the other hand, MALAT1 can regulate MM cell autophagy by binding to high mobility group box 1 (HMGB1) at the post-translational level. HMGB1 is a kind of DNA-binding protein closely correlated to hematological malignancies, including lymphoma and MM, and contributes to the growth and proliferation of MM cells. Da Gao et al. found that MALAT1 increased the expression level of HMGB1 in MM, and HMGB1-mediated autophagy could help in the suppression of apoptosis and the promotion of tumor cell survival. All these results suggest that MALAT1 may be a potential therapeutic target for the treatment of MM.

2.2 | MEG3

Located on chromosome 14q32, maternally expressed gene 3 (MEG3) is an imprinted gene, which consists of 10 exons and encodes an approximately 1.6-Kb IncRNA, and is expressed in many normal tissues. It is well known that MEG3 is an important tumor suppressor, and the loss of MEG3 expression is responsible for several types of human cancers, including nasopharyngeal carcinoma and breast cancer.

It has been reported that a high percentage of patients with MM presented with hypermethylated MEG3 promoter differentially methylated regions (DMR), especially those with advanced-stage disease. By downregulating murine double minute 2 (MDM2), MEG3 can activate p53, which functions as a transcription factor to regulate the expression of many target genes, leading to the suppression of tumor development and growth. The decreased expression of MEG3 due to hypermethylation might result in decreased p53 levels, and this might be a potential pathway in MM. In addition, MEG3 can promote the BMP4-induced osteogenic differentiation of MSCs from MM patients. Compared with MSCs from normal donors, the expression levels of MEG3 and BMP4 are low in MSCs derived from MM patients. The decreased level of MEG3 may contribute to osteoblast deficiency in MM.

Emerging evidences have shown that the deletion or promoter hypermethylation of the MEG3 gene promotes angiogenesis. He et al. found that MEG3 suppressed the proliferation and angiogenesis of vascular endothelial cells through the interaction and suppression of miR-9. Angiogenesis is one of the important mechanisms for the progression of MM.

2.3 | DLEU2

LncRNA deleted in leukemia 2 (DLEU2), which is located at chromosome 13q14.3, hosts miR-15a and miR-16-1. DLEU2 consists of 15 exons and encodes a 3.1-Kb IncRNA. The 13q14 deletions are found at high frequencies in many types of lymphoid malignancies, such as mantle cell lymphoma (MCL), diffuse large B-cell lymphoma, and MM.

A recent study revealed that DLEU2 was downregulated in MM patients with del13, and its expression was significantly correlated with that of miR-15a and miR-16-1 located in the same region. Another study reported that DLEU2 negatively regulated G1 cyclins E1 and D1 through miR-15a/miR-16-1 at the translational level, and in this way, inhibited the excessive cell cycle progression. Thus, DLEU2 may act as a tumor suppressor, and its loss contributes to the emergence of tumors, as multiple cyclin proteins are affected.
Previous studies have also revealed that DLEU2 is negatively correlated to Myc, while Myc is overexpressed in MM cells.\textsuperscript{36,37} Myc can regulate the expression of genes in cells, such as genes related to DNA synthesis, cell adhesion, and cell cycle progression, which are closely correlated to cell proliferation, differentiation, and apoptosis, and the disorders of its expression or function have been observed in various tumors. These findings show that Myc may mediate the derepression of cyclins D1 and E1 through DLEU2/miR-15a/miR-16-1. Interestingly, we know that cyclin D1 and cyclin E are downregulated in MALAT1-silenced MM cells. There may be some interactions between MALAT1 and Myc or DLEU2.

2.4 | KIAA0495

KIAA0495, also known as TP73-AS1, consists of five exons. Its transcript is about 4.1 kb. Zhan et al found that KIAA0495, an lncRNA transcribed from chromosome 1p36, was progressively downregulated from normal plasma cells to monoclonal gammopathy of undetermined significance (MGUS) and to symptomatic myeloma by gene expression profiling.\textsuperscript{38} DNA methylation has been implicated in the pathogenesis and prognosis of MM.\textsuperscript{39} However, the methylation of KIAA0495, which leads to the reversible silencing of KIAA0495 expression in MM, has been rarely detected in primary samples of MM at diagnosis or relapse. This means that it may not be associated with its progressive downregulation in cells from normal plasma cells to MGUS and to MM.\textsuperscript{40} Haploinsufficiency and chromosome deletion probably involve the loss of expression of KIAA0495.\textsuperscript{41} Related mechanisms on the downregulation of KIAA0495 in MM require further research.

