Pathology & Oncology Research (2019) 25:859–874
https://doi.org/10.1007/s12253-019-00614-3

REVIEW

MEG3: an Oncogenic Long Non-coding RNA in Different Cancers

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Received: 29 November 2018 / Accepted: 8 February 2019 / Published online: 21 February 2019

Abstract

Long noncoding RNAs (lncRNAs) have recently considered as central regulators in diverse biological processes and emerged as vital players controlling tumorigenesis. Several lncRNAs can be classified into oncogenes and tumor suppressor genes depending on their function in cancer. A maternally expressed gene 3 (MEG3) gene transcripts a 1.6 kb lncRNA whose act as an antitumor component in different cancer cells, such as breast, liver, glioma, colorectal, cervical, gastric, lung, ovarian and osteosarcoma cancer cells. The present review highlights biological function of MEG3 to repress tumor through regulating the major tumor suppressor genes p53 and Rb, inhibiting angiogenesis-related factor, or controlling miRNAs. On the other hand, previous studies have also suggested that MEG3 mediates epithelial-mesenchymal transition (EMT). However, deregulation of MEG3 is associated with the development and progression of cancer, suggesting that MEG3 may function as a potential biomarker and therapeutic target for human cancers.

Keywords MEG3 · lncRNA · p53 · Cancer · Methylation · Angiogenesis

Introduction

In fact, cancer is a complex disease and genetic alterations only reflect a piece. Recent studies proved that, lncRNAs can also contribute in numerous biological and cellular aspects for instance cell proliferation, differentiation, and apoptosis represent vital roles for lncRNAs in the etiology of several disease state [1, 2]. Recently, the scientific research found that there is a clear association between lncRNAs and tumorigenesis processes [3]. Although, dysregulation of various lncRNAs in tumor samples compared with their normal counterparts have been reported in different types of cancer [4]. This dysregulation might affect the cellular functions to develop cancer cells, for example increasing cell proliferation, prevention of apoptosis, promotion of angiogenesis, induction of metastasis, and inhibition of tumor suppressors [5, 6]. Interestingly, a vast variety of lncRNAs can be classified according to the expression pattern and function at the cellular level into tumor suppressor genes and oncogenes [7]. Previous studies have been revealed that the p53 pathway is regulated through lncRNAs, directly or indirectly [8]. One of these lncRNAs is MEG3 which regulate the key tumor suppressor genes and inhibit angiogenesis [9]. This review article will provide an overview of the MEG3 gene, the association between MEG3 and tumor suppressor protein coding genes, the role of MEG3 to inhibit angiogenesis, and alternations of MEG3 in different types of cancer.

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MEG3

Maternally expressed gene 3 (MEG3), located in human chromosome 14q32.3 within DLK1-MEG3 locus [10]. This gene composed of 35 kb size and consists of ten exons [9]. MEG3 is a maternally imprinted gene contains ten exons and encodes an approximately 1.6 Kb long noncoding RNA [11]. Gene trap locus 2 (Gtl2) is the mouse homolog of human MEG3 [9]. The promoter of MEG3 comprises a TATA- and CCAAT-box, the RNAs transcripted from this gene by RNA polymerase II are polyadenylated at 3′ end [12, 13]. LncRNA MEG3 localize in the nucleus and cytoplasm [14]. The gene expression in the DLK1-MEG3 region controlled by two differentially methylated regions (DMRs) that comprised of multiple methylated CpG sites: the intergenic DMR (IG-DMR) located about 13 kb upstream from MEG3 transcription start site, and post fertilization-derived secondary (MEG3-DMR) overlapped with the promoter 1.5 kb upstream [15] (Fig. 1). In addition, MEG3 expression induced by cyclic AMP

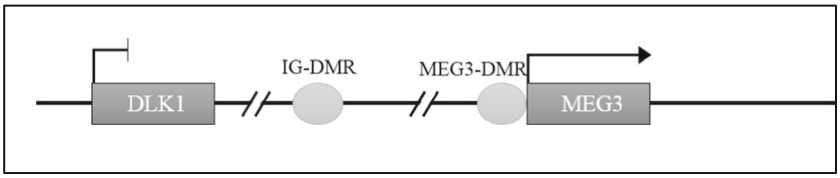

Fig. 1 Schematic diagram of the DLK1–MEG3 locus. The maternal allele prevented the expression of DLK1 through methylation at this region while the MEG3 gene expression controlled by two DMRs, IG-DMR and MEG3-DMR

(cAMP), the positive regulatory element, which regulates gene expression via cAMP response element (CRE) site resides in MEG3 proximal promoter between −69 and − 49 sequences [16].

MEG3 expressed at abundant levels in many tissues and which plays a vital role in development and growth [17]. Failure to control imprinting locus may cause moderate to severe developmental disorders [18]. Furthermore, a single nucleotide polymorphism (SNP) within the MEG3 intron which increased the susceptibility to type 1 diabetes [19]. Additionally, the MEG3 expression has been demonstrated to be deregulated in a variety of primary human cancers [20]. Interestingly, MEG3 act as a tumor suppressor through the accumulation of p53 protein which activates its downstream target genes [21].

Correlation between MEG3 and p53 in Tumor Suppression

TP53

The TP53 gene (Tumor Suppressor Protein p53) is found on chromosome 17p13.1 [22]. It encodes a 53 kDa p53 protein and composed of 393-amino-acid [23]. p53 has been referred to as "guardian of the genome" [24], which controls cell growth through preservation of DNA integrity at a critical point from cellular damage [25]. The p53 protein is kept at an extremely low levels under normal conditions, mainly by MDM2 (Murine/human double minute 2), which mediates a ubiquitin degradation of p53 [26]. p53 can be activated through various types of cellular stressors, such as DNA damage, telomere erosion, hypoxia, metabolic deprivation, or oncogenic stress [27, 28]. This activation resulting in stimulation of a numerous of molecular pathways including cell cycle arrest, DNA repair, senescence, or apoptosis [25, 29]. Around half of all cancers p53 is mutated in human, therefore, p53 is considered one of the most extensively reported tumor suppressor protein [30]. Previous data reported the ability of MEG3 to regulate p53 [21].

