

Role and mechanistic study of long non-coding RNA maternally expressed gene 3 in gastric cancer (Review)

BUYUN JIA¹⁻³, HUI CHENG², PEIZHENG YANG¹, XIANGYU WANG¹, SHANSHAN LI²⁻⁴ and JINGHUI WANG¹

¹School of Integrated Chinese and Western Medicine, Anhui University of Chinese Medicine, Hefei, Anhui 230012, P.R. China;

²Key Laboratory of Xi'an Medicine, Ministry of Education, Anhui University of Chinese Medicine, Hefei, Anhui 230012, P.R. China;

³Anhui Province Key Laboratory of Chinese Medicinal Formula, Hefei, Anhui 230012, P.R. China;

⁴School of Traditional Chinese Medicine, Anhui University of Chinese Medicine, Hefei, Anhui 230012, P.R. China

Received May 27, 2025; Accepted September 25, 2025

DOI: 10.3892/ol.2025.15329

Abstract. Long non-coding (lnc)RNAs are notable participants in gene regulation, and maternally expressed gene 3 (MEG3) has been implicated in the development and progression of several types of cancer, underscoring its potential as a key player in oncogenesis. The present review aimed to explore the functional role of MEG3 in gastric cancer (GC) and elucidate the underlying molecular mechanisms, as well as to summarize the expression changes of MEG3 in GC, its influence on tumor cell biological behaviors and the potential signaling pathways involved. Ultimately, the present synthesis of current knowledge seeks to provide novel insights for the diagnosis and treatment of GC, highlighting MEG3 as a promising target for future therapeutic strategies.

Contents

1. Introduction
2. MEG3 structure and function
3. MEG3 expression changes in GC
4. Impact of MEG3 on the biological behavior of GC cells

5. MEG3 signaling pathways and mechanisms
6. MEG3 as a potential biomarker for GC
7. Conclusions and limitations

1. Introduction

Gastric cancer (GC) ranks among the most prevalent malignancies worldwide, with a notable clinical burden. According to GLOBOCAN 2022, GC accounts for ~1 million new cases annually, and remains the fourth leading cause of cancer-related mortality, characterized by a poor 5-year survival rate of <30% in advanced stages (1). For patients with GC with an adequate performance status and organ function, those who receive combination chemotherapy have a median overall survival (OS) of ~1 year, compared with 3-4 months for those treated solely with supportive care (2). In recent years, immunotherapy has markedly expanded treatment options for solid tumors, and chemo-immunotherapy holds particular promise for advanced GC; however, GC prognosis remains poor. Over half of patients are diagnosed with advanced/metastatic stage disease, with a median OS of ~1 year (3).

The pathogenesis of GC involves multifactorial etiologies, including a genetic predisposition, *Helicobacter pylori* (*H. pylori*) infection, inflammatory stimulation and environmental factors (4-7). Early diagnosis of GC is challenging due to nonspecific symptoms, leading to delayed therapeutic interventions and poor prognosis (8). In addition, chemoresistance notably undermines treatment efficacy, as standard regimens often fail to achieve durable responses (9,10). This resistance is attributed to dynamic molecular adaptations in tumor cells, such as drug efflux mechanisms and apoptosis evasion (11). Furthermore, GC progression is driven by an intricate regulatory network involving aberrant signaling pathways, epigenetic modifications and tumor microenvironment (TME) interactions (12-15). Despite advances in understanding GC biology, key gaps persist (16). The molecular mechanisms underlying tumorigenesis, metastasis and chemoresistance remain incompletely elucidated, particularly regarding context-dependent roles of non-coding RNAs (17). Addressing these knowledge gaps is critical for developing targeted therapies and improving clinical outcomes.

Correspondence to: Professor Jinghui Wang, School of Integrated Chinese and Western Medicine, Anhui University of Chinese Medicine, 350 Longzihu Road, Hefei, Anhui 230012, P.R. China
E-mail: jhwang_dlut@163.com

Dr Shanshan Li, School of Traditional Chinese Medicine, Anhui University of Chinese Medicine, 350 Longzihu Road, Hefei, Anhui 230012, P.R. China
E-mail: shanshanli@ahtcm.edu.cn

Abbreviations: GC, gastric cancer; lncRNA, long non-coding RNA; MEG3, maternally expressed gene 3; EMT, epithelial-to-mesenchymal transition; ceRNA, competing endogenous RNA; miRNA, microRNA

Key words: lncRNA, MEG3, GC, tumor biology, molecular mechanisms

Previous studies have increasingly focused on the role of long non-coding (lnc)RNA in the progression of several cancers, including GC. Among them, maternally expressed gene 3 (MEG3) has emerged as a critical player in tumor suppression. MEG3 is known for its ability to regulate several cellular processes such as proliferation, apoptosis and migration, which are essential for cancer progression (18-20). Therefore, understanding the role of MEG3 in GC could provide novel insights into its pathogenesis and open new avenues for early diagnosis and targeted therapies.

Studies have reported that MEG3 is frequently downregulated in GC tissues, compared with in normal gastric tissues, suggesting its potential role as a tumor suppressor (21-23). Moreover, *in vitro* studies have reported that reintroducing MEG3 into GC cell lines leads to increased apoptosis and decreased cell viability, migration and invasion (24,25). This is achieved through the modulation of epithelial-to-mesenchymal transition (EMT), a process critical for cancer metastasis (26). MEG3 has been reported to enhance the expression of epithelial markers such as E-cadherin, whilst suppressing mesenchymal markers such as vimentin and fibronectin, effectively inhibiting the EMT process (27). Furthermore, the interaction between MEG3 and numerous signaling pathways has been a focus of research. MEG3 has been reported to interact with microRNAs (miRNAs/miRs), particularly miR-21, which is known to promote tumorigenesis in several types of cancer. By acting as a competing endogenous (ce)RNA, MEG3 can sequester miR-21, thereby reducing its oncogenic effects (28). This regulatory axis highlights the intricate network of interactions among non-coding RNAs in cancer biology and reinforces the importance of lncRNAs such as MEG3 in modulating tumor behavior.

In addition to its role in cellular processes, MEG3 expression has been associated with the presence of *H. pylori*, a notable risk factor for GC. Studies have reported that *H. pylori* infection is associated with altered expression levels of MEG3 and other lncRNAs, suggesting that microbial factors may influence the lncRNA landscape in GC (29,30). Understanding how *H. pylori* and other environmental factors interact with lncRNAs such as MEG3 could provide valuable insights into the multifactorial nature of GC development. Furthermore, the therapeutic implications of targeting MEG3 in GC are profound. Given its role in inhibiting tumor growth and metastasis, strategies aimed at restoring MEG3 expression or mimicking its function could serve as potential therapeutic approaches. For instance, the use of small molecules or gene editing technologies to enhance MEG3 levels in GC cells may reverse the malignant phenotype and sensitize tumors to conventional therapies (31).

Therefore, the role of lncRNA MEG3 in GC is a burgeoning area of research that holds promise for both understanding the mechanisms of the disease and developing novel therapeutic strategies. The evidence supporting the tumor-suppressive functions of MEG3, its interactions with key signaling pathways and its potential as a biomarker underscore the importance of further investigations into this lncRNA. As research continues to unravel the complexities of GC biology, MEG3 may emerge as a pivotal target for innovative treatment modalities aimed at combating this formidable malignancy.

2. MEG3 structure and function

MEG3 gene structure. MEG3 is a lncRNA located within the imprinted δ -like non-canonical Notch ligand 1-MEG3 locus on chromosome 14q32.3 (32). This gene spans ~35 kb and consists of 10 exons, which are crucial for its functional integrity (33). The MEG3 gene is characterized by its imprinted expression, meaning it is expressed from the maternal allele, whilst the paternal allele is silenced (34). This unique genetic regulation is notable, as it contributes to the functional diversity of lncRNAs in several biological processes. The transcription of MEG3 results in a 1.6 kb lncRNA that does not code for proteins but serves essential roles in regulating gene expression through numerous mechanisms, including through its interaction with miRNAs and proteins (35,36). Notably, MEG3 has been reported to form secondary structures, including pseudoknots, which are vital for its interaction with the p53 pathway, further emphasizing the importance of its structural features in mediating biological functions (37).

