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Review

Aberrant lncRNA Expression in Multiple Myeloma

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Multiple myeloma (MM), a type of malignant tumor, is characterized by dysplasia of clonal plasma cells in the bone marrow. People with MM will have damaged organs or tissues due to secretion of large amounts of monoclonal immunoglobulin or fragments (M protein). Despite improved survivability by novel treatment strategies over the last decade, MM is still incurable by current therapies. Long noncoding RNAs (lncRNAs), with length of more than 200 nucleotides, have been reported to act as important regulators in many diseases, including MM. Recent studies have reported aberrant lncRNA expression in MM; these dysregulated lncRNAs can play oncogenic and/or tumor-suppressive roles in the development and progression of MM. In this article, we present a general overview on the role of lncRNAs in MM pathogenesis and discuss their potential as prognostic biomarkers and targets for treatment.

Key words: Long noncoding RNAs (lncRNAs); Multiple myeloma (MM); Expression

INTRODUCTION

Multiple myeloma (MM), as a malignant plasmocyte disease, features proliferation of monoclonal malignant plasma cells and generation of monoclonal immunoglobulin. MM commonly occurs in elderly people. The early clinical symptoms of MM include musculoskeletal pain, anemia, and susceptibility to infection, while late stage MM is characterized by fracture, pancytopenia, renal insufficiency, and occurrence of some neurological signs[1]. In Western countries, MM is the second most common malignant tumor in the blood system, with onset age over 65[2]. Although the MM onset age in China is lower than that in Western countries, with the aging of the population, MM morbidity in China is increasing annually.

In general, MM is a multistage disease wherein the pathogenetic process can be divided into the following stages: 1) monoclonal gammopathy of undetermined significance (MGUS), 2) smoldering MM (SMM), 3) MM, and 4) MM with extramedullary infiltration[3]. The morbidity of MM has been increasing. The clinical prognosis is highly heterogeneous; however, the mechanism within remains unclear. More and more evidence has shown that the molecular cytogenetic heterogeneity and molecular biologic heterogeneity of MM determine its clinical prognosis heterogeneity. The genetic change of MM is mainly complex chromosomes containing both quantity abnormality and structural change. The chromosome number abnormality mainly involves trisomy 3, 5, 7, 9, 11, 15, 19, and 21 as well as monosomic 8, 13, 16, 17, 22, and Y chromosome. Structural abnormality mainly contains 14q32 translocation; 13q14, 1p21, 6q, 11q, and 7p deletion; and 1q21 amplification[4–9]. Chromosome abnormality can lead to activation of oncogenes, inactivation of anti-oncogenes, and disorder of transcription factors. At present, oncogenes such as N-RAS and FGFR3, tumor suppressor genes such as TP53 and RB1, and apoptosis-related gene BCL2 have been found to take part in the development of MM[10–14]. In addition to cytogenetic abnormalities, epigenetic alterations, especially abnormal expressions of some noncoding RNAs (ncRNAs), have been verified to be involved in the development of MM. A number of international research groups have analyzed the abnormal expression of ncRNAs in MM development using gene expression profiling to further elucidate the molecular pathogenesis of MM.

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lncRNAs

The human genome mainly consists of DNA sequences. Of all the DNA sequences, only 2% have the function of protein coding whereas the other 98% cannot code protein but are transcribed into the RNA. Long noncoding RNAs (lncRNAs) are a type of RNA with a length longer than 200 nucleotides. lncRNAs locate in the nucleus or cytoplasm and do not have the function of protein coding due to a lack of an open reading frame[15,16]. Previously, lncRNAs were only considered as a structure without significant biological function. With further study of tumor disease pathogenesis in recent years, lncRNAs have gradually become a hot research topic. lncRNAs play a vital role in gene transcription and assist protein-coding genes in the regulation of gene expression. Regulation of gene expression by lncRNAs may involve epigenetic regulation, transcriptional regulation, and posttranscriptional regulation (Fig. 1).

