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Maternally expressed gene 3 (*MEG3*): A tumor suppressor long non coding RNA

Soudeh Ghafouri-Fard[a], Mohammad Taheri[b,c,*]

[a] Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Urogenital Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Maternally expressed gene 3 (*MEG3*) is a long non-coding RNA (lncRNA) located on chromosome 14q32.3. Direct sequencing experiments have shown monoallelic expression of this lncRNA. Several studies have shown down-regulation of this lncRNA in human cancers. In some cases, hypermethylation of the promoter region has been suggested as the underlying mechanism. Functional studies have shown that this lncRNA controls expression of several tumor suppressor genes and oncogenes among them are p53, RB, MYC and TGF-β. Through regulation of Wnt-β-catenin pathway, it also affects epithelial-mesenchymal transition. *In vitro* studies have demonstrated contribution of *MEG3* in defining response to chemotherapeutic agents such as paclitaxel, cisplatin and oxaliplatin. Certain polymorphisms within MEG3 are implicated in cancer risk (rs7158663, rs4081134 and rs11160608) or therapeutic response of cancer patients (rs10132552). Taken together, this lncRNA is regarded as a putative cancer biomarker and treatment target. In the current review, several aspects of the participation of *MEG3* in carcinogenesis are discussed.

1. Introduction

Human *maternally expressed gene 3* (*MEG3*) and its mouse homologue (*Meg3*) have been identified through a subtraction-hybridization strategy using androgenetic and normally fertilized embryos and subsequent EST database searching [1]. This gene has been mapped on distal chromosome 12 and chromosome 14q in mouse and human respectively [1]. Alternative RNA splicing has resulted in production of numerous transcript isoforms from this genetic locus. The principally expressed isoform includes exons 1–4 and 8–10 [2]. Sequence analyses failed to identify significant open reading frame in *MEG3*, so this gene has been further classified as a long non-coding RNA (lncRNA). *MEG3* is a chromatin-interacting lncRNAs that interacts with the polycomb repressive complex 2 (PRC2). This lncRNA has similar targets with EZH2 among them are genes involved in the transforming growth factor-β (TGF-β) pathway. *MEG3* recognizes its targets through RNA–DNA triplex establishment [3]. The first evidences for contribution of *MEG3* in human cancers have been obtained from pituitary non-functioning adenomas where expression of this gene is totally lost [2]. Subsequently, expression of *MEG3* was shown to be decreased in several cancer types. Allelic loss of *MEG3* has been detected in high grade meningiomas but not low grade ones [4]. Promoter hypermethylation is another underlying cause of *MEG3* down-regulation in non-functioning adenoma [5], meningioma [4] and neuroblastoma [6]. A number of miRNAs have been shown to regulate expression of *MEG3* at post-transcriptional level. In turn, *MEG3* acts ac competing endogenous RNA for a number of miRNAs [7].

MEG3 regulates expression p53 tumor suppressor gene and induces p53-dependent transcription through different mechanisms. First, it decreases MDM2 levels and subsequently inhibits ubiquitin-mediated degradation of p53. This speculation has been verified by the observed down-regulation of MDM2 after forced over-expression of *MEG3* [8]. *MEG3* can also directly bind with DNA binding domain of p53 and numerous p53 target genes. Co-transfection of a p53-responsive reporter vector with *MEG3* expression vector has shown that *MEG3* augments the transcriptional activity of p53. Construction of deletion mutants of *MEG3* has confirmed that all three domains of *MEG3* are needed to stimulate the transcriptional activity of p53. As *MEG3* up-regulation has enhanced protein levels of p53 without affecting its transcript levels, it probably increases the stability of the p53 protein. Besides, *MEG3* and p53 direct interaction is mediated by M3 domain of MEG3 and DNA binding domain of p53 [9]. Notably, *MEG3* can suppress cell proliferation even in the absence of p53 [8]. Expression of this lncRNA has been up-regulated in endothelial cells following p53

* Corresponding author at: Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail address: mohammad.taheri@sbmu.ac.ir (M. Taheri).