Major biological functions of MEG3. MEG3 has emerged as a critical player in several biological processes, particularly in tumor suppression. Its primary functions include regulating cell proliferation, apoptosis and migration, particularly in the context of cancer (38). MEG3 exerts its tumor-suppressive effects by modulating key signaling pathways, such as the p53 pathway, where it enhances p53 activity, leading to increased apoptosis in cancer cells (39). In addition, MEG3 functions as a molecular sponge for multiple oncogenic miRNAs, including miR-21, which is known to promote oncogenesis (40). By sequestering miR-21, MEG3 indirectly upregulates tumor suppressor genes and inhibits pathways that contribute to cancer progression (41). Studies have reported that MEG3 downregulation is associated with poor prognosis in several types of cancer, including hepatocellular carcinoma, GC and colorectal cancer, indicating its potential as a diagnostic and therapeutic target (42-44). In addition, beyond its role in cancer, MEG3 has been implicated in other physiological processes, such as fibrosis and metabolic regulation. It has been reported to influence the expression of genes involved in EMT, a critical process in cancer metastasis, and to regulate insulin signaling pathways, highlighting its multifaceted role in both cancer biology and metabolic diseases (45,46).

Expression characteristics of MEG3 in cells. MEG3 exhibits distinct expression patterns across numerous tissues and cell types, reflecting its functional diversity. In healthy tissues, MEG3 is generally expressed at higher levels, particularly in the brain, liver and skeletal muscle (47). However, its expression is often markedly reduced in several cancer types, where it is associated with tumor progression and metastasis (48,49). This downregulation is frequently attributed to epigenetic modifications, such as the hypermethylation of the MEG3 promoter. Specifically, the downregulation of MEG3 is driven by abnormal CpG methylation in its promoter region. Among these CpG sites, linear changes in MEG3 expression show a negative correlation with the methylation levels of two specific CpG sites: MEG3_4_CpG_9 and MEG3_5_CpG_2 (50,51). The methylation process of MEG3 promoters is mainly mediated by DNA methyltransferases (DNMTs) including

three major DNMTs: DNMT1, DNMT3a and DNMT3b in mammals. In addition, MEG3 expression is influenced by several physiological conditions (52,53). For instance, studies have reported that MEG3 levels can be modulated in response to inflammatory stimuli and metabolic changes, indicating its potential role as a biomarker for disease states (54,55). In the context of obesity and insulin resistance, MEG3 expression has been reported to be negatively associated with the severity of these conditions, suggesting its involvement in metabolic regulation (56). Furthermore, the dynamic association between MEG3 and nuclear speckles, and its transient expression in response to transcriptional activity, highlight its regulatory role in gene expression within the cellular context, suggesting that MEG3 may serve as a sensor for cellular stress and a regulator of gene expression in response to environmental cues (57).

3. MEG3 expression changes in GC

Comparison of expression in normal and cancerous tissues. The expression levels of the lncRNA MEG3 have been reported to markedly differ between normal gastric and GC tissues (58). In normal gastric cells, MEG3 is typically expressed at higher levels, functioning as a tumor suppressor that regulates several cellular processes, including apoptosis and cell proliferation (59). However, studies have consistently reported that MEG3 expression is markedly decreased in GC cells, as compared with their normal counterparts (25,60). For instance, a study indicated that MEG3 transfection in GC cells led to an increased expression of E-cadherin, a key epithelial marker, whilst simultaneously inhibiting the expression of mesenchymal markers, such as vimentin and fibronectin. This suggests that MEG3 serves a crucial role in suppressing EMT (24). Furthermore, the differential expression of MEG3 has been reported to be associated with several clinical parameters in patients with GC. Lower levels of MEG3 have been associated with advanced disease stages and worse prognostic outcomes, indicating its potential as a biomarker for disease progression (60). The downregulation of MEG3 in cancerous tissues not only highlights its role in GC pathogenesis but also underscores its potential as a therapeutic target (61).

Association between MEG3 expression and clinical pathological features. The association between MEG3 expression and clinical pathological features in GC has been a focal point in recent studies (62,63). Numerous studies have reported that the expression levels of MEG3 are notably associated with several clinicopathological characteristics, including tumor size, lymph node metastasis and overall patient survival (61,64). For instance, lower MEG3 expression levels have been associated with larger tumor sizes and a higher incidence of lymph node metastasis, suggesting that MEG3 may serve a critical role in tumor aggressiveness (65). These findings indicate that MEG3 could serve as a valuable prognostic marker in GC, aiding in the stratification of patients based on their risk of disease progression. Furthermore, the expression of MEG3 has been associated with the OS rates of patients with GC. Studies have reported that patients with higher levels of MEG3 expression tend to have improved survival outcomes, as compared with those with lower expression levels (66). This association suggests that MEG3 may not only be involved in

the tumorigenic processes, but it also serves as a potential therapeutic target.

4. Impact of MEG3 on the biological behavior of GC cells

Cell proliferation. lncRNA MEG3 has emerged as a critical regulator of cell proliferation in several types of cancer, including GC (67). Studies have reported that MEG3 functions as a tumor suppressor, with its downregulation associated with increased cell proliferation and malignancy (68,69). This reduction in MEG3 has been associated with the activation of oncogenic pathways that promote cell cycle progression and proliferation (70). For instance, MEG3 has been reported to inhibit the expression of cyclin D1 and other cell cycle regulators, thereby slowing down the transition from the G1 phase to the S phase of the cell cycle (71). In addition, the overexpression of MEG3 in GC cell lines has been reported to markedly reduce cell growth and proliferation rates, suggesting that MEG3 acts to restrain the proliferative capacity of these cells (72). Furthermore, the interaction between MEG3 and several miRNAs has been implicated in its regulatory role, as MEG3 can act as a sponge for miRNAs that promote proliferation, thus further inhibiting cancer cell growth (73).

Cell apoptosis. The role of MEG3 in promoting apoptosis in GC cells has been extensively investigated, and it has been established that it is critically involved in the regulation of programmed cell death (58). MEG3 has been reported to enhance the sensitivity of GC cells to apoptotic stimuli, effectively increasing the rate of apoptosis in these cells (74). This is particularly important given that numerous types of GC exhibit resistance to apoptosis, contributing to tumor progression and treatment failure (75,76). Mechanistically, MEG3 facilitates apoptosis through several pathways. It has been reported to upregulate pro-apoptotic proteins such as Bax and downregulate anti-apoptotic proteins such as Bcl-2, thereby tipping the balance in favor of cell death (77,78). In addition, MEG3 can activate the caspase cascade, a series of proteolytic enzymes critical for the execution of apoptosis. For instance, the increased expression of MEG3 has been associated with the enhanced activation of caspase-3 and caspase-9, leading to the induction of apoptosis in GC cells (79,80). Beyond direct protein regulation, MEG3 further potentiates its pro-apoptotic effects by interacting with miRNAs. Studies have indicated that MEG3 can interact with miRNAs that regulate apoptosis, further enhancing its pro-apoptotic effects. For example, MEG3 has been reported to sequester miR-21, a known anti-apoptotic miRNA, thereby promoting apoptosis in GC cells (21). The ability of MEG3 to induce apoptosis not only highlights its potential as a tumor suppressor, but also suggests that therapeutic strategies aimed at increasing MEG3 expression or mimicking its function could enhance the efficacy of existing treatments for GC.

Cell migration and invasion. MEG3 also serves a central regulatory role in regulating the migration and invasion of GC cells, processes that are decisive for metastasis. The downregulation of MEG3 has been associated with increased migration and invasion rates of GC cells, which is a hallmark of aggressive tumor behavior (72). Moreover, studies have reported that MEG3 overexpression is associated with a marked reduction

in the migration and invasion rates of GC cells, indicating its function as a suppressor of these malignant behaviors (21,24). The mechanisms through which MEG3 exerts its effects on cell migration and invasion involve the modulation of EMT, a process that is critical for cancer cell dissemination (81). MEG3 has been reported to inhibit EMT by promoting the expression of epithelial markers, such as E-cadherin, whilst suppressing mesenchymal markers such as N-cadherin and vimentin (82). This shift in cellular phenotype is crucial for maintaining the adhesive properties of cancer cells and reducing their invasive potential (83). Furthermore, MEG3 has been reported to interact with several signaling pathways that regulate cell motility, including the Rho GTPase family, which is known to control cytoskeletal dynamics and cell movement (84). By affecting these pathways, MEG3 can alter the migratory behavior of GC cells, thereby reducing their ability to invade surrounding tissues and cause distant metastasis (72). Given the importance of migration and invasion in the progression of GC, targeting MEG3 or its regulatory networks may provide a novel therapeutic strategy to inhibit metastasis and improve patient prognosis.