Association of p53 and MEG3

Several lincRNAs found to regulate the p53 tumor suppressor pathway directly or indirectly [8]. One of these, MEG3 could suppress cancer cell proliferation or induce apoptosis [31]. Under physiological conditions, p53 has an enormously short lifespan because of the degradation mediated by MDM2, a RING finger E3 ubiquitin ligase [32]. Stabilization of p53 occurs through inhibition of MDM2 which achieved through posttranslational modifications, including phosphorylation, acetylation, and sumoylation of the amino terminus of p53 at specific amino acids to prevent p53 interaction with MDM2 [33–35] (Fig. 2).

Numerous studies reported that upregulation of MEG3 result in a noteworthy induce p53 stability and, therefore, protein levels [18, 21]. Furthermore, previous studies observed that MEG3 decreased MDM2 expression consequently activates p53 [21, 36]. Remarkably, there are other likely mechanisms that MEG3 regulates p53 [21, 36]. An interesting feature about the regulation of p53 is a number of transcriptional coactivators contribute to the maintenance of stability and control p53 function [37]. In the light of recent studies in lncRNA that function as a transcriptional coactivator of the p53 [38]. It is likely that MEG3 functions as a coactivator by folding into a complicated structure to trigger its transcriptional activity [21, 36]. Moreover, the p53 protein is active conformation a homotetramer, and in this form, p53 allowed to act as a transcription factor [39]. Meanwhile, another possible way for MEG3 to activate p53 through contributions in its tetramer formation [36]. The p53 protein consists of three main domains: the transactivation domain (TAD), the DNA binding domain (DBD), and the tetramerization domain (TET) [40]. In cancer, most p53 mutations occur in the DBD and thus lose the capacity to stimulate gene transcription [41–43]. However, a study showed that DBD of p53 is important for the direct association with MEG3. Researchers suggested that MEG3 dissociated afterwards and p53 activated its target genes [36].

However, twelve MEG3 isoforms have been discovered, all these isoforms fold into three main conserved motifs, M1, M2, and M3 [11]. M2 is essential for the positive regulation of p53-mediated transactivation [11]. Interestingly, p53 activated by MEG3 induces expression of GDF15 (Growth/differentiation factor-15) which belongs to the transforming growth factor (TGF)-β superfamily, a potent growth inhibitor [21, 44, 45]. Although MEG3 promotes expression of p21 via p53 to enhance cell cycle arrest and apoptosis [46]. Also, researchers found that other some genes could be activated by MEG3 like caspase 3 which is an essential element of the apoptotic

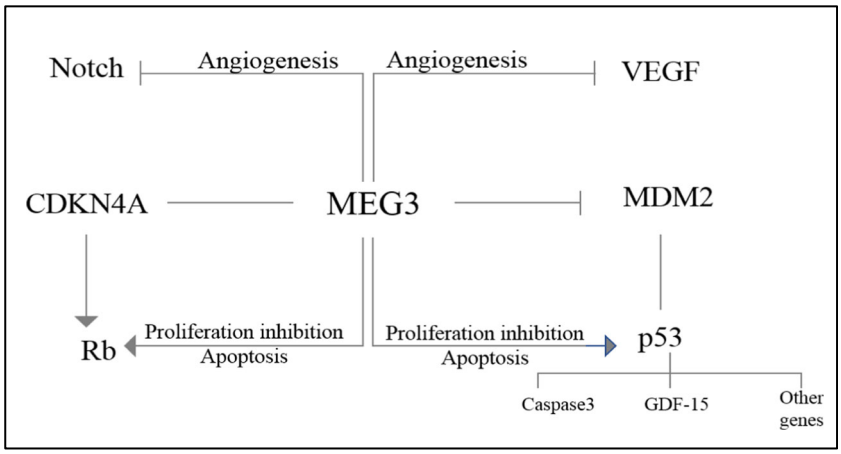

Fig. 2 The interaction of MEG3 with proliferation inhibition proteins p53 and Rb through inhibition of MDM2 and activation of CDKN4A respectively. Also, inhibition of the expression of VEGF and Notch to suppress angiogenesis

machinery while decreased the expression of Bcl-2 and cyclin D1 to inhibit cell proliferation [47].

p53 Independent Pathway

On the other hand, MEG3 could arrest cell growth through retinoblastoma (Rb), a potent suppressor of G1-S phase [48, 49] (Fig. 2). Since MEG3 inhibits MDM2 leading to elevating the active form of Rb levels. After stimulation, Rb interacts with transcription factor E2F and block transcription of target their genes [48, 50]. Furthermore, MEG3 regulate Rb directly or indirectly through RNA-protein bindings or CDKN4A, respectively [51, 52].

MEG3 Negatively Regulates Angiogenesis

Recently, researchers discovered that lncRNAs existed in the endothelium and may be involved in endothelial pathological processes and physiological behaviors [53]. Angiogenesis is pivotal for cancer growth through neovessels sprout from pre-existing vessels and consequently activating invasion and metastasis [54]. Vascular endothelial growth factor (VEGF) is the crucial signaling molecule for angiogenesis by regulating proliferation, survival, and migration [55]. Moreover, Notch signaling pathway, which coordinates VEGF in vascular development and highly expressed in arteries compared to veins [56]. Previous studies strongly suggested the association between MEG3 and angiogenesis [57] (Fig. 2). Gordon et al. reported remarkable elevated in the gene expression of some genes of VEGF pathway and strongly increased density of cortical microvessel the Meg3- knockout embryos [58]. Moreover, the MEG3 level is inversely associated with VEGF gene expression in cartilage samples from osteoarthritis patients [59]. However, upregulation of MEG3 arrest cell growth, invasion, and angiogenesis in breast cancer cells via declining expression of the PI3K/Akt signaling pathway and its downstream target genes MMP-9, VEGFA, PGF, bFGF, TGF-β1, and PCNA (proliferating-cell nuclear antigen) [60]. Furthermore, angiogenesis after ischemic brain injury required increased expression of Hes1 and Hey1 target genes for Notch pathway which enhanced through MEG3 silencing while reversed by notch inhibitor [61].