EPIGENETIC REGULATION BY lncRNAs

Epigenetics is the study of stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence, including DNA methylation, histone modification, and chromatin remodeling. Growing evidence has shown that lncRNAs play a crucial role in epigenetic regulation[17].

lncRNAs and DNA Methylation

In mammalian cells, DNA methylation is a crucial component of epigenetic modification. Methylation of DNA is typically restricted to the 5-position of the pyrimidine ring of cytosine residues that are located in CpG dinucleotides[18]. lncRNAs can recruit some specific modified complexes to the corresponding sites, so that the methylation status of DNA can be changed, thereby regulating the expression of genes. It is found that gene silencing of the X chromosome has been interpreted to indicate that Xist RNA recruits polycomb repressive complex 2 (PRC2) to repress the promoter[19]. lncRNAs also can interact with DNA methyltransferases to change the methylation status of DNA and regulate gene expression. A lncRNA named ecCEBP (extra-coding CEBPA) expressed from the CEBPA locus was shown to physically associate with DNMT1 to regulate DNA methylation patterns[20]. Moreover, other DNA methyltransferase enzymes, like DNMT3a and DNMT3b, may also display an association with lncRNAs to modulate enzymatic activity and regulate the patterns of DNA methylation[20,21].

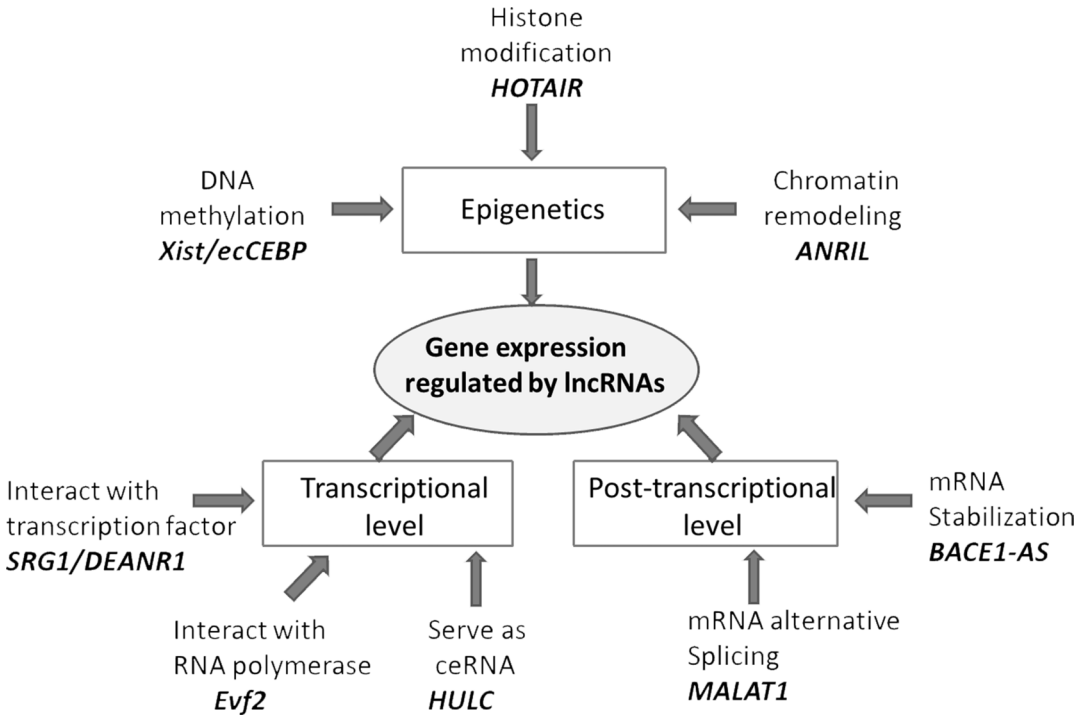

Figure 1. The mechanisms of gene expression regulated by long noncoding RNAs (lncRNAs). lncRNAs regulate gene expression through epigenetic mechanisms including DNA methylation, histone modification, and chromatin remodeling. lncRNAs can also regulate gene expression at the transcriptional level by interacting with promoters, transcription factors, and RNA polymerase. At the posttranscriptional level, lncRNAs regulate gene expression through interacting with miRNAs, controlling of alternative pre-mRNA splicing, and increasing mRNA stability, among others.