5. MEG3 signaling pathways and mechanisms

Relationship between MEG3 and the p53 signaling pathway. The p53 signaling pathway is a crucial regulator of the cell cycle, apoptosis and genomic stability, often referred to as the 'guardian of the genome'. MEG3 has been reported to interact with this pathway in multiple cancer types and research has indicated that MEG3 can enhance the expression of p53, thereby promoting apoptosis in cancer cells (85). For instance, in neuroblastoma, MEG3 overexpression led to increased p53 levels, which in turn activated pro-apoptotic factors and inhibited cell proliferation (86). This interaction suggests that MEG3 may function as a tumor suppressor by stabilizing p53 and enhancing its tumor-suppressive activities (87). In addition to directly regulating p53 expression, MEG3 also indirectly influences p53 activity through interactions with miRNAs. MEG3 has been identified as a ceRNA that can sponge several miRNAs, including miR-21, which is known to inhibit p53 expression. By sequestering miR-21, MEG3 indirectly promotes p53 activity, leading to enhanced apoptosis and reduced tumor growth (88). This regulatory mechanism highlights the potential of MEG3 in modulating the p53 pathway and its implications for cancer therapy, particularly in tumors where p53 is often mutated or dysfunctional. In addition to its role in apoptosis, the interaction between MEG3 and p53 also extends to cellular senescence and DNA damage response. Studies have reported that MEG3 can influence the expression of genes involved in these processes, thereby contributing to the maintenance of genomic integrity (89,90). The ability of MEG3 to modulate p53 activity positions it as a critical player in cancer progression and treatment resistance, making it a promising target for therapeutic intervention (Fig. 1).

Role of MEG3 in miRNA regulation. MEG3 serves a pivotal role in the regulation of miRNAs, which are small non-coding RNAs that post-transcriptionally regulate gene expression. By acting as a ceRNA, MEG3 can bind to specific miRNAs, thereby preventing them from interacting with their target mRNAs. This

function has been particularly noted with miR-21, which is often overexpressed in several types of cancer and is associated with poor prognosis (91). The ability of MEG3 to sponge miR-21 results in the downregulation of its target genes, including those involved in apoptosis and cell cycle regulation (92). In GC, for example, MEG3 has been reported to inhibit the expression of miR-21, leading to the upregulation of pro-apoptotic proteins and the downregulation of anti-apoptotic factors, thus promoting apoptosis in cancer cells (21). This regulatory axis underscores the importance of MEG3 in maintaining cellular homeostasis and preventing tumorigenesis. Furthermore, the interaction of MEG3 with other miRNAs, such as miR-548d-3p and miR-376a, has been documented, indicating its broader role in modulating several signaling pathways associated with cancer progression (93,94). By regulating these miRNAs, MEG3 can influence key cellular processes, including proliferation, migration and invasion, thereby contributing to the overall TME and its dynamics. The therapeutic potential of targeting the MEG3-miRNA axis is notable, as restoring MEG3 levels in tumors with low expression could enhance the efficacy of existing therapies by re-establishing normal apoptotic signaling and inhibiting oncogenic pathways (95).

Impact of MEG3 on the TME. The TME exerts a pivotal influence on cancer progression and metastasis, influencing tumor behavior and response to therapy. Emerging evidence demonstrates that MEG3 markedly impacts the TME by modulating the behavior of several cell types within it, including immune cells, fibroblasts and endothelial cells. For instance, MEG3 can promote the polarization of macrophages towards the M1 phenotype, which is associated with antitumor immunity, whilst inhibiting the M2 phenotype that supports tumor growth and metastasis (96). In addition, MEG3 has been reported to inhibit M2 macrophage polarization, thereby reducing tumor growth and metastasis (97). This effect is mediated through its interaction with miR-145-5p, which regulates the expression of disabled-2, a protein involved in macrophage polarization. By modulating macrophage phenotypes, MEG3 can alter the inflammatory landscape of the TME, potentially leading to improved therapeutic outcomes. Furthermore, the role of MEG3 in regulating angiogenesis is notable. For example, MEG3 has been reported to inhibit angiogenesis by reducing the levels of miR-421, which promotes endothelial cell migration and tube formation (98). These findings imply that MEG3 not only influences immune cell behavior, but also impacts the vascular components of the TME, further underscoring its multifaceted role in cancer biology. The ability of MEG3 to shape the TME underscores its promising potential as a therapeutic target. By restoring or enhancing MEG3 expression, it may be possible to reprogram the TME to favor antitumor responses, and lead to an improved drug delivery and enhanced efficacy of existing therapies (21). This comprehensive understanding of the signaling pathways and mechanisms of MEG3 provides valuable insights into its potential as a therapeutic target in cancer treatment (Fig. 2).

6. MEG3 as a potential biomarker for GC

Diagnostic value of MEG3. The lncRNA MEG3 has been established as a promising biomarker in the diagnosis and

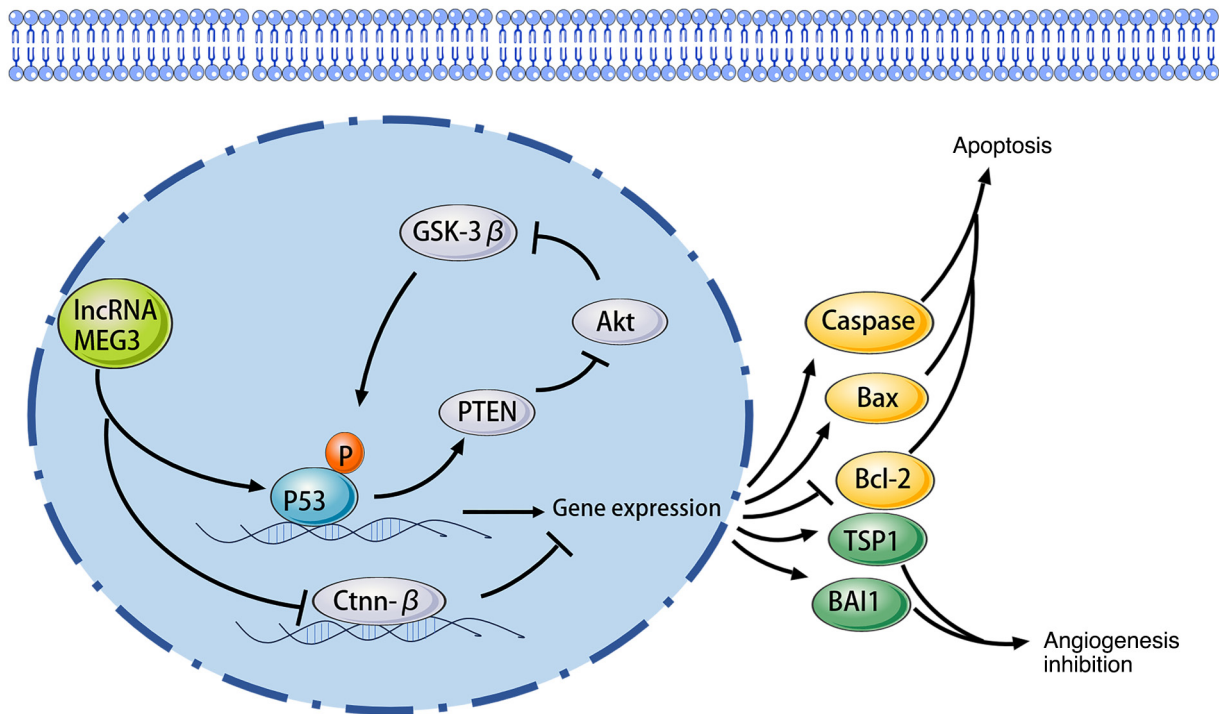


Figure 1. Relationship between MEG3 and the p53 signaling pathway. MEG3, maternally expressed gene 3; p53, protein 53; IncRNA, long non-coding RNA; GSK-3 β , glycogen synthase kinase-3; Akt, protein kinase B; PTEN, phosphatase and tensin homologue deleted on chromosome ten; Ctnn- β , catenin beta; Caspase, cysteinyl aspartate specific proteinase; Bcl-2, B-cell lymphoma-2; Bax, Bcl-2 associated X; TSP1, thrombin sensitive protein 1; BAI1, brain-specific angiogenesis inhibitor 1.