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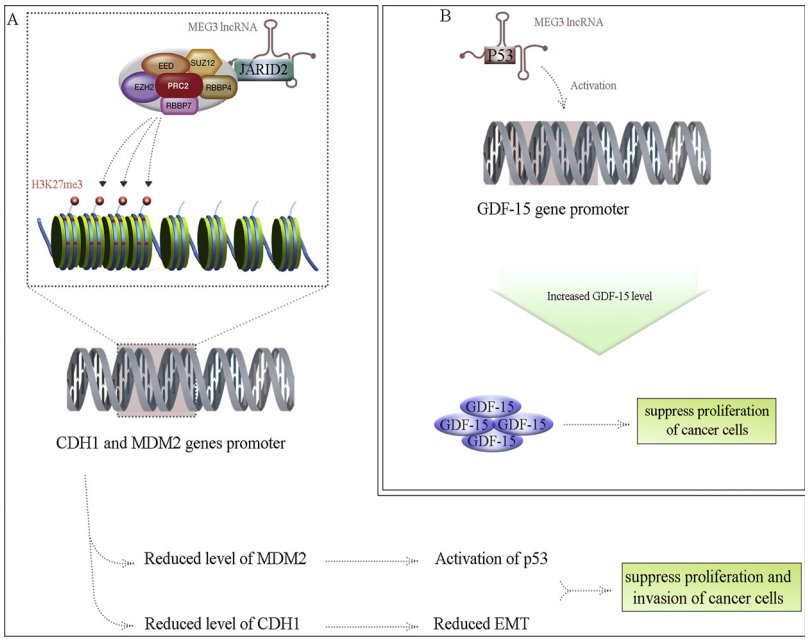

Fig. 1. (A) *MEG3* interacts with PRC2 and its cofactor JARID2 to regulate expression of genes related to TGF-β signaling through trimethylation of histone H3 at lysine 27 (H3K27me3). Expression of CDH1 and MDM2 is inhibited through this mechanism [3,8]. MDM2 has been regarded as one of the downstream targets of TGF-β [13]. CDH1 expression is inhibited by TGF-β-SNAI2 signaling in the process of epithelial-mesenchymal transition [14]. (B) *MEG3* directly binds to p53 and increases its stability. Growth differentiation factor 15 (GDF15) is among p53 targets whose expression is increased by *MEG3* [8,9].

activation [10]. Fig. 1 shows the molecular mechanism of *MEG3* interaction with p53 and its effects on TGF-β signaling.

MEG3 has interactions with the other important tumor suppressor namely retinoblastoma protein (Rb). *MEG3* expression is modulated by this tumor suppressor in association with cell proliferation. Genetic deletion of Rb family members in mice has resulted in remarkable silencing of *MEG3* expression. Conversely, activation of pRb enhanced the expression of *MEG3* [11]. *MEG3* effects on Rb can be exerted directly by modulation of Rb phosphorylation and indirectly by induction of $p16^{INK4A}$ which enhances Rb expression [12].

Moreover, *MEG3* has distinct interactions with the PRC2 complex. Such interaction contributes in regulation of expression of transforming growth factor-β (TGF-β) pathway genes. An altered chromatin oligo affinity precipitation (ChOP) strategy has shown direct interactions between a number of TGF-β pathway genes and *MEG3*. Further experiments have shown the role of GA-rich sequences in facilitation of *MEG3* RNA transport to these target sequences [3].