lncRNAs and Histone Modification

The structural unit of chromatin is the nucleosome, which consists of 146 bp of DNA around a histone octamer. The N-terminal domains of the core histones stretch out the DNA superhelix and come under several epigenetic modifications, such as methylation, acetylation, phosphorylation, and ubiquitination[22]. These modifications constitute a rich histone code and play an important role in gene regulation. HOTAIR is a lncRNA transcribed from the HOXC gene cluster. Its 5′ domain binds PRC2 (a histone H3 lysine 27 methylase) to silence the HOXD gene, whereas the 3′ domain of HOTAIR targets the LSD1/CoREST/REST complex, which acts as a demethylase that mediates enzymatic demethylation of H3K4me2, to silence the HOXD gene cluster[23,24]. These results indicate that lncRNAs can regulate gene expression of either adjacent or distal genes.

lncRNA and Chromatin Remodeling

Chromatin remodeling is able to regulate gene expression by altering the structure of nucleosomes and the accessibility of regulatory DNA sequences to transcription factors[25]. lncRNA ANRIL (CDKN2B antisense RNA 1) is transcribed from the INK4B–ARF–INK4A gene cluster in the opposite direction[26], which has been indicated to be related to coronary disease, intracranial aneurysm, type 2 diabetes, and also cancers[27]. It has been shown that ANRIL is required for repressing the p15/CDKN2B–p16/CDKN2Ap14/ ARF gene cluster in Cis by recruiting PRC2[26,28].

TRANSCRIPTIONAL REGULATION BY lncRNAs

lncRNAs can regulate gene transcription and expression by acting as transcription factors to interact with target genes at the transcriptional level. lncRNA SRG1 is transcribed from the *Saccharomyces cerevisiae* SER3 gene. Current data have indicated that the transcription 3′ of SRG1 can be complementary to the corresponding sequence of SER3 to form an RNA–DNA complex structure, and SER3 transcription is significantly derepressed due to SRG1 overexpression[29]. Another endoderm-associated lncRNA, DEANR1, played an important role in human endoderm differentiation by facilitating SMAD2/3 recruitment to the FOXA2 promoter[30]. lncRNAs also can regulate the activity of transcription factors and RNA polymerase. The lncRNA Evf2 is transcribed from a conserved distal enhancer region of the Dlx-5/6 gene. It cooperates with transcription factor Dlx2 and specifically binds to the Dlx-5/6 enhancer to increase its transcriptional activity[31,32]. In addition, recent data indicated that lncRNA can act as a competing endogenous RNAs (ceRNAs) that compete for miRNAs and regulate gene expression[33]. lncRNA HULC, as a "sponge," downregulates a series of miRNAs, including miR-372, and thus promotes liver cancer development[34].

POSTTRANSCRIPTIONAL REGULATION BY lncRNAs

lncRNAs work not only on the regulation of transcription but also on alternative splicing of pre-mRNA. Tripathi et al. first reported that metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) interacts with the serine/arginine (SR) splicing factor to regulate gene expression at the posttranscriptional level[35]. Bernard et al.[36] have also observed aberrant alternative splicing of a subset of pre-mRNAs in MALAT1-depleted HeLa cells. These results further confirm the regulatory function of lncRNAs at the posttranscriptional level. lncRNAs also have additional function in mRNA stability. Formation of RNA duplexes between lncRNAs and mRNAs can mask regulatory elements or provide binding sites for trans-acting factors[37]. Some antisense lncRNAs, such as the BACE1-antisense transcript (BACE1-AS), are able to regulate gene expression by increasing mRNA stability. In Alzheimer's disease, the upregulated expression of BACE1-AS increases the stability of BACE1 mRNA and then alters amyloid-β 1–42 production through a post-transcriptional feed-forward mechanism[38].