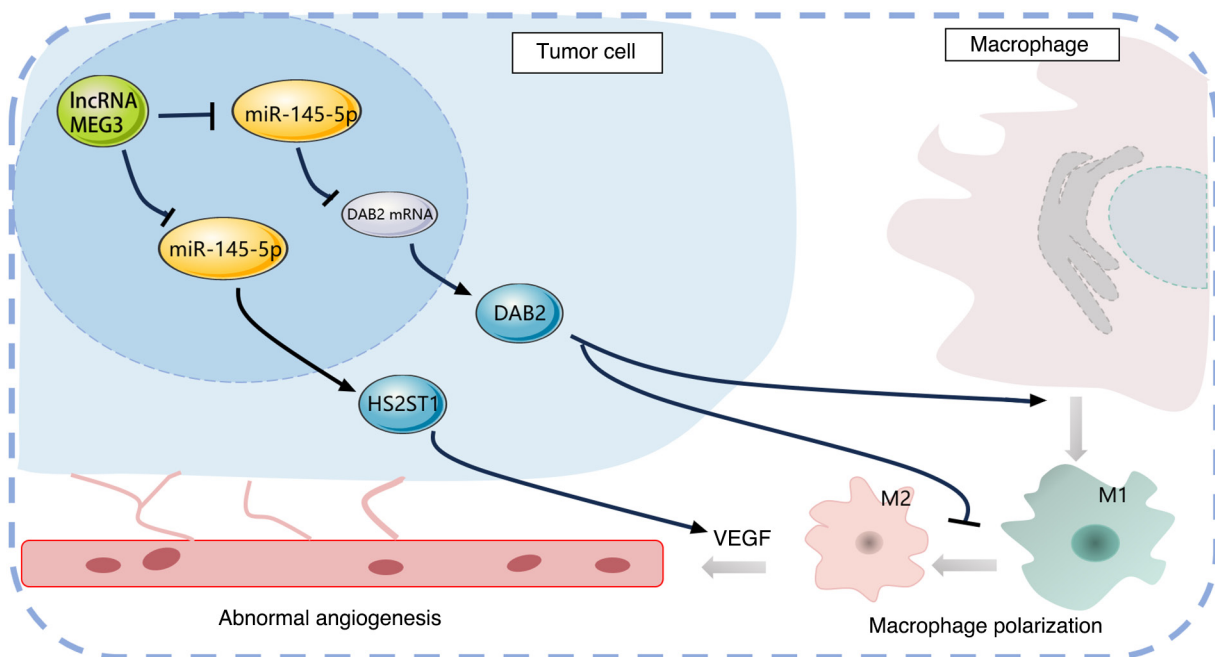


Figure 2. Impact of MEG3 on the tumor microenvironment. MEG3, maternally expressed gene 3; IncRNA, long non-coding RNA; miR, microRNA; DAB2, disabled homolog 2; HS2ST1, heparan sulfate-2-O-sulfotransferase 1; VEGF, vascular endothelial growth factor; M1, classically activated macrophage; M2, alternatively activated macrophage.

prognosis of GC. Numerous studies have reported that MEG3 is downregulated in GC tissues and cell lines compared with normal gastric tissues and cell lines, indicating its potential as a diagnostic biomarker (25,54,55). For instance, research has shown that the expression of the IncRNA MEG3 was

markedly lower in GC cells than in normal gastric cells, and its transfection led to an increased expression of E-cadherin, a marker associated with epithelial cells, whilst inhibiting the expression of mesenchymal markers, such as vimentin and fibronectin (24). This suggests that MEG3 serves a crucial

role in EMT, a process that is pivotal in cancer progression and metastasis. Furthermore, a previous study demonstrated the diagnostic utility of MEG3 using receiver operating characteristic curve analyses, which indicated that MEG3 levels could effectively discriminate between tumor and non-tumor tissues. The area under the curve of MEG3 was 0.8736, and using the cut-off value of 0.0014, the sensitivity and specificity of MEG3 were 79 and 86%, respectively, indicating the strong diagnostic performance of GC (32). In addition, another study reported that the A allele at the rs7158663 19 loci of MEG3 was a risk factor for GC (odds ratio, 1.41; 95% confidence interval, 1.14-1.74; $P=0.002$) (99). This association underscores the potential of MEG3 not only as a diagnostic marker but also as a prognostic indicator for patient outcomes. The role of MEG3 in GC is further supported by its involvement in several molecular pathways that regulate cell proliferation, apoptosis and migration. Studies have reported that MEG3 can inhibit tumor growth by modulating the expression of key oncogenic pathways, such as the PI3K/Akt and Wnt/ β -catenin signaling pathways (21). The downregulation of MEG3 has been associated with the increased expression of oncogenic microRNAs, such as miR-21, which promotes tumor growth and metastasis (28). Thus, the restoration of MEG3 expression in GC cells has been proposed as a therapeutic strategy that could reverse the malignant phenotype and improve patient prognosis (72). Furthermore, the potential of MEG3 as a biomarker extends beyond tissue expression levels. Its presence in the serum has been investigated, with studies suggesting that circulating MEG3 could serve as a non-invasive biomarker for GC diagnosis (100,101). The ability to detect MEG3 in serum samples adds a layer of practicality to its application in clinical settings, allowing for early detection and monitoring of disease progression. This is particularly important given the asymptomatic nature of early-stage GC, which can lead to late diagnosis and poor outcomes. The diagnostic value of MEG3 in GC is supported by its downregulation in tumor tissues, association with clinical parameters, involvement in critical signaling pathways, and potential as a circulating biomarker. These findings collectively highlight the potential of MEG3 as a valuable tool for the early detection and management of GC, warranting further exploration in clinical trials and translational research.

Feasibility of MEG3 as a therapeutic target. The feasibility of targeting MEG3 for therapeutic interventions in GC is increasingly supported by research that underscores its role as a tumor suppressor. MEG3 has been reported to exert notable antitumor effects through several mechanisms, making it an attractive candidate for targeted therapies. For instance, studies have indicated that MEG3 can inhibit cell proliferation, migration and invasion in GC cells by modulating the expression of several key genes involved in these processes (24,60). Specifically, MEG3 has been reported to inhibit the expression of anti-apoptotic proteins, such as Bcl-2, whilst promoting pro-apoptotic proteins, such as caspase-3 and caspase-9, thereby enhancing apoptosis in GC cells (24). The therapeutic potential of MEG3 is further highlighted by its ability to regulate the EMT process, which is crucial for cancer metastasis (102). By inhibiting EMT, MEG3 can potentially reduce the invasive capabilities of GC cells, thereby limiting the spread

of the disease (103). This regulatory function aligns with the growing interest in targeting EMT as a therapeutic strategy for several types of cancer, including GC. Furthermore, the restoration of MEG3 expression in cancer cells has been reported to reverse EMT and restore the epithelial phenotype, suggesting that MEG3 could serve as a therapeutic target to inhibit cancer progression (104). In addition to its direct effects on tumor cells, the interactions of MEG3 with other non-coding RNAs and signaling pathways further enhance its therapeutic feasibility. For example, MEG3 has been identified as a ceRNA that can sponge miRNAs, such as miR-21, which are known to promote oncogenic processes (29). By sequestering these miRNAs, MEG3 can counteract their effects, providing a novel mechanism through which MEG3 exerts its tumor-suppressive functions (105). This interplay between MEG3 and miRNAs presents an opportunity for developing RNA-based therapies that could enhance the expression of MEG3 or mimic its function in GC cells. Furthermore, the potential for using MEG3 as a therapeutic target is supported by its association with patient outcomes (106-108). Studies have reported that patients with low MEG3 expression levels tend to have worse prognoses, reinforcing the notion that MEG3 serves a critical role in tumor suppression (102,103,109). This association suggests that therapies aimed at restoring or enhancing MEG3 function could improve patient survival and quality of life. Furthermore, the feasibility of targeting MEG3 as a therapeutic intervention in GC is supported by its role as a tumor suppressor, its ability to inhibit critical cancer processes, such as EMT, and its interactions with other regulatory RNAs. The development of strategies to enhance MEG3 expression or mimic its function holds promise for improving therapeutic outcomes in patients with GC. Further research into the mechanisms underlying the effects of MEG3 and its potential applications in clinical settings is warranted to fully realize its therapeutic potential.

7. Conclusions and limitations

The exploration of lncRNAs has notably expanded the understanding of the molecular mechanisms underlying numerous types of cancer, particularly GC. Among these lncRNAs, MEG3 has emerged as a critical player, demonstrating a complex relationship with the biological characteristics of GC. The present review highlights the multifaceted roles of MEG3 in the initiation and progression of GC, suggesting that its expression levels are intricately associated with the behavior of the tumor and patient outcomes.