Under hypoxia circumstance, HIF-1α (Hypoxia-Inducible Factor) induced the expression of MEG3 in human umbilical vein endothelial cells via interacting with CREB-binding protein (CBP)/p300 to elevate CREB activity found on MEG3 promoter region. Strangely, the absence of MEG3 gene repress VEGFR2 mRNA in contrast had no association with VEGFR1. Moreover, decline expression of MEG3 blocked VEGF-stimulated endothelial cell proliferation, migration and angiogenesis [62]. Besides, miRNAs may involve in the suppression of angiogenesis mediated by MEG3 [63].

Effect of Methylation on MEG3

The other piece of cancer puzzle is epigenetics, which investigates alternations in gene expression not expressed by DNA sequence mediated by at least two main mechanisms: DNA methylation and modifications of histone protein [64]. Aberrant DNA methylation is frequently associated with genetic instability and cancer development through inactivation of specific cancer-related genes [65]. DNA methylation is an epigenetic modification established by DNA methyltransferases (DNMTs) whose catalyzed attachments of methyl group to the carbon of cytosine residue in the CpG islands (genomic regions rich in CpG dinucleotides) which present in ~ 70% of human promoters this leads to directly interfere with transcription factors and RNA polymerase II assembly at promoters. Alternatively, DNA methylation can function as a platform for different chromatin remodeling enzymes including HDACs (Histone Deacetylases) therefore condensation of the chromatin [66]. Several studies describe repression of tumor

suppressor genes by hypermethylation of their promoters during carcinogenesis [67].

However, several human cancers carry loss of expression of MEG3 as a result of an epigenetic modification [20]. Specifically, hypermethylation in the MEG3 promoter region, enhancer or IG-DMR are negatively impact on the expression level. Methylation within the IG-DMR occurred at very few particular CpG positions, especially at CpG positions 7 and 8 in human clinically nonfunctioning tumors [68]. In addition, the MEG3 CRE region involves the CpG islands which could be methylated to block CREB binding and disrupt promoter activity [16]. Although the first intron of MEG3 show aberrant methylation in acute myeloid leukemia which is demethylated by TET2 (The ten–eleven translocation), whose catalyze the oxidation of 5-methylcytosine to form 5-hydroxymethylcytosine, resulting in stimulation of MEG3 expression [48].

Normally, several proteins interact with DNMT1 such as PCNA and URHF1 (E3 ubiquitin-protein ligase) to form a complex for targeting DNMT1 to replication forks and maintaining DNA methylation in mammalian cells during DNA replication. In contrast, this complex plays both maintenance and de novo DNA in cancer [69]. Expression of MEG3 is inversely correlated with PCNA in non-small cell lung cancer (NSCLC) [70]. Although UHRF1 caused hypermethylation of MEG3 promoter through modulation of DNMT1 in hepatocellular carcinoma (HCC) [71]. Interestingly, cancer cells treated with DNMT1 inhibitors such as 5-AzadC and RNAi or miR-148a in glioma [72] and gastric cancer [73] respectively, result in the reduction of DNMT1 and MDM2 expressions, and noteworthy positive changes in MEG3 expression levels and encouraged re-expression of tumor suppressor genes, therefore, induced apoptosis. Notably, Rb protein also regulates DNMT1 and hence regulates promoter methylation of variant genes [74]. Specifically, it has been shown that stimulation of Rb protein causes downregulation of expression of DNMT1 [75]. Furthermore, miR-26a has been showed to control MEG3 expression through regulating DNMT3b expression [76]. Moreover, the hypermethylation of MEG3 correlated with poor survival of retinoblastoma patients in retinoblastoma [77]. Collectively, these findings establishing embroiled DNMTs in the decreasing expression of MEG3 and subsequently MEG3 target genes in cancer.

Downregulation of MEG3 in Cancer

Breast Cancer

Breast cancer is a heterogeneous disease threatening the health of women [78]. Several reports demonstrate that lncRNAs are critical regulators of breast cancer progression, such as HOTAIR [79], lncRNA ROR [80], lncRNA 00617 [81], lncRNA SOX2OT [82], CCAT2 [83], GAS5 [84], and MALAT-1 [85]. Likewise, the MEG3 expression was remarkably decreased in breast cancer tissues compared to adjacent normal tissues and related to poor overall survival rate, progression-free survival rate, lymph nodes metastasis, differentiation grade and tumor node metastasis (TNM) stage. MEG3 also may act as a novel biomarker in breast cancer patients [86]. The ectopic expression of MEG3 RNA in breast tumor cells was decreased levels of MDM2 mRNA. Therefore, MEG3 capable of inducing p53 accumulation and stability through downregulating MDM2 levels. Consequently, ectopic expression of MEG3 enhanced the binding of p53 to metastasis suppressor genes in breast cancer; Maspin, KAI1's, and apoptosis-related genes; p21, but not to Bcl-2 or Bax. As a result, MEG3 inhibit tumor growth, migration and invasion [87]. Moreover, the MEG3 repressed EMT process and invasion in breast cancer mainly via sponge miR-421 resulting in upregulation of E-cadherin which is considered to be a negative regulator of EMT event. Thus, MEG3 suppressed cell invasion and EMT by increasing E-cadherin levels and also decreasing ZEB1, ZEB2, and Vimentin whose expression levels correlated with increasing cell invasion [88]. Mondal et al. discovered the mechanism whereby MEG3 interreact with chromatin to detect MEG3 binding sites from a genome-wide chromatin in breast cancer cells via a modified chromatin oligo affinity precipitation and other various experiments. Analysis of MEG3 binding sites showed enrichment of a GA-rich motifs to direct MEG3 to its target genes through RNA–DNA triplex and facilitate the recruitment of transcriptional repression proteins; PRC2 (polycomb repressive complex 2) and H3K27me3 to specific genes, such as TGFB2, TGFBR1 and SMAD2 that are involved in TGF-β pathway [89].