lncRNA EXPRESSION IN MM

lncRNAs are associated with the occurrence, development, and prognosis of various tumors, such as breast cancer[39], hepatocellular carcinoma (HCC)[40], colon cancer[41], and lung cancer[42]. Currently, it has been found that several hematopoiesis-related lncRNAs take part in proliferation, differentiation, and apoptosis of red blood cells, lymphocytes, and myeloid cells[43,44]. The abnormal expression of lncRNAs may lead to various malignant hematologic diseases, including lymphoma, leukemia, and MM[44–46]. Studies on MM have shown that many different abnormal expressions of lncRNAs occur at different stages of progress of MM. Being closely correlated with the MM evolution process, these lncRNAs may not only become the molecular evidence accounting for the occurrence, development, and drug resistance of MM, but also may serve as biomarkers for diagnosis and prognosis.

MALAT1

MALAT1 is a lncRNA located on chromosome 11q13. It was previously found related with lung cancer metastasis and prognosis, but later proved to be associated with MM[47]. Cho et al. performed qPCR detection of MALAT1 levels in 45 samples with newly diagnosed patients, 61 after myeloma treatment, and 18 samples with relapsed or advanced MM. Data showed that MALAT1 expression was higher in the newly diagnosed patients compared with the posttreatment patients or the healthy group.

The expression of MALAT1 strongly correlated with disease status, and the magnitude of change in MALAT1 posttreatment had prognostic relevance. The patients with early progression had a significantly smaller change in MALAT1 after treatment, and the patients with a greater decrease in MALAT1 had a significantly longer progression-free survival compared with the patients with a smaller MALAT1 change[46]. In MM mesenchymal stem cells (MSCs), Li et al. found that MALAT1 enhanced the expression of the LTBP3 gene by modulating recruitment of the transcription factor Sp1 to the LTBP3 gene promoter[48]. Some studies report that the LTBP3 gene can regulate the bioavailability of TGF-β within the bone, whereas abundant TGF-β in the bone marrow environment surrounding myeloma cells plays an important role in bone differentiation and cell growth[49]. Therefore, MALAT1 may take part in the outcome of MM, serving as a molecular predictor for the early examination of MM progression and probably likely to become a new therapeutic target for MM.

MEG3

Maternally expressed 3 (MEG3), a kind of lncRNA, is adjacent to the BMP4 gene, located on chromosome 14q9. Recent studies have identified MEG3 as a tumor suppressor gene in various malignant tumors[50]. Damaged osteogenic differentiation of mesenchymal stromal cells is characteristic of MM. Zhuang et al. found lower expression levels of MEG3 in MM MSCs relative to those from normal donors during osteogenic differentiation. After knocking out the MEG3 gene, the key osteogenic markers, such as transcription factor 2 (RUNX2), osterix (Osx), and osteocalcin (OCN), showed significantly decreased expression. Additionally, MEG3 could specifically activate the transcription factor SOX2 from the BMP4 promoter to repress BMP4 transcription[51]. It is conceivable that MEG3 played a prominent role in osteogenic differentiation in bone marrow MSCs. Abnormal expression of MEG3 has also been reported to be associated with epigenetic regulation. Benetatos et al.[52] found that the loss of MEG3 expression in MM was associated with MEG3 promoter methylation. Further results indicated that 64.7% of the IgG MM patients and 100% of the IgM MM patients presented MEG3 hypermethylation. Moreover, compared with the earlier stage patients, the advanced stage patients exhibited hypermethylation of the MEG3 gene. These findings suggested that the methylation pattern of the MEG3 gene was correlated with MM subtypes and stages of this disease. Other pathways have been described in order to elucidate the mechanism of MEG3. MEG3 might inhibit tumor growth by regulating p53[53] and vascular endothelial growth factor (VEGF)[54], and the loss of MEG3 expression in tumor cells could be used as a novel prognostic marker.