The development of research surrounding MEG3 underscores the need for a balanced approach when interpreting diverse findings across studies. As the understanding deepens, it is crucial to integrate data from molecular biology, clinical observations and bioinformatics to construct a comprehensive picture of the function of MEG3. However, the dual nature of MEG3 as both a tumor suppressor and a potential contributor to tumorigenesis presents a challenge: Whilst certain studies have elucidated its role in inhibiting GC cell proliferation and promoting apoptosis, others have pointed to contexts where MEG3 may be involved in facilitating tumor growth. This dichotomy emphasizes the necessity of contextualizing research findings within specific biological and environmental frameworks.

Furthermore, the impact of MEG3 on GC not only pertains to its mechanistic insights but also extends to its potential as a biomarker for early diagnosis and a target for therapeutic interventions. The association between MEG3 expression and several clinicopathological features of GC suggests that it could serve as a prognostic indicator, aiding in risk stratification and personalized treatment plans. However, for MEG3 to transition from bench to bedside, future research must rigorously validate its clinical utility across diverse patient populations and genetic backgrounds.

Additionally, when considering the clinical application of MEG3, it is essential to address the challenges and limitations inherent in translating basic research into therapeutic strategies. The heterogeneity of GC, characterized by its diverse molecular subtypes and varying responses to treatment, necessitates a nuanced understanding of how MEG3 interacts with other molecular pathways. Collaborative efforts that bring together oncologists, molecular biologists and bioinformaticians are critical to deciphering these complex interactions and refining the potential therapeutic applications of MEG3.

Moreover, the evolving landscape of cancer treatment, particularly with the advent of precision medicine, provides a fertile ground for investigating the role of MEG3 in targeted therapies. As the intricate networks in which MEG3 is involved continue to be elucidated, there lies an opportunity to develop innovative approaches that leverage the properties of this lncRNA to enhance treatment efficacy and minimize adverse effects. The integration of MEG3 modulation into existing treatment regimens, such as chemotherapy or immunotherapy, could yield notable benefits, warranting further exploration.

In conclusion, whilst MEG3 presents promising avenues for both research and clinical application in GC, a concerted effort is needed to harmonize the diverse findings and perspectives within the field. Future studies should strive for a multidisciplinary approach, focusing on elucidating the precise roles of MEG3 in GC biology and its implications for patient management. By fostering collaboration and innovation, MEG3 could become a cornerstone in the future of GC diagnosis and therapy, ultimately improving outcomes for patients affected by this challenging disease.

Despite the comprehensive synthesis of current knowledge on MEG3 in GC, this review had several limitations that should be acknowledged. Most included studies relied on *in vitro* cell line models and animal xenograft experiments, with relatively few well-powered clinical trials or prospective cohort studies. This discrepancy limited the direct translation of findings to human GC patients, as cell lines and animal models may not fully recapitulate the complex TME and genetic heterogeneity of clinical tumors. In addition, the molecular mechanisms underlying MEG3's regulatory role remain partially elusive. While key signaling pathways, such as p53 and PI3K/Akt are discussed in existing literature, the crosstalk between MEG3 and other non-coding RNAs or epigenetic modifiers is insufficiently explored, leaving gaps in understanding its multifaceted functions. These limitations highlight the need for more uniform, large-scale clinical and mechanistic studies to advance MEG3-related research in GC.

Acknowledgements

Not applicable.

Funding

The present work was supported by the Open Project of Key Laboratory of Xi'an Medicine, Ministry of Education, Anhui University of Chinese Medicine (grant nos. 2024xayx09 and 2024xayx10), Scientific Research Project of Anhui Higher Education Institutions (grant nos. 2022AH050450 and 2023AH050742) and Talent Support Program of Anhui University of Chinese Medicine (grant nos. 2022rcyb002 and 2022rcyb007).

Availability of data and materials

Not applicable.

Authors' contributions

BJ designed and conceived the study, wrote the manuscript and acquired funding. HC, PY and XW performed the literature analysis and visualization. SL and JW revised the manuscript. All authors 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.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 74: 229-263, 2024.
2. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC and Lordick F: Gastric cancer. *Lancet* 396: 635-648, 2020.
3. Rihawi K, Ricci AD, Rizzo A, Brocchi S, Marasco G, Pastore LV, Llimpe FLR, Golfieri R and Renzulli M: Tumor-associated macrophages and inflammatory microenvironment in gastric cancer: Novel translational implications. *Int J Mol Sci* 22: 3805, 2021.
4. Zhang Y, Liu C, Peng H, Zhang J and Feng Q: IL1 receptor antagonist gene IL1-RN variable number of tandem repeats polymorphism and cancer risk: A literature review and meta-analysis. *PLoS One* 7: e46017, 2012.
5. He J, Hu W, Ouyang Q, Zhang S, He L, Chen W, Li X and Hu C: Helicobacter pylori infection induces stem cell-like properties in Correa cascade of gastric cancer. *Cancer Lett* 542: 215764, 2022.
6. Mommersteeg MC, Simovic I, Yu B, van Nieuwenburg SAV, Bruno IMJ, Doukas M, Kuipers EJ, Spaander MCW, Peppelenbosch MP, Castaño-Rodríguez N and Fuhler GM: Autophagy mediates ER stress and inflammation in Helicobacter pylori-related gastric cancer. *Gut Microbes* 14: 2015238, 2022.
7. Molaei F, Forghanifard MM, Fahim Y and Abbaszadegan MR: Molecular signaling in tumorigenesis of gastric cancer. *Iran Biomed J* 22: 217-230, 2018.
8. Wang J, Du L and Chen X: Adenosine signaling: Optimal target for gastric cancer immunotherapy. *Front Immunol* 13: 1027838, 2022.