Liver Cancer

Liver cancer is the fifth most widespread cancer around the globe, accounting for 9.1% of all cancer-related deaths worldwide in 2012 [89]. Among liver cancers, HCC is the sixth most prevalent cancer worldwide [90]. However, dysregulation of lncRNAs is associated with the incidence and progression of liver cancer, for example, lncRNA CUDR [91], HOTAIR [92], lncTCF7 [93], and DILC [94]. MEG3 levels were comparatively decreased in HCC Huh7 cells, whereas miR-664 expression was significantly upregulated. However, the expression levels of miR-664 target gene which is responsible for metabolizing the ethanol, ADH4 (Alcohol dehydrogenase 4) were remarkably lower in Huh7 cells. While overexpression of MEG3 is negatively regulated miR-664 expression and may be promoted its degradation resulting in increased ADH4 in Huh7 cells. Furthermore, MEG3 promoter involved some transcription factor binding sites, for instance, Stat6, Ets, Stat3, Stat5, CREB and NF-κB; however, NF-κB

in HCC cells may regulate expression of MEG3 and leads to cancer development [95]. Interestingly, it was confirmed that MEG3 suppress liver cancer cells by boosting the expression and maturation of miR-122 that is mediated downregulation of glycolytic enzyme, PKM2 (Pyruvate kinase muscle isozyme M2). Thus, MEG3 could arrest liver cancer development in some way through decreasing PKM2 levels, the positive regulator of cyclin D1 and C-Myc levels. Remarkably, MEG3 overexpression is closely associated with increasing the expression and phosphorylation of ubiquitin-proteasome system dependent on PTEN2 resulting in degradation of β-catenin in liver cancer cells [96]. Researchers reported a noteworthy decline in MEG3 levels in both CCl4-induced mouse liver fibrosis models and human fibrotic livers. Methylation-specific PCR (MSP) results indicated that decline expression of MEG3 is roughly linked with promoter hypermethylation in human hepatic fibrotic tissues, liver tissues of mice treated with CCl4, and LX-2 cells treated with TGF-β1, however, treatment of TGF-β1-treated LX-2 cells with 5-azadC remarkably reversed MEG3 promoter hypermethylation mediated by TGF-β1 and subsequently inhibiting hepatic stellate cell activation and proliferation. Strikingly, increased expression of MEG3 in LX-2 cells treated with TGF-β1 suppressed cell proliferation through decreasing α-SMA and Col1A1 levels, while induced cell apoptosis by activating p53 and enhancing cytochrome c release, therefore, activating caspase-3 [97].

Glioma

Glioma is the most common and aggressive malignant in the central nervous system [98]. Some of lncRNAs participate in glioma progression such as lncRNA uc.283-plus [99], CRNDE [100], XIST [101], and lncRNA-ROR [101]. Wang et al. demonstrated that levels of MEG3 were declined in 82% of glioma tissues compared to normal tissues. However, upregulation of MEG3 expression significantly blocked development of cancer in U87 MG and U87 MG human glioma cell lines by inducing p53 expression resulted in G0/G1 arrest [102]. Amazingly, abnormal stimulation of Wnt induced assembly of β-catenin in the nucleus and is stimulated transcription of several oncogenes [103], whereas inversely high expression of MEG3 could suppress cell proliferation by inactivating Wnt/β-catenin signaling pathway [104]. Although, the negative regulator of PI3K, PTEN, is suppressed by miR-19a which is overexpressed in glioma in contrast to MEG3; however, MEG3 overexpression abolished this suppression through sponging miR-19a [105]. Besides, MEG3 overexpression by transfection restrained the function of miR-93 in inducing proliferation and preventing apoptosis in U-251 cells. Correspondingly, MEG3 overexpresion decreased levels of the cell proliferation antigen Ki67 and PCNA, while upregulated levels of caspase-3 and caspase-9. Moreover, levels of p-PI3K and p-AKT were diminished by lncRNA-MEG3 and elevated through miR-93 mimics. These outcomes revealed that MEG3 overexpression may take part in glioma by suppressing the PI3K/AKT pathway [106].

Colorectal Cancer

Colorectal cancer (CRC) is the third most common malignancy in the most parts of the world [107]. Several studies reported that lncRNAs play a crucial role in CRC occurrence and progression such as lncRNA CASC11 [108], RP11-708H21.4 [109], CRNDE [110], PRNCR1 [111], H19 [112], ncRAN [113], and loc285194 [114]. A study found that MEG3 levels were decreased in CRC tissues and evidently associated with histological grade, tumor invasion depth, and TNM stage [115]. Although downregulation of MEG3 in CRC patients exhibited poorer overall survival and disease-free survival than those with higher MEG3 level [116]. Induction of MEG3 expression resulted in accumulation of p53 protein and downregulation of cyclin D1 in HCT-116 cells transfected with pCDNA-MEG3 [115]. Interestingly, MEG3 bind with Clusterin, the positive regulator of NF-κB and Bcl-2 signaling pathways, thus reducing the oncogene's capacity of Clusterin through preventing its binding with target proteins. Strikingly, the upregulation of vitamin D treatment or vitamin D receptor associated with increasing levels of MEG3 in CRC cells resulting in better overall survival. The mechanism of action of the vitamin D is dependent on binding vitamin D receptor to the promoter of MEG3 and may enhanced its expression through regulating Clusterin [116]. Remarkably, decreasing levels of MEG3 is closely linked to oxaliplatin therapy resistance. In contrast, MEG3 overexpression enhanced chemoresponse by promoting oxaliplatin-induced cell cytotoxicity in CRC cells [117]. However, the correlation between MEG3 SNPs and the risk of CRC was showed that people with rs7158663 AA genotype contributed to high risk of CRC in Chinese population with a noteworthy correlation with age ≤ 60 and family history [118].