CRNDE

Colorectal neoplasia differentially expressed (CRNDE) gene, localized in the human chromosome 16q12.2 region, was initially identified as a lncRNA whose expression was markedly upregulated in colorectal cancer, but expression was also elevated in other solid tumors and leukemias[55–58]. Researchers revealed that CRNDE expression was increased in a chronic lymphocytic leukemia (CLL) sample cohort, and survival analysis indicated that hypermethylation of CRNDE correlated with poor prognosis[59]. Meng et al. recently found that the expression of CRNDE was significantly upregulated in serum from MM patients and MM cell lines and was closely associated with tumor progression and inferior outcome[60]. The CRNDE gene has various alternative splicings. In different diseases, the form of CRNDE transcript may be different as well[61]. Ellis et al.[58] found that the expression of the CRNDE transcript can be regulated by two signaling pathways (PI3K/Akt/mTOR and Raf/MAPK). After inhibiting the nuclear transcript GVC-IN4, the expression of many insulin/IGF-related genes can be affected. In ovarian cancer[56], the elevated expression of CRNDE longer variant (FJ466685) highly improved the recurrence and mortality of the disease. Moreover, activation of the TP53 protein correlated with decreased expression of CRNDE transcripts. However, the target genes and signaling pathways regulated by CRNDE in these tumors still need to be further investigated.

GAS5

Growth arrest-specific transcript 5 (GAS5) is a type of lncRNA located in a small open reading frame of chromosome 1q25.1[62]. It has been discovered in growth-arrested mouse NIH3T3 fibroblasts, attributed to its high expression[63]. GAS5 is a member of the 5′-terminal oligopyrimidine (5′-TOP) gene family, which comprises 12 exons and encodes 10 boxC/D small nucleolar RNAs (snoRNAs)[64]. Although GAS5 does not have protein-coding function, its RNA can still be spliced, polyadenylated, and interacted with ribosome[65]. Hence, the GAS5 transcript is upregulated during growth arrest owing to serum starvation or treatment with translation inhibitors. Kino et al. found that GAS5 bound to the DNA-binding domain of the glucocorticoid receptor (GR) by serving as a decoy glucocorticoid response element (GRE), thus competing with DNA GREs for binding to the GR[66]. Currently, it has been shown that the expression of GAS5 is downregulated in many tumors[67–69]. Isin et al.[62] revealed that the expression of GAS5 was significantly decreased in the serum of MM patients. Inhibiting the expression of GAS5

can inhibit MM cell apoptosis and accelerate cell cycle progress. The result is in concordance with a recent study indicating that GAS5 protects leukemic cells from the antiproliferative effects of chemotherapeutic agents[70].

PCAT-1

Prostate cancer-associated transcript 1 (PCAT-1), located on chromosome 8q24.21 region, was originally observed to be involved in the progression of prostate cancer[71]. Research suggested that PCAT-1 was upregulated in prostate tumor tissues and promoted prostate cancer cell proliferation by repressing the expression of BRCA2[72]. The upregulated expression of PCAT-1 has also been found in other solid tumors. Yan et al. showed that PCAT-1 expression was upregulated in HCC tissues, and the increased expression was significantly associated with TNM stage and metastasis[73]. Bi et al. showed that PCAT-1 upregulation was associated with poor overall survival in gastric cancer patients. PCAT-1 knockdown contributed to the inhibition of cell proliferation, migration, and invasion by regulating CDKN1A, suggesting that PCAT-1 could be a novel biomarker of poor prognosis for gastric cancer[74]. In hematological malignancies, Shen et al.[75] revealed that the relative expression of serum PCAT-1 in MM patients was higher than that in healthy controls and was significantly correlated with β2M concentration, but not with LDH, κ light, and λ light chain concentration. Additionally, serum PCAT-1 expression in MM patients was significantly correlated with different isotypes of MM. Therefore, PCAT-1 may be an efficient and sensitive serum index for MM, which can be adopted as a key molecular marker for evaluating clinical features and prognosis of MM.