It has been reported that KIAA0495 level significantly decreases in oligodendrogial tumors. Promoter hypermethylation, chromosome 1p loss, and balanced chromosome 1p are the major mechanisms that contribute to KIAA0495 downregulation.\textsuperscript{42} The knockdown of KIAA0495 can induce cisplatin resistance via the upregulation of anti-apoptotic B-cell CLL/lymphoma 2-like 1 (BCL2L1), which possesses anti-apoptotic activity.

2.5 | PCAT1

Consisting of two exons, prostate cancer-associated transcript 1 (PCAT1) is located on chromosome 8q24, whose transcript, a 2.0-kb lncRNA, has been identified as a novel prostate-specific regulator of cell proliferation in patients with prostate cancer.\textsuperscript{43} In addition, PCAT1 is also upregulated in colorectal cancer and hepatocellular carcinoma, and its overexpression is always associated with poor prognosis.\textsuperscript{44} In recent years, a study revealed that PCAT1 in serum was significantly higher in the MM group than in healthy control groups.\textsuperscript{45} These results indicate that it has good sensitivity and high specificity as a predictive biomarker. However, the molecular mechanisms of PCAT1 in MM are not identified. A recent report revealed that PCAT1 silencing could inhibit Wnt/β-catenin signaling via miR-122 repression and WNT1 expression in extrahepatic cholangiocarcinoma.\textsuperscript{46} The activation of Wnt/β-catenin signaling can increase the proliferation activity of MM cells, thereby promoting the growth, survival, and migration of MM cells.\textsuperscript{47} It is possible that there is a similar PCAT1/miR-122/WNT1/Wnt/β-catenin signaling axis in MM, which requires further studies.

2.6 | PVT1

Plasmacytoma variant translocation 1 (PVT1), consisting of nine exons and encoding an approximately 2.0-kb IncRNA, is located on chromosome 8q24 region, which is approximately 55 kb distal to the c-Myc gene. It has been found that c-Myc and PVT1 are co-implicated in many human tumors, including MM.\textsuperscript{48} Carramusa et al found that c-Myc promoted the transcription of PVT1, and PVT1 expression level and c-Myc mRNA levels were well correlated in the transformed cells.\textsuperscript{49} The co-amplification of Myc and PVT1 was observed to be involved in the rapid progression and poor clinical survival of breast cancer patients.\textsuperscript{50} Although RQ-PCR results revealed the high expression of PVT1 and c-Myc in most MM cell lines,\textsuperscript{51} the molecular mechanisms between c-Myc and PVT1 warrant further research in MM.

In addition, Nagoshi et al also found that the rearrangement of the PVT1 gene was frequently observed in MM harboring 8q24 rearrangements, which are associated with tumor progression.\textsuperscript{51} PVT1 has been reported to be involved in variants t(2;8), t(8;22), or t(8;14) in human Burkitt lymphoma,\textsuperscript{52,53} and its overexpression has been responsible for the suppression of apoptosis.\textsuperscript{54} Furthermore, several studies have reported the breakpoints within a region centromeric to PVT1, suggesting that PVT1 is one of the target genes of rearrangement that may play a role in driving MM.\textsuperscript{55,56}

2.7 | UCA1

Localized on chromosome 19, encoding a 2.3-kb IncRNA, urothelial carcinoma associated 1 (UCA1) consists of three exons and was first identified in human bladder carcinoma. Upregulated UCA1 can increase bladder cancer cell proliferation, migration, and invasion, and inhibit apoptosis by regulating CREB expression, which encodes a transcriptional factor that affects oncogenesis.\textsuperscript{57} In acute myeloid leukemia (AML), UCA1 promotes the proliferation of malignant cells by suppressing p27kip1.\textsuperscript{58} Sedlarikova et al found that UCA1 was downregulated in MM patients, when compared to healthy donors.\textsuperscript{58} Their results also revealed that higher levels of UCA1 were correlated to advanced ISS stage and 1q21 gain. Due to the fact that IL-6 contains a site for CREB binding, which results in the suppression of IL-6 autocrine secretion, the investigators assumed that higher UCA1 levels induce CREB suppression, and consequently, higher IL-6 secretion, which leads to the survival of MM cells, bone resorption, and M-Ig secretion. However, the underlying mechanisms remain to be explored.