Cervical Cancer

Cervical cancer is the second most common cancer around the world affecting the female reproductive system [119]. Several lncRNAs displayed aberrant expression in cervical cancer including HOTAIR [120], GAS5 [121], XLOC_010588 (TUSC8) [122], lncRNA LET [123], and lncRNA-CCHE1 [124]. Moreover, expression of MEG3 was notably declined in cervical cancer tissues; however, ectopic expression of MEG3 resulting in repression development of cervical cancer in HeLa and C-33A cells through inducing G2/M cell cycle arrest and apoptosis [125]. Correspondingly, decreased levels of MEG3 in cervical cancer tissues were inversely correlated with miR-21-5p whose expression is indirectly suppressed p53, while re-expression of MEG3 levels participated at least

in part to p53 and caspase-3 accumulations through miR-21-5p suppression in cervical cancer in HeLa and CaSki cells [126]. Using MSP, Zhang et al. found that MEG3 promoter in cervical cancer was hypermethylated in 65.3% of tissues [127] and 53.6% of plasma samples [128] whereas both were conflicted with MEG3 expression. Remarkably, methylation levels of MEG3 promoter associated with shorter recurrence-free survival, however, demethylation of MEG3 promoter enhanced its expression in cervical cancer cells [127]. Interestingly, MEG3 promoter methylation in plasma can be considered as a risk factor for HR-HPV (High Risk-Human papillomavirus) infection, cervical intraepithelial neoplasia, and lymph node metastasis, therefore, plasma MEG3 methylation levels may be used as a diagnostic and prognostic biomarker for cervical cancer [128]. Unlike DNA methylation, inhibition of EZH2 histone methyltransferase through 3-Deazaneplanocin treatment had no effect on MEG3 dysregulation [127]. Ectopic MEG3 expression suppressed development of cervical cancer cells through regulating PI3K/Akt signaling pathway, and controlling MMP-2, MMP-9, Bax, Bcl-2 and p21 expressions to promote apoptosis [129].

Gastric Cancer

Gastric cancer is the second cancer leading death in the world [130]. Accumulating evidences showed that lncRNAs' expression may be deregulated in gastric cancer such as HOXA11-AS [131], FENDRR [132], GClnc1 [133], CCAT2 [134], and lncRNA-SNHG1 [135]. Moreover, MEG3 expression levels were markedly depressed in 69.23% of gastric cancer tissues and cell lines [136] whereas MEG3 overexpression promoted p53 transcription to suppress gastric cancer growth and metastasis [137]. A low level of MEG3 in gastric cancer tissues was significantly associated with size of tumor, TNM stages, and depth of invasion. Furthermore, patients with high levels of MEG3 had better overall survival rate than other patients [138]. Interestingly, the capability of MEG3 to stimulate apoptosis via sequestering miR-181 family in gastric cancer cells to upregulate Bcl-2 levels, and then suppressing gastric carcinogenesis [139]. Researchers observed that 5-aza-CdR treatment enhanced expression of MEG3 in AGS and MGC803 gastric cancer cell lines, which is indicated methylation may affects the expression of MEG3 [138]. Noteworthy, it has been found that miR-148a enhances MEG3 expression by directly targeting DNMT1 resulted in the proliferation suppression in gastric cancer cells [136].

Lung Cancer

Lung cancer is the most frequently cause of cancer deaths worldwide for both men and women [140]. The two main histological types of lung cancer are NSCLC and small cell lung cancer (SCLC) [141]. Scientists have found that lncRNAs participated in lung cancer progression for example, ZXF1 [142], GHSROS [143], MVIH [144], HOTAIR [145], CCAT2 [146], and SPRY4-IT1 [147]. However, MEG3 levels were strongly decreased in NSCLC tissues compared to adjacent normal tissues, while upregulation of MEG3 could remarkably increase p53 protein level by decreasing levels of MDM2. In addition, DNA methylation was reported in 96% of NSCLC tissues in MEG3 promoter and associated with its downregulation [70]. Another report demonstrated that expression of MEG3 in NSCLC cell lines was negatively correlated with miR-205-5p whose expression enhanced cell proliferation and repressed apoptosis through targeting low-density lipoprotein (LDL) receptor-related protein-1 (LRP1). Previous studies reported that LRP1 acted as a tumor suppressor in cancer [148, 149]. However, MEG3 may act as a competing endogenous RNAs (ceRNA) to increase expression of LRP1 by competitively binding miR-205-5p in NSCLC. In addition, overexpression of MEG3 enhanced p53, p21 and caspase-3 protein levels, while miR-205-5p upregulation suppressed these proteins [46]. Despite the fact that MEG3 suppress EMT process, Terashima et al. found that MEG3 interact with JARID2, the cofactor of PRC2, thus enhanced accumulations of JARID2 and PRC2 that were involved in TGF-β-dependent regulation of H3K27 methylation and EZH2 assembly on the regulatory regions of CDH1 and miR-200 family genes therefore induced EMT process in A549 and LC-2/ad lung cancer cell lines. However, MEG3 knockdown could represent a mechanism for the silencing of EMT process through blocking EZH2 assembly, H3K27 methylation, and transcriptional suppression of these genes [150]. On the other hand, MEG3 level was remarkably declined in cisplatin-resistant A549/DDP lung cancer cells. In contrast, increased expression of MEG3 enhanced the sensitivity of A549 cells to cisplatin and promoted apoptosis via p53 and Bcl-xl regulation [151].