UCA1

One lncRNA that has received significant attention is urothelial carcinoma-associated 1 (UCA1), which is located on chromosome 19p13.12 and contains three exons encoding two transcripts. It is reported that UCA1 is highly expressed in bladder cancer[76], colorectal cancer[77], breast cancer[78], and other tumors, suggesting that UCA1 may serve as a biomarker for the diagnosis of these cancers. Moreover, upregulated UCA1 contributed to promote bladder cell proliferation and metastasis through the PI3K, Wnt, or Akt signaling pathway[79–81]. In addition, miR-1 inhibited cell growth and induced cell apoptosis through downregulating UCA1 expression in bladder cancer[82]. These results indicate that there is a mutual accommodation between UCA1 and miRNAs in tumor cells. Instead, Sedlarikova et al.[83] found that UCA1 expression was downregulated in MM by microarray screening, and UCA1 expression levels correlated with albumin and monoclonal immunoglobulin serum levels, cytogenetic aberrations, and prognosis of MM patients. The results indicated that lncRNAs may play different roles in different tumors, and UCA1 was arising as a highly specific biomarker with potential clinical application for MM.

FURTHER IMPLICATIONS

To date, over 15,000 lncRNAs have been characterized in the human genome[84,85], and they can be found in exons, introns[86], and intergenic regions of genes[87]. lncRNAs are involved in a number of biologic and pathologic processes including cell proliferation, apoptosis, differentiation, and metabolism. Given the diversity of the function of lncRNAs and the specificity of their cell distribution, the functional properties of such ncRNA molecules are being challenged. Numerous studies have shown that lncRNAs may play an important regulatory role like miRNAs and may serve as potential molecular markers for clinical applications. Here we reviewed the recent research progress of lncRNAs involved in MM and discussed its potential relevance on the diagnosis, prognosis, and treatment of MM.

Compared with normal hematopoiesis and other tumors, the role of lncRNAs in hematologic malignancies has not been extensively described. Recent data have provided evidence that a small number of lncRNAs have been found participating in MM initiation and development. MEG3 expression was downregulated in MM MSCs, and expression of osteogenic markers, such as RUNX2, Osx and OCN, were significantly decreased by its absence[51]. Epigenetic regulation can also regulate the expression of lncRNAs. The lower expression level of MEG3 in MM was associated with MEG3 promoter methylation[52]. Interestingly, p53 binding sites are required for MEG3 to stimulate transcription, and MEG3 functions as a transcriptional coactivator to stimulate expression of proteins that modify p53 and/or mouse double minute 2 homolog (MDM2)[53]. Another finding is that lncRNAs can function as ceRNAs by competitively combining with an miRNA response element (MRE) to regulate target gene expression. GAS5 overexpression suppressed cervical cancer cell proliferation, whereas it induced cell apoptosis through sponging miR-196a and miR-205[88]. MALAT1 accelerated TGF-β1-induced EMT progression via the MALAT1–miR-145–TGFBR2/SMAD3 signaling pathway[89]. Therefore, the association between lncRNAs and epigenetic modifications, tumor suppressor p53, and miRNAs may provide important clues to the mechanism of MM. A key objective in the future is to look for MM-specific lncRNAs and explore the complex biological function. It would not only help us understand the molecular mechanism of MM development but could

also provide a new basis for early diagnosis and treatment of MM.

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