2.8 | TUG1

Taurine-upregulated gene 1 (TUG1) is located on chromosome 22q and is a newly characterized oncogene that can be transcriptionally
regulated by p53 in response to DNA damage. It consists of four exons and encodes a 7.5-kb lncRNA. It is involved in cell proliferation, migration, invasion, metastasis, and apoptosis in many tumors. The overexpression of TUG1 is always responsible for the high risk of poor prognosis and pathological outcome. In contrast, the downregulation of TUG1 suppresses cell proliferation, invasion, and induced apoptosis by blocking the Wnt/β-catenin pathway.

Isin et al measured the levels of TUG1 by RT-PCR in MM patients. The results revealed that the level of TUG1 was significantly higher in MM patients than in healthy volunteers, indicating that TUG1 may play a role in disease progression in MM. Furthermore, it has been observed that higher TUG1 expression levels are associated with the disease state in bladder carcinoma samples. Functional studies have revealed that TUG1 is induced in a p53-dependent manner, binds to polycomb repressive complex 2 (PRC2), and plays a role in repressing important cell cycle-related genes. In addition, a number of studies have reported that deregulated PRC2-related lncRNA expression is associated with tumorigenesis and progression. Yang et al implied that TUG1 caused growth control genes to relocate from the repressive environment of polycomb bodies by interacting with methylated polycomb 2 protein. In contrast, the knockdown of TUG1 caused the dramatic redistribution of growth control gene promoters out of polycomb bodies, thereby resulting in the signal-independent activation of growth, which is correlated with increased gene expression and cell proliferation.

2.9 | OIP5-AS1

Located on chromosome 15q, OIP5-AS1 consists of nine exons and encodes an 8.8-kb lncRNA. It plays an important role in the early development of the central nervous system, where it is highly repressed. Kim et al demonstrated that high levels of OIP5-AS1 could increase HuR-OIP5-AS1 complexes and prevent HuR interaction with target mRNAs. Furthermore, HuR is highly rich in tumor tissues, and HuR target mRNAs can encode proteins that are associated with tumorigenesis, including cell proliferation and angiogenesis. Moreover, OIP5-AS1 can suppress cell proliferation by reducing GAK levels.

In MM, downregulated OIP5-AS1 can increase the level of miR-410. It is well known that miR-410, which acts as an oncogene or tumor suppressor, is dysregulated in cancers. Researchers have found that upregulated miR-410 in MM increases cell proliferation and promotes cell cycle transition from G1 to S phase, and apoptosis resistance by increasing the levels of cyclin-dependent protein, cyclin D1, and apoptosis inhibition protein Bcl-2. These data reveal that the levels of OIP5-AS1 are inversely correlated with the expression of miR-410 in MM, and OIP5-AS1 knockdown increases the expression of miR-410 in NCI-H929 cells. By negatively regulating miR-410, OIP5-AS1 promotes the KLF10-mediated PTEN/AKT signaling pathway in MM cells, which exerts key functions in cell proliferation, cell cycle progression, and apoptosis inhibition.

2.10 | CRNDE

With seven exons, colorectal neoplasia differentially expressed (CRNDE), which is localized on chromosome 16q12 and encodes a 1.1-kb lncRNA, was first identified as a mediator of oncogenesis by promoting growth and suppressing apoptosis in colorectal adenomas and carcinomas. Recent reports have demonstrated that CRNDE is able to regulate certain serum components with cell cycle, growth, and differentiation by binding specific transcription factors (TFs), such as FosJ, JunD, and SRF. In addition, CRNDE may also play a role in the Myc regulatory pathway by binding with Max, which is one of the Myc partner proteins.