Ovarian Cancer

Ovarian cancer is among the most lethal gynecological malignancy in the world [152]. Recent studies identified a number of lncRNA associated with ovarian cancer including ASAP1-IT1 [153], BACE1-AS [154], BCYRN1 [155] CRNDE [156], FAL1 [157], and HOST2 [158]. Researchers observed that MEG3 expression was lost in more than 70% of ovarian cancer tissues which is consistent with hypermethylation of the MEG3 promoter. However, absence of MEG3 expression correlated to grade of the tumor. Noteworthy, 5-aza-CdR treatment induced MEG3 levels in OVCAR3 cells. Upregulation of MEG3 expression was elevated p53, GDF15 and RB1 mRNA and protein levels and this caused prolifration inhibition and apoptosis [159]. MEG3 also capable to initiate atuophagy through increased levels of LC3, LAMP1, and

ATG3 (autophagy-related proteins) while decrease p62. MEG3 interact with ATG3 resulting in type II cell death. Furthermore, overexpression of MEG3 enhance stabilization and prevent decay of ATG3 after treated with actinomycin [160].

Osteosarcoma

Osteosarcoma is the most common primary skeletal malignancy in the world [161]. Aberrant expression of specific lncRNAs led to osteosarcoma. For instance, HOTAIR [162], MALAT1 [163], H19 [164], SNHG12 [165], and MFI2 [166]. MEG3 expression was significantly diminished in osteosarcoma patients and remarkably associated with clinical stage, distant metastasis, and poor survival [167]. Re-expression of MEG3 in osteosarcoma cell lines induced expression of p53 through decreasing expression of MDM2 and its target gene MMP9. Although MEG3 enhanced expression of caspase-3 while reduced expression of Bcl-2 and cyclin D1. Therefore, MEG3 could inhibit cell proliferation and induce apoptosis [47]. Among miRNAs, miR-664a was upregulated in osteosarcoma which function as an onco-microRNA through suppression of MEG3 expression. However, reducing expression level of miR-664a induced expression of MEG3 [168].

These findings imply that MEG3 suppresses progression and enhances apoptosis of cancer. Nevertheless, the precise molecular roles of MEG3 need to be elucidated. More advanced studies are necessary to determine the association between MEG3 and EMT process. Table 1 summarizes the role of MEG3 in cancer.

The Role of MEG3 and miRNAs in Cancer

Increasing data provides a role for the MEG3 to repress cell proliferation and promote apoptosis through interacting or sponging and sequestering miRNAs from their target genes. It has been detected that MEG3 is required for suppression EMT process through miRNAs. Interestingly, MEG3 could suppress Hh-mediated EMT process in hepatic stellate cells by sponging miR-212 and reducing Smo (Smoothened) protein to regulate Hh (Hedgehog) pathway activation while miR-212 could increase Ptch1 protein [169]. Moreover, renal fibrosis symptoms include EMT of tubular epithelial cell and thus can be induced by TGF-β1. However, upregulated expression of MEG3 by help of miR-185, the negative regulator of DNMT1, is associated with inhibition of TGF-β1-induced renal fibrosis [170]. Besides, MEG3 may function as a ceRNA to increase expression of RASL11B by competitively binding miR-7 to enhance G0/G1 cell cycle arrest and apoptosis in clear cell renal cell carcinoma [171]. Moreover, MEG3 is negatively regulating miR-499-5p to induce expression of CYLD which acts as an antitumor by suppressing JNK/AP-1 and β1-integrin signaling pathways in melanoma tissues consistently promoting cell apoptosis [172]. MEG3 also enhanced the expression of Bax and decreased bcl-2 in chronic myeloid leukemia cells through silencing the expression of miR-21 to inhibit proliferation and induce apoptosis [173]. Although high MEG3 expression levels inhibited miR-16 expression, thereby increasing levels of SMAD7 in IL-1β-induced chondrocytes of rat osteoarthritis model [174]. However, MEG3 acts as a tumor suppressor in leukemia through competitively binding miR-184 [175]. Also, miR-29 enhanced MEG3 expression to inhibit HCC progression by targeting DNMT-1 and DNMT3B [176]. In gastric cardia adenocarcinoma, researchers found that expression of miR-770 and its host gene MEG3 were decreased due to aberrant hypermethylation [177]. Surprisingly, MEG3 promoted osteosarcoma cells proliferation and metastasis through sponging miR-127, the negative regulator of JNK and Wnt signaling pathways through reducing ZEB1 levels [178].

Emerging reports had found that miRNAs played a key role in chemotherapy. Remarkably, overexpression of MEG3 in CRC cells was improved sensitivity to oxaliplatin through serving as an endogenous sponge of miR-141 to induce expression of PDCD4 (programmed cell death 4) [179]. Moreover, MEG3 induced sensitivity to cisplatin in NSCLC cells through sponging miR-21-5p and this cause SOX7 expression by [180]. Although MEG3 expression in thyroid carcinoma enhanced the sensitivity to radioiodine (^{131}I) treatment and promoted apoptosis and DNA damage through sponging miR-182 [181]. Furthermore, curcumin upregulates expression of MEG3, leading to the silencing of miR-214 in ovarian cancer cells and decreasing extracellular vesicles, which contributes to suppression of chemoresistance [182].

Overall, several studies revealed that MEG3 display an important role in cancer through interacting with different miRNAs to regulate target genes, however, dysregulation these interactions are closely associated with the initiation and progression of cancer. The network visualization ONCOIO was used to link target genes with miRNAs mentioned in the text (Fig. 3).