1.1. Expression of MEG3 in human cancers

Consistent with the proposed tumor suppressor role for *MEG3*, several studies have reported down-regulation of this lncRNA in tumoral tissues compared with non-tumoral tissues of the same origin (Table 1). *MEG3* over-expression has halted cell proliferation and induced apoptosis in several cancer cell lines including lung cancer [15], squamous cell carcinoma [16], gastrointestinal cancer [17] and so on. Contrary to the bulk of evidence, Wang et al. have shown over-expression of *MEG3* in osteosarcoma cell lines when compared to a human osteoblast cell line. Knock down of this lncRNA inhibited cells growth and metastasis and induced apoptosis in an osteosarcoma cell line through modulating the expression of miR-127 [18]. However, other studies in osteosarcoma cell lines sand clinical samples did not confirm the results of the mentioned study [19–21]. A recent pilot study has shown higher levels of *MEG3* in plasma samples obtained from colorectal cancer patients compared with non-cancerous controls [22].

1.2. Diagnostic/ prognostic value of MEG3

A pilot study has shown that a three-lncRNA panel including *91H*, *PVT-1* and *MEG3* can differentiate colorectal cancer patients from non-cancerous individuals with area under curve (AUC) value of 0.877, sensitivity of 82.76% and specificity of 78.57%. Notably, this panel was more sensitive (but not more specific) in the recognition of early-stage patients than the combination of two traditionally used biomarkers namely carcinoembryonic antigen (CEA) and CA19-9 [22]. Several studies have shown association between expression level of this lncRNA and patients' survival. A systematic literature search has shown association between *MEG3* down-regulation and poor patients' outcome in the pooled analysis [106]. Moreover, hypermethylation of *MEG3* in plasma has been linked with poor outcome in cervical cancer patients [107]. Table 2 summarizes studies reporting diagnostic/prognostic value of *MEG3* in cancers.

1.3. MEG3 polymorphisms and cancer

Cao et al. have genotyped six tag single nucleotide polymorphisms (SNPs) of *MEG3* in a population of Chinese colorectal cancer patients and healthy subjects. They reported that *MEG3* rs7158663 AA genotype, but not the heterozygote genotype, confers risk of colorectal cancer in this population. Although the increased risk was correlated with lower age of disease onset and family history of cancer, it was not associated with tumor site or stage [114]. Zhou et al. have genotyped rs7158663 and rs4081134 in neuroblastoma children and controls. Although they found no association between mentioned SNPs and neuroblastoma risk, they reported associations between rs4081134 AG/AA genotypes and early disease onset and high clinical stage. They suggested *MEG3* as a weak-effect risk locus for this kind of cancer [115]. Yang et al. have genotyped these two SNPs in a population of Chinese patients with lung cancer and healthy subjects. They reported associations between rs4081134 AA genotype and risk of lung cancer in total participants as well as several subgroups analyses. However, they did not find association between rs7158663 SNP and lung cancer [116]. Recently, Hou et al. have assessed association between selected *MEG3* SNPs and risk of oral squamous cell carcinoma. They demonstrated significant associations between rs11160608 CC genotype and cancer risk especially among drinkers [117]. Finally, assessments in a population of nasopharyngeal cancer patients have shown association between *MEG3* rs10132552 CC genotype and higher risk of grade 3–4 anemia following chemoradiotherapy (CRT). Besides, the rs10132552 CT genotype was associated with better response to CRT [118]. Table 3 summarizes the data on the association between *MEG3* polymorphisms and cancer risk or therapeutic response.

Table 1
Summary of studies regarding the role of *MEG3* in human cancers.

Cancer type	Sub-type	Expression pattern	Numbers of clinical samples (tissues, serum, *etc.*)	Assessed cell line	Targets/Regulators	Signaling Pathways	Function	Ref.
Lung cancer	NSCLC	–	–	A549, A549/DDP	p53, β-catenin, survivin	WNT/β-catenin signaling	↓cisplatin resistance, ↑apoptosis	[23]
			–	A549, SK-MES-1	Rb, p107, DNMT1,	RB pathway	↓Proliferation, ↑apoptosis	[15]
				A549, LC-2/ad	TGF-β