9. Wang Q, Cao T, Zhang X, Hui J, Wang C, Zhang W, Wang P, Zhou Y and Han S: ATXN2-mediated PI3K/AKT activation confers gastric cancer chemoresistance and attenuates CD8+ T cell cytotoxicity. *J Immunol Res* 2022: 6863240, 2022.
10. Liu K, Yuan S, Wang C and Zhu H: Resistance to immune checkpoint inhibitors in gastric cancer. *Front Pharmacol* 14: 1285343, 2023.
11. Khan I, Kamal A and Akhtar S: Diabetes driven oncogenesis and anticancer potential of repurposed antidiabetic drug: A systemic review. *Cell Biochem Biophys* 82: 1907-1929, 2024.
12. Li J, Ye D, Shen P, Liu X, Zhou P, Zhu G, Xu Y, Fu Y, Li X, Sun J, *et al*: Mir-20a-5p induced WTX deficiency promotes gastric cancer progressions through regulating PI3K/AKT signaling pathway. *J Exp Clin Cancer Res* 39: 212, 2020.
13. Yu Z, Jiang X, Qin L, Deng H, Wang J, Ren W, Li H, Zhao L, Liu H and Jiao Z: A novel UBE2T inhibitor suppresses Wnt/ β -catenin signaling hyperactivation and gastric cancer progression by blocking RACK1 ubiquitination. *Oncogene* 40: 1027-1042, 2021.
14. Zeng W, Zhu J, Zeng D, Guo J, Huang G, Zeng Y, Wang L, Bin J, Liao Y, Shi M and Liao W: Epigenetic modification-associated molecular classification of gastric cancer. *Lab Invest* 103: 100170, 2023.
15. Chen D, Xiong L, Zhang L, Yu H, Xu Y, Wang M, Jiang X and Xiong Z: CSF1R is a prognostic biomarker and correlated with immune cell infiltration in the gastric cancer microenvironment. *Pharmgenomics Pers Med* 14: 445-457, 2021.
16. van Schooten TS, Derks S, Jiménez-Martí E, Carneiro F, Figueiredo C, Ruiz E, Alsina M, Molero C, Garrido M, Riquelme A, *et al*: The LEGACY study: A European and Latin American consortium to identify risk factors and molecular phenotypes in gastric cancer to improve prevention strategies and personalized clinical decision making globally. *BMC Cancer* 22: 646, 2022.
17. Peña-Flores JA, Enríquez-Espinoza D, Muela-Campos D, Álvarez-Ramírez A, Sáenz A, Barraza-Gómez AA, Bravo K, Estrada-Macías ME and González-Alvarado K: Functional relevance of the long intergenic non-coding RNA regulator of reprogramming (linc-ROR) in cancer proliferation, metastasis, and drug resistance. *Noncoding RNA* 9: 12, 2023.
18. Liu W, Luo M, Zou L, Liu X, Wang R, Tao H, Wu D, Zhang W, Luo Q and Zhao Y: uNK cell-derived TGF- β 1 regulates the long noncoding RNA MEG3 to control vascular smooth muscle cell migration and apoptosis in spiral artery remodeling. *J Cell Biochem* 120: 15997-16007, 2019.
19. Ye HH, Yang SH and Zhang Y: MEG3 damages fetal endothelial function induced by gestational diabetes mellitus via AKT pathway. *Eur Rev Med Pharmacol Sci* 22: 8553-8560, 2018.
20. Wang X, Li X and Wang Z: lncRNA MEG3 inhibits pituitary tumor development by participating in cell proliferation, apoptosis and EMT processes. *Oncol Rep* 45: 40, 2021.
21. Zhang Y, Wang Y, Jiang Y, Bai H and Wen Y: The meaningful function of the emerging clinical targets-lncRNA MEG3 in gastric cancer. *Curr Pharm Des* 29: 2204-2212, 2023.
22. Guo W, Dong Z, Liu S, Qiao Y, Kuang G, Guo Y, Shen S and Liang J: Promoter hypermethylation-mediated downregulation of miR-770 and its host gene MEG3, a long non-coding RNA, in the development of gastric cardia adenocarcinoma. *Mol Carcinog* 56: 1924-1934, 2017.
23. Li CY, Liang GY, Yao WZ, Sui J, Shen X, Zhang YQ, Ma SM, Ye YC, Zhang ZY, Zhang WH, *et al*: Identification and functional characterization of long non-coding RNAs in human gastric cancer. *Oncol Lett* 15: 8805-8815, 2018.
24. Jiao J and Zhang S: Long non-coding RNA MEG-3 suppresses gastric carcinoma cell growth, invasion and migration via EMT regulation. *Mol Med Rep* 20: 2685-2693, 2019.
25. Najafi D, Siri G, Sadri M, Yazdani O, Esbati R, Karimi P, Keshavarz A, Mehmandar-Oskuei A and Ilktac M: Combination MEG3 lncRNA and Ciprofloxacin dramatically decreases cell migration and viability as well as induces apoptosis in GC cells in vitro. *Biotechnol Appl Biochem* 71: 809-816, 2024.
26. Löönd F, Sugiyama N, Bill R, Bornes L, Hager C, Tang F, Santacrose N, Beisel C, Ivanek R, Bürglin T, *et al*: Distinct contributions of partial and full EMT to breast cancer malignancy. *Dev Cell* 56: 3203-3221, 2021.
27. Leung DHL, Phon BWS, Sivalingam M, Radhakrishnan AK and Kamarudin MNA: Regulation of EMT markers, extracellular matrix, and associated signalling pathways by long non-coding RNAs in glioblastoma mesenchymal transition: A scoping review. *Biology (Basel)* 12: 818, 2023.
28. Giordo R, Ahmadi FAM, Husaini NA, Al-Nuaimi NRAM, Ahmad SMS, Pintus G and Zayed H: microRNA 21 and long non-coding RNAs interplays underlie cancer pathophysiology: A narrative review. *Noncoding RNA Res* 9: 831-852, 2024.
29. Amini F, Khalaj-Kondori M, Moqadami A and Rajabi A: Expression of HOTAIR and MEG3 are negatively associated with H. pylori positive status in gastric cancer patients. *Genes Cancer* 13: 1-8, 2022.
30. Khosroshahi NS, Akbarzadeh S, Abbaslou EM, Rajabi A, Abdi A, Saber A, Pakmanesh AR and Safarizadeh R: Upregulation of lncRNA ANRASSF1 is associated with the lymph node metastasis and H. pylori infection in gastric cancer. *Biomark Med* 19: 571-576, 2025.
31. Rashwan HH, Taher AM, Hassan HA, Awaji AA, Kiriacos CJ, Assal RA and Youness RA: Harnessing the supremacy of MEG3 lncRNA to defeat gastrointestinal malignancies. *Pathol Res Pract* 256: 155223, 2024.
32. Xu J, Wang X, Zhu C and Wang K: A review of current evidence about lncRNA MEG3: A tumor suppressor in multiple cancers. *Front Cell Dev Biol* 10: 997633, 2022.
33. Laurentino S, Beygo J, Nordhoff V, Kliesch S, Wistuba J, Borgmann J, Buiting K, Horsthemke B and Gromoll J: Epigenetic germline mosaicism in infertile men. *Hum Mol Genet* 24: 1295-1304, 2015.
34. Dirks RAM, van Mierlo G, Kerstens HHD, Bernardo AS, Kobolák J, Bock I, Maruotti J, Pedersen RA, Dinnyés A, Huynen MA, *et al*: Allele-specific RNA-seq expression profiling of imprinted genes in mouse isogenic pluripotent states. *Epigenetics Chromatin* 12: 14, 2019.
35. Wu JL, Meng FM and Li HJ: High expression of lncRNA MEG3 participates in non-small cell lung cancer by regulating microRNA-7-5p. *Eur Rev Med Pharmacol Sci* 22: 5938-5945, 2018.
36. Qiu YY, Wu Y, Lin MJ, Bian T, Xiao YL and Qin C: lncRNA-MEG3 functions as a competing endogenous RNA to regulate Treg/Th17 balance in patients with asthma by targeting microRNA-17/ROR γ t. *Biomed Pharmacother* 111: 386-394, 2019.
37. Uroda T, Anastasakou E, Rossi A, Teulon JM, Pellequer JL, Annibale P, Pessey O, Inga A, Chillón I and Marcia M: Conserved Pseudoknots in lncRNA MEG3 are essential for stimulation of the p53 pathway. *Mol Cell* 75: 6789-6797, 2019.
38. Zhang M, Wang F and Zhang X: miRNA-627 inhibits cell proliferation and cell migration, promotes cell apoptosis in prostate cancer cells through upregulating MAP3K1, PTPRK and SRA1. *Int J Clin Exp Pathol* 11: 255-261, 2018.
39. Zhang Y, Wu J, Jing H, Huang G, Sun Z and Xu S: Long noncoding RNA MEG3 inhibits breast cancer growth via upregulating endoplasmic reticulum stress and activating NF- κ B and p53. *J Cell Biochem* 120: 6789-6797, 2019.
40. Sannigrahi MK, Sharma R, Panda NK and Khullar M: Role of non-coding RNAs in head and neck squamous cell carcinoma: A narrative review. *Oral Dis* 24: 1417-1427, 2018.
41. Zhu M, Wang X, Gu Y, Wang F, Li L and Qiu X: MEG3 overexpression inhibits the tumorigenesis of breast cancer by downregulating miR-21 through the PI3K/Akt pathway. *Arch Biochem Biophys* 661: 22-30, 2019.
42. Zhan QY, Xie LX and Wang C: Promoting critical care system and capacity building in pulmonary and critical care medicine subspecialties. *Zhonghua Yi Xue Za Zhi* 103: 3149-3151, 2023 (In Chinese).
43. Zamani M, Sadeghizadeh M, Behmanesh M and Najafi F: Dendrosomal curcumin increases expression of the long non-coding RNA gene MEG3 via up-regulation of epi-miRs in hepatocellular cancer. *Phytomedicine* 22: 961-967, 2015.
44. Yin DD, Liu ZJ, Zhang E, Kong R, Zhang ZH and Guo RH: Decreased expression of long noncoding RNA MEG3 affects cell proliferation and predicts a poor prognosis in patients with colorectal cancer. *Tumour Biol* 36: 4851-4859, 2015.
45. Wu W, Zhou S, Fei G and Wang R: The role of long noncoding RNA MEG3 in fibrosis diseases. *Postgrad Med J* 100: 529-538, 2024.
46. Dunn-Davies H, Dudnakova T, Nogara A, Rodor J, Thomas AC, Parish E, Gautier P, Meynert A, Ulitsky I, Madeddu P, *et al*: Control of endothelial cell function and arteriogenesis by MEG3/EZH2 epigenetic regulation of integrin expression. *Mol Ther Nucleic Acids* 35: 102173, 2024.
47. Liu W, Huang L, Zhang C and Liu Z: lncRNA MEG3 is down-regulated in ankylosing spondylitis and associated with disease activity, hospitalization time and disease duration. *Exp Ther Med* 17: 291-297, 2019.