Conclusion(S)

The Human Genome Project was the gate of discovering that much of the genome consist of ncRNA genes were initially considered as "junk" or "noise". Recently, with the development of technologies such as high-throughput sequencing and microarray to whole genome gives an evidence of the contribution of ncRNAs in various pathways. Aberrant expression of lncRNAs is associated with different cancer types progression and diseases; however, few have been recognized as a drop in the sea. Several lncRNAs involved in the regulation of p53 directly or indirectly, including MEG3

Table 1 MEG3 molecular mechanism in different cancer

Cancer type	MEG3 Role	Cell Biology	Clinicopathological features	Related gene/ miRNA	Molecular Mechanism	Reference
Breast	• Decrease MDM2 mRNA levels • Repress cell invasion and EMT process • RNA-DNA triplex formation to enable the recruitment of transcriptional repression proteins	MEG3 inhibit tumor cells proliferation, migration and invasion	Differentiation grade, TNM stage, lymph nodes metastasis and overall survival	E-cadherin, H3K27me3, KAI1's, Maspin, miR-421, p21, PRC2, SMAD2, TGFB2, TGFBR1, TP53, Vimentin, ZEB1, ZEB2	• MEG3 enhance the binding of p53 to metastasis suppressor genes after decreasing levels of MDM2 • MEG3 block EMT process by sponging miR-421 and subsequently upregulating E-cadherin resulting in decrease cell invasion proteins • GA-rich motifs able to direct MEG3 to its target genes PRC2 and H3K27me3 to target sites, such as TGF-β pathway genes	[86–89]
Liver	• Increase ADH4 levels • Negatively regulate the activity of glycolytic enzyme, PKM2 • β-catenin degradation • Activating caspase-3	Induce cell apoptosis and suppress cell proliferation	–	ADH4, C-Myc, Col1A1, CREB, cyclin D1, Ets, miR122, MiR-664, NF-κB, PKM2, PTEN2, Stat3, Stat5, Stat6, TP53, α-SMA, β-catenin	• MEG3 negatively regulate miR-664 expression resulting in increased ADH4 • MEG3 boost the expression and maturation of miR122 which is decreased PKM2 levels and therefore suppressed expression of cyclin D1 and C-Myc • MEG3 increased the expression and phosphorylation of ubiquitin-proteasome system dependent on PTEN2 resulting in degradation of β-catenin • MEG3 decreased α-SMA and Col1A1 expression in TGF-β1 treated cells • MEG3 activated p53 and mediate-cytochrome c release, therefore, activating caspase-3	[95–97]
Glioma	• Induce G0/G1 arrest • Suppress accumulation of β-catenin and the transcription of several oncogenes • Induce PTEN expression • Inhabit the role of miR-93 • Suppress the PI3K/AKT pathway	Induce cell apoptosis and suppress cell proliferation	Tumor grade and overall survival	Caspase-3, caspase-9, Ki67, miR-19a, miR-93, PCNA, PI3K, PTEN, TP53, Wnt/β-catenin	• MEG3 block proliferation by inducing p53 expression • MEG3 inactivated Wnt/β-catenin signaling • MEG3 suppressed PI3K through sponging miR-19a resulting in inducing PTEN expression • MEG3 may decreased expression of Ki67 and PCNA while upregulated the level of caspase-3 and caspase-9	[102–106]
Colorectal	• Accumulation of p53 protein • Inhibit Clusterin transcription • Enhance the chemoresponse • MEG3 SNPs contribute to increase risk of CRC	Induce cell apoptosis and suppress cell proliferation	Histological grade, tumor invasion depth, TNM stage and overall survival	Clusterin, cyclin D, TP53	• The upregulation of MEG3 associated with Clusterin transcription inhibition • Vitamin D treatment or vitamin D receptor increased MEG3 expression through regulating Clusterin	[115–118]
Cervical	• Induce G2/M cell cycle arrest	Induce cell apoptosis and	Tumor size, advanced FIGO stage, lymph	Bax, Bcl-2, caspase-3, EZH2, miR-21-5p, MMP-2, MMP-9, p21, PI3K/Akt, TP53	• Re-expression of MEG3 levels participated at least in part to p53 and caspase-3 accumulations through miR-21-5p suppression	[125–129]

Table 1 (continued)

Cancer type	MEG3 Role	Cell Biology	Clinicopathological features	Related gene/ miRNA	Molecular Mechanism	Reference
	• Methylation level of MEG3 promoter associated with shorter recurrence-free survival. • Methylation of MEG3 might serve as a biomarker	suppress cell proliferation	nodes metastasis and HR-HPV infection		• MEG3 regulated PI3K/Akt signaling pathway, and controlling MMP-2, MMP-9, Bax, Bcl-2 and p21 expressions to promote apoptosis	
Gastric	• Promote p53 expression • upregulate Bcl-2 • Positive correlation with miRNA	Suppress the proliferation and metastasis	TNM stages, depth of invasion, tumor size and overall survival	Bcl-2, DNMT1, miR-148a, miR-181, TP53	• MEG3 expression upregulated Bcl-2 by sequestering miR-181 family • miR-148a enhances MEG3 expression by directly targeting DNMT1	[136–139]
Lung	• Increase p53 protein • Increase expression of LRP1 • Interact with JARID2 • Induce EMT • Enhance the chemoresponse	Growth arrest and induce apoptosis	Tumor size, lymph nodes metastasis and TNM stage	Caspase-3, CDH1, EZH2, JARID2, LRP1, MDM2, miR-200, miR-205-5p, p21, PRC2, TGF-β, TP53	• MEG3 elevated p53 protein level by decreasing MDM2 level • MEG3 act as a sponge of miR-205-5p to induce expression of LRP1 • MEG3 enhanced expression p53, p21 and caspase-3 • MEG3 enhanced accumulations of JARID2 and PRC2 that were involved in TGF-β-dependent regulation	[46, 70, 148–151]
Ovarian	• Initiate autophagy • potential biomarker	Inhibit cell proliferation and induce cell apoptosis	Grade of the tumor	ATG3, GDF15, LAMP1, LC3, TP53, P62, RB1	• Upregulation of MEG3 expression was elevated p53, GDF15 and RB1 levels • MEG3 increased levels of LC3, LAMP1, and ATG3 and decreased p62.	[159, 160]
Osteosarcoma	• Induce the expression of p53 • Negative correlation with onco-microRNA	Inhibit cell proliferation and induce cell apoptosis	Associated with clinical stage, distant metastasis, and poor survival	Bcl-2, caspase-3, cyclin D1, MDM2, miR-664a, MMP9	• Induce the expression of p53 through decreasing MDM2 and MMP9 while enhanced caspase-3 and reduced the expression of Bcl-2 and cyclin D1	[47, 167, 168]