The altered expression of CRNDE is observed in many types of cancers, including hepatocellular carcinoma and acute myeloid leukemia (AML). Le Dieu et al reported that there was a dramatic increase in CRNDE in both CD4(+) and CD8(+) cells in AML patients, which indicates that loss of CRNDE expression may be associated with the transition to a single-positive stage. Keller et al also found that CRNDE involves cellular differentiation. For example, CD34(+) hematopoietic progenitor cells experience a significant increase in CRNDE levels when induced to differentiate using erythropoietin, interleukin-3, and stem cell factor.

In MM, Meng et al found that CRNDE was upregulated in the serum of MM patients. Compared with patients with a low expression of CRNDE, patients with a high expression always have poorer prognosis and lower overall survival. Further research demonstrated that CRNDE knockdown resulted in inhibited proliferation and increased apoptosis in MM cells. Moreover, loss of CRNDE induced cell cycle arrest in the G0/G1 phase. By using bioinformatics analysis and Pearson's correlation, the investigators revealed that CRNDE was negatively correlated to the expression of miR-451 in human MM samples, which was proven by the fact that the miR-451 inhibitor could rescue the inhibition of CRNDE knockdown on the tumorigenesis of MM. It has been reported that miR-451 can target the tuberous sclerosis 1 (TSC1) gene and activate the PI3K/Akt/mTOR signaling pathway in MM SP cells.

2.11 | STAiRs

STAT3-induced long non-coding RNAs (STAiRs) are induced by IL-6-activated STAT3 in INA-6 MM cells, which include STAiR1, STAiR2, STAiR6, STAiR15, and STAiR18. With length of its transcript ranging from 20 to 420 kb, they are located on different chromosomes. IL-6 can regulate the survival of MM cells by activating the STAT3 pathway.

The investigators revealed that STAiR1 and 2 were restricted to MM cells and were not detected in any of the other cell lines tested. Furthermore, STAiR6 expression was similarly restricted, with the exception of SU-DHL-4 follicular B-cell lymphoma and A172 glioblastoma cells. These evidences suggest that these three lncRNAs may have potential value as markers for MM. Due to the fact that STAiR2 is expressed from the first intron of the protein-coding deleted in colorectal cancer (DCC) gene, it was found that STAiR2
regulated its tumor suppressor host gene DCC by alternative splicing. In addition, the IL-6-induced alternative splicing of the DCC locus probably resulted in the impaired protein function and may contribute to myeloma cell survival.

STAiR18 (also known as MIR4435-2HG) is found in both the nucleus and cytoplasm. Overexpressed STAiR18 is observed in many tumors, which indicates a potential role in tumor occurrence or maintenance. At the same time, it is noted that in the nucleus, STAiR18 is found to be associated with H3K27me3, which is known as a marker for silenced chromatin. Therefore, STAiR18 probably plays a role in silencing transcription, heterochromatin regulation, and other epigenetic processes, which is similar to HOTAIR.\textsuperscript{84,85} However, the molecular mechanisms remain unclear.

STAiR15 has already annotated ncRNA gene MIAT, which is known to be differentially expressed in cardiovascular diseases and mental disorders.\textsuperscript{86} STAiR15 is upregulated in breast and kidney cancer samples. In MM cells, it is enriched in the nucleus.\textsuperscript{87} However, its function needs to be verified through further studies.

3 | SUMMARY

Emerging studies have defined IncRNAs as an important aspect of research, and an increasing number of evidences suggest that IncRNAs play central roles in MM. However, what we have performed is far from enough. There are still many unknowns worth exploring. As noted above, those MM patients with higher risk stratification always presented with hypermethylated MEG3 promoter differentially methylated regions. Can we use demethylilation therapy for these patients? This deserves our further study. Besides, some IncRNAs are upregulated in MM, such as MALAT1, while others are downregulated, such as OIP5-AS1. Can we build a or some relationships between them or among them? What’s more, Durie-Salmon (DS) staging system and Revised International Staging System (R-ISS) are mainly used for risk stratification of MM now. If we introduce IncRNAs into the risk stratification system of MM, will it improve the accuracy of risk stratification system? There are still many pending issues to be addressed; next-generation sequencing may be our future steps and give us a hand.

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CONFLICT OF INTEREST

The authors declare that they have no competing interest.

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