48. Zheng Q, Lin Z, Xu J, Lu Y, Meng Q, Wang C, Yang Y, Xin X, Li X, Pu H, *et al*: Long noncoding RNA MEG3 suppresses liver cancer cells growth through inhibiting β -catenin by activating PKM2 and inactivating PTEN. *Cell Death Dis* 9: 253, 2018.
49. Yang Y, Tian Z, He L, Meng H, Xie X, Yang Z, Wang X, Zhao Y and Huang C: RhoGDI β inhibition via miR-200c/AUF1/SOX2/miR-137 axis contributed to lncRNA MEG3 downregulation-mediated malignant transformation of human bronchial epithelial cells. *Mol Carcinog* 63: 977-990, 2024.
50. Cheng X, Ali MS, Moran M, Viana MP, Schlichte SL, Zimmerman MC, Khalimonchuk O, Feinberg MW and Sun X: Long non-coding RNA Meg3 deficiency impairs glucose homeostasis and insulin signaling by inducing cellular senescence of hepatic endothelium in obesity. *Redox Biol* 40: 101863, 2021.
51. Yao H, Duan M, Lin L, Wu C, Fu X, Wang H, Guo L, Chen W, Huang L, Liu D, *et al*: TET2 and MEG3 promoter methylation is associated with acute myeloid leukemia in a Hainan population. *Oncotarget* 8: 18337-18347, 2017.
52. Yan J, Guo X, Xia J, Shan T, Gu C, Liang Z, Zhao W and Jin S: MiR-148a regulates MEG3 in gastric cancer by targeting DNA methyltransferase 1. *Med Oncol* 31: 879, 2014.
53. Pan T, Ding H, Jin L, Zhang S, Wu D, Pan W, Dong M, Ma X and Chen Z: DNMT1-mediated demethylation of lncRNA MEG3 promoter suppressed breast cancer progression by repressing Notch1 signaling pathway. *Cell Cycle* 21: 2323-2337, 2022.
54. McMinn J, Wei M, Schupf N, Cusmai J, Johnson EB, Smith AC, Weksberg R, Thaker HM and Tycko B: Unbalanced placental expression of imprinted genes in human intrauterine growth restriction. *Placenta* 27: 540-549, 2006.
55. El Said NH, Abdrabou W, Mahmood SR, Venit T, Idaghdour Y and Percipalle P: Nuclear actin-dependent Meg3 expression suppresses metabolic genes by affecting the chromatin architecture at sites of elevated H3K27 acetylation levels. *Nucleic Acids Res* 53: gkaf280, 2025.
56. Luo Y, Wang H, Wang L, Wu W, Zhao J, Li X, Xiong R, Ding X, Yuan D and Yuan C: LncRNA MEG3: Targeting the molecular mechanisms and pathogenic causes of metabolic diseases. *Curr Med Chem* 31: 6140-6153, 2024.
57. Hasenson SE, Alkalay E, Atrash MK, Bocholez A, Gershbaum J, Hochberg-Laufer H and Shav-Tal Y: The association of MEG3 lncRNA with nuclear speckles in living cells. *Cells* 11: 1942, 2022.
58. Ding L, Tian Y, Wang L, Bi M, Teng D and Hong S: Hypermethylated long noncoding RNA MEG3 promotes the progression of gastric cancer. *Aging (Albany NY)* 11: 8139-8155, 2019.
59. Zhou X, Ji G, Ke X, Gu H, Jin W and Zhang G: MiR-141 inhibits gastric cancer proliferation by interacting with long noncoding RNA MEG3 and down-regulating E2F3 expression. *Dig Dis Sci* 60: 3271-3282, 2015.
60. Peng W, Si S, Zhang Q, Li C, Zhao F, Wang F, Yu J and Ma R: Long non-coding RNA MEG3 functions as a competing endogenous RNA to regulate gastric cancer progression. *J Exp Clin Cancer Res* 34: 79, 2015.
61. Cui HB, Ge HE, Wang YS and Bai XY: MiR-208a enhances cell proliferation and invasion of gastric cancer by targeting SFRP1 and negatively regulating MEG3. *Int J Biochem Cell Biol* 102: 31-39, 2018.
62. Guo LL, Song CH, Wang P, Dai LP, Zhang JY and Wang KJ: Competing endogenous RNA networks and gastric cancer. *World J Gastroenterol* 21: 11680-11687, 2015.
63. Li C, Liang G, Yao W, Sui J, Shen X, Zhang Y, Ma S, Ye Y, Zhang Z, Zhang W, *et al*: Differential expression profiles of long non-coding RNAs reveal potential biomarkers for identification of human gastric cancer. *Oncol Rep* 35: 1529-1540, 2016.
64. Soghala S, Harsiny K, Momeni P, Hatami M, Oskoei VK, Hussen BM, Taheri M and Ghafouri-Fard S: Down-regulation of LINC-ROR, HOXA-AS2 and MEG3 in gastric cancer. *Heliyon* 8: e11155, 2022.
65. Sun M, Xia R, Jin F, Xu T, Liu Z, De W and Liu X: Downregulated long noncoding RNA MEG3 is associated with poor prognosis and promotes cell proliferation in gastric cancer. *Tumour Biol* 35: 1065-1073, 2014.
66. Gao S, Zhao ZY, Wu R, Zhang Y and Zhang ZY: Prognostic value of long noncoding RNAs in gastric cancer: A meta-analysis. *Oncotargets Ther* 11: 4877-4891, 2018.
67. Wei GH and Wang X: lncRNA MEG3 inhibit proliferation and metastasis of gastric cancer via p53 signaling pathway. *Eur Rev Med Pharmacol Sci* 21: 3850-3856, 2017.
68. Li Y, Lou S, Zhang J, Zhao S and Lou G: m6A methylation-mediated regulation of LncRNA MEG3 suppresses ovarian cancer progression through miR-885-5p and the VASH1 pathway. *J Transl Med* 22: 113, 2024.
69. Ye M, Lu H, Tang W, Jing T, Chen S, Wei M, Zhang J, Wang J, Ma J, Ma D and Dong K: Downregulation of MEG3 promotes neuroblastoma development through FOXO1-mediated autophagy and mTOR-mediated epithelial-mesenchymal transition. *Int J Biol Sci* 16: 3050-3061, 2020.
70. An C, Wang I, Li X, Xia R and Deng F: Long non-coding RNA in prostate cancer. *Am J Clin Exp Urol* 10: 170-179, 2022.
71. Ramezani M, Shamsabadi FT and Shahbazi M: Harnessing the TP53INP1/TP53I3 axis for inhibition of colorectal cancer cell proliferation through MEG3 and Linc-ROR Co-expression. *Heliyon* 10: e34075, 2024.
72. Dan J, Wang J, Wang Y, Zhu M, Yang X, Peng Z, Jiang H and Chen L: LncRNA-MEG3 inhibits proliferation and metastasis by regulating miRNA-21 in gastric cancer. *Biomed Pharmacother* 99: 931-938, 2018.
73. Terashima M, Tange S, Ishimura A and Suzuki T: MEG3 long noncoding RNA contributes to the epigenetic regulation of epithelial-mesenchymal transition in lung cancer cell lines. *J Biol Chem* 292: 82-99, 2017.
74. Li T, Zhang X, Cheng L, Li C, Wu Z, Luo Y, Zhou K, Li Y, Zhao Q and Huang Y: Modulation of lncRNA H19 enhances resveratrol-inhibited cancer cell proliferation and migration by regulating endoplasmic reticulum stress. *J Cell Mol Med* 26: 2205-2217, 2022.
75. Kuai X, Jia L, Yang T, Huang X, Zhao W, Zhang M, Chen Y, Zhu J, Feng Z and Tang Q: Trop2 promotes multidrug resistance by regulating Notch1 signaling pathway in gastric cancer cells. *Med Sci Monit* 26: e919566, 2020.
76. Ma Y, Wei X and Wu Z: HNF-4 α promotes multidrug resistance of gastric cancer cells through the modulation of cell apoptosis. *Oncol Lett* 14: 6477-6484, 2017.
77. Zhu YX, Yao J, Liu C, Hu HT, Li XM, Ge HM, Zhou YF, Shan K, Jiang Q and Yan B: Long non-coding RNA MEG3 silencing protects against light-induced retinal degeneration. *Biochem Biophys Res Commun* 496: 1236-1242, 2018.
78. Tu Y, Xie L, Chen L, Yuan Y, Qin B, Wang K, Zhu Q, Ji N, Zhu M and Guan H: Long non-coding RNA MEG3 promotes cataractogenesis by upregulating TP53INP1 expression in age-related cataract. *Exp Eye Res* 199: 108185, 2020.
79. Zhang X, Wu N, Wang J and Li Z: LncRNA MEG3 inhibits cell proliferation and induces apoptosis in laryngeal cancer via miR-23a/APAF-1 axis. *J Cell Mol Med* 23: 6708-6719, 2019.
80. Wu D, Ma Z, Ma D and Li Q: Long non-coding RNA maternally expressed gene 3 affects cell proliferation, apoptosis and migration by targeting the microRNA-9-5p/midkine axis and activating the phosphoinositide-dependent kinase/AKT pathway in hepatocellular carcinoma. *Oncol Lett* 21: 345, 2021.
81. Mitra R, Chen X, Greenawalt EJ, Maulik U, Jiang W, Zhao Z and Eischen CM: Decoding critical long non-coding RNA in ovarian cancer epithelial-to-mesenchymal transition. *Nat Commun* 8: 1604, 2017.
82. Wang R, Zou L and Yang X: microRNA-210/ Long non-coding RNA MEG3 axis inhibits trophoblast cell migration and invasion by suppressing EMT process. *Placenta* 109: 64-71, 2021.
83. Liu H, Chen C, Zeng J, Zhao Z and Hu Q: MicroRNA-210-3p is transcriptionally upregulated by hypoxia induction and thus promoting EMT and chemoresistance in glioma cells. *PLoS One* 16: e0253522, 2021.
84. Wang Z, Xia P, Hu J, Huang Y, Zhang F, Li L, Wang E, Guo Q and Ye Z: LncRNA MEG3 alleviates diabetic cognitive impairments by reducing mitochondrial-derived apoptosis through promotion of FUNDC1-related mitophagy via Rac1-ROS axis. *ACS Chem Neurosci* 12: 2280-2307, 2021.
85. Elimam H, Zaki MB, Abd-Elmawla MA, Darwish HA, Hatawsh A, Aborehab NM, Mageed SSA, Moussa R, Mohammed OA, Abdel-Reheim MA and Doghish AS: Natural products and long non-coding RNAs in prostate cancer: Insights into etiology and treatment resistance. *Naunyn Schmiedeberg Arch Pharmacol* 18, 2025.
86. Bai Z, Hu K, Yu J, Shen Y and Chen C: Macrophage migration inhibitory factor protects bone marrow mesenchymal stem cells from hypoxia/ischemia-induced apoptosis by regulating lncRNA MEG3. *J Zhejiang Univ Sci B* 23: 989-1001, 2022.
87. Zhu J, Liu S, Ye F, Shen Y, Tie Y, Zhu J, Wei L, Jin Y, Fu H, Wu Y and Zheng X: Long Noncoding RNA MEG3 interacts with p53 protein and regulates partial p53 target genes in hepatoma cells. *PLoS One* 10: e0139790, 2015.

88. Ali MS, Cheng X, Moran M, Haemmig S, Naldrett MJ, Alvarez S, Feinberg MW and Sun X: LncRNA Meg3 protects endothelial function by regulating the DNA damage response. *Nucleic Acids Res* 47: 1505-1522, 2019.
89. Zheng H, Li BH, Liu C, Jia L and Liu FT: Comprehensive analysis of lncRNA-mediated ceRNA crosstalk and identification of prognostic biomarkers in Wilms' tumor. *Biomed Res Int* 2020: 4951692, 2020.
90. Bauer NC, Yang A, Wang X, Zhou Y, Klibanski A and Soberman RJ: A cross-nearest neighbor/Monte Carlo algorithm for single-molecule localization microscopy defines interactions between p53, Mdm2, and MEG3. *J Biol Chem* 296: 100540, 2021.
91. Luo Q, Cui M, Deng Q and Liu J: Comprehensive analysis of differentially expressed profiles and reconstruction of a competing endogenous RNA network in papillary renal cell carcinoma. *Mol Med Rep* 19: 4685-4696, 2019.
92. Kumar S, Williams D, Sur S, Wang JY and Jo H: Role of flow-sensitive microRNAs and long noncoding RNAs in vascular dysfunction and atherosclerosis. *Vascul Pharmacol* 114: 76-92, 2019.
93. Tan J, Xiang L and Xu G: LncRNA MEG3 suppresses migration and promotes apoptosis by sponging miR-548d-3p to modulate JAK-STAT pathway in oral squamous cell carcinoma. *IUBMB Life* 71: 882-890, 2019.
94. Li Y, Zhang L, Zhao Y, Peng H, Zhang N and Bai W: MEG3 sponges miRNA-376a and YBX1 to regulate angiogenesis in ovarian cancer endothelial cells. *Heliyon* 9: e13204, 2023.
95. Zhang C, Qin Y, Tang Y, Gu M, Li Z and Xu H: MEG3 in hematologic malignancies: from the role of disease biomarker to therapeutic target. *Pharmacogenet Genomics* 34: 209-216, 2024.
96. Wei Q, Liu G, Huang Z, Huang Y, Huang L, Huang Z, Wu X, Wei H and Pu J: LncRNA MEG3 inhibits tumor progression by modulating macrophage phenotypic polarization via miR-145-5p/DAB2 axis in hepatocellular carcinoma. *J Hepatocell Carcinoma* 10: 1019-1035, 2023.
97. Lin J, Huang J, Tan C, Wu S, Lu X and Pu J: LncRNA MEG3 suppresses hepatocellular carcinoma by stimulating macrophage M1 polarization and modulating immune system via inhibiting CSF-1 in vivo/vitro studies. *Int J Biol Macromol* 281: 136459, 2024.
98. Huang CY, Chou ST, Hsu YM, Chao WJ, Wu GH, Hsiao JR, Wang HD and Shiah SG: MEG3-mediated oral squamous-cell-carcinoma-derived exosomal miR-421 activates angiogenesis by targeting HS2ST1 in vascular endothelial cells. *Int J Mol Sci* 25: 7576, 2024.
99. Kong X, Yang S, Liu C, Tang H, Chen Y, Zhang X, Zhou Y and Liang G: Relationship between MEG3 gene polymorphism and risk of gastric cancer in Chinese population with high incidence of gastric cancer. *Biosci Rep* 40: BSR20200305, 2020.
100. Liu H, Ye D, Chen A, Tan D, Zhang W, Jiang W, Wang M and Zhang X: A pilot study of new promising non-coding RNA diagnostic biomarkers for early-stage colorectal cancers. *Clin Chem Lab Med* 57: 1073-1083, 2019.
101. Ghaedi H, Mozaffari MAN, Salehi Z, Ghasemi H, Zadian SS, Alipoor S, Hadianpour S and Alipoor B: Co-expression profiling of plasma miRNAs and long noncoding RNAs in gastric cancer patients. *Gene* 687: 135-142, 2019.
102. Li MK, Liu LX, Zhang WY, Zhan HL, Chen RP, Feng JL and Wu LF: Long non-coding RNA MEG3 suppresses epithelial-to-mesenchymal transition by inhibiting the PSAT1-dependent GSK-3 β /Snail signaling pathway in esophageal squamous cell carcinoma. *Oncol Rep* 44: 2130-2142, 2020.
103. Li J, Jiang X, Li C, Liu Y, Kang P, Zhong X and Cui Y: LncRNA-MEG3 inhibits cell proliferation and invasion by modulating Bmi1/RNF2 in cholangiocarcinoma. *J Cell Physiol* 234: 22947-22959, 2019.
104. Ji Y, Feng G, Hou Y, Yu Y, Wang R and Yuan H: Long noncoding RNA MEG3 decreases the growth of head and neck squamous cell carcinoma by regulating the expression of miR-421 and E-cadherin. *Cancer Med* 9: 3954-3963, 2020.
105. Ning J, Zhang L, Guo H, Zhou S, Sun X and Bao W: LncRNA MEG3 inhibits the development of nasopharyngeal carcinoma by sponging miR-543 targeting KLF4. *Transl Cancer Res* 9: 958-971, 2020.
106. Jin L, Cai Q, Wang S, Wang S, Mondal T, Wang J and Quan Z: Long noncoding RNA MEG3 regulates LATS2 by promoting the ubiquitination of EZH2 and inhibits proliferation and invasion in gallbladder cancer. *Cell Death Dis* 9: 1017, 2018.
107. Liu L, Liu Y, Zhang S, Zhang J, Meng Y, Liu D, Gu L, Zhang Y, Xu L, Zhang Z, *et al*: Celastrol promotes apoptosis of breast cancer MDA-MB-231 cells by targeting HSDL2. *Acupuncture and Herbal Medicine* 4: 92-101, 2024.
108. Huang D, Tang Z, Pu X, Gao F and Chong L: A novel cabazitaxel liposomes modified with ginsenoside Rk1 for cancer targeted therapy. *Acupuncture and Herbal Medicine* 4: 113-121, 2024.
109. Zhang L, Zhao F, Li W, Song G, Kasim V and Wu S: The biological roles and molecular mechanisms of long non-coding RNA MEG3 in the hallmarks of cancer. *Cancers (Basel)* 14: 6032, 2022.