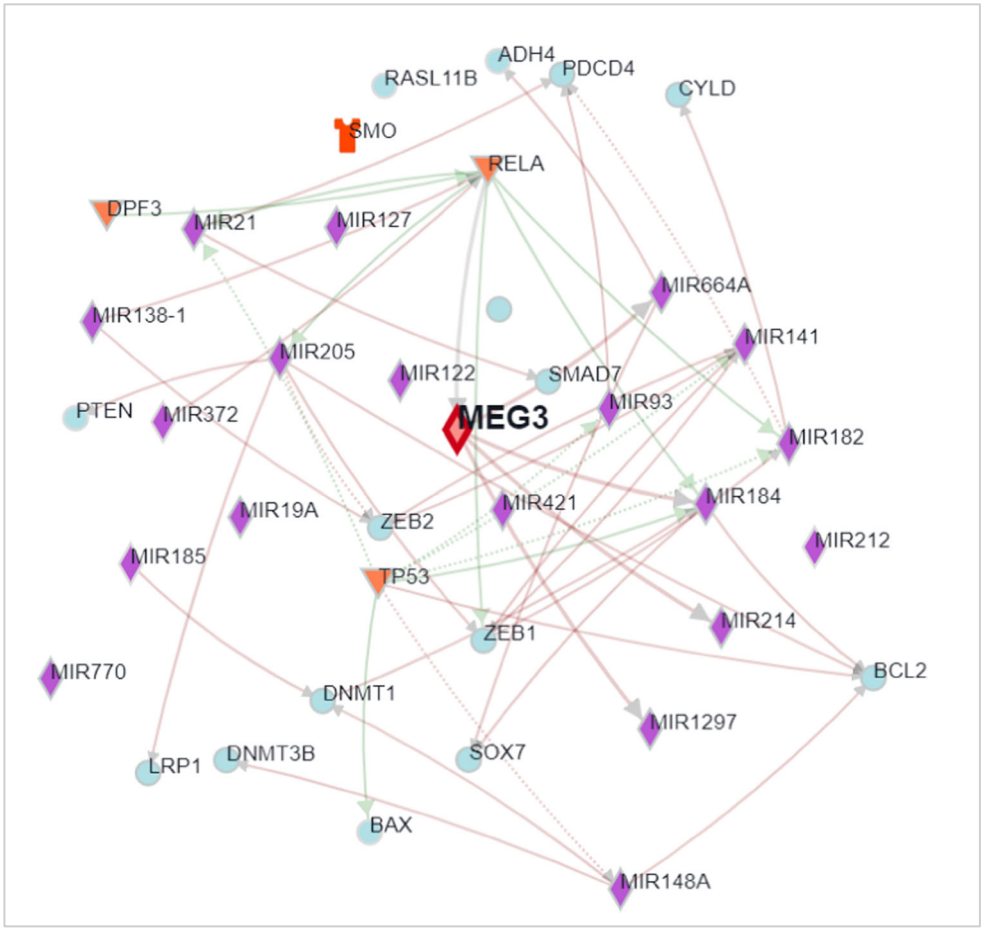

Fig. 3 The MEG3-miRNA-mRNA network. The rombus represent MEG3 and miRNA and circles indicate mRNAs

which act as a tumor suppressor in several types of cancer. Researchers have reported the mechanisms of MEG3 to suppress cancer include the stimulation of p53 and Rb pathways while inhibiting their negative regulator MDM2. In particular, MEG3 involved in the inhibition of EMT, contribution with miRNAs, preventing angiogenesis, regulation of PI3K/Akt and Wnt/β-catenin signaling pathways. Thus, MEG3 regulate genes at the DNA, RNA, or protein level to inhibit cell proliferation and induce apoptosis. Interestingly, epigenetic changes in MEG3 promoter abolish its function. Although MEG3 may act as a cancer biomarker and enhance the chemoresponse. Further characterization of the MEG3 mechanism will clarify how MEG3 control several pathways and elucidate its association with miRNAs and maybe other lncRNAs to provide prognostic biomarker and cancer therapeutic.

Acknowledgments This work was supported by the King Abdulaziz City for Science and Technology (KACST) under the grant 1-17-01-001-0066.

Compliance with Ethical Standards

Conflict of Interest We declare that we have no conflict of interest.

Acronyms and Abbreviations *CRC*, Colorectal cancer; *cAMP*, Cyclic AMP; *DMRs*, Differentially methylated regions.; *DBD*, DNA binding domain; *DNMTs*, DNA methyltransferases; *URHF1*, E3 ubiquitin-protein ligase; *GDF15*, Growth/differentiation factor-15; *HCC*, Hepatocellular carcinoma; *HDACs*, Histone Deacetylases; *HIF-1α*, Hypoxia-Inducible Factor; *IG-DMR*, Intergenic DMR; *MEG3*, Maternally expressed gene 3; *MDM2*, Murine/human double minute 2; *NSCLC*, Non-small cell lung cancer; *PCNA*, Proliferating-cell nuclear antigen; *CRE*, Response element; *Rb*, `Retinoblastoma; *TET2*, The ten–eleven translocation; *TGF-β*, Transforming growth factor; *TNM*, Tumor node metastasis; *TP53*, Tumor Suppressor Protein p53; *VEGF*, Vascular endothelial growth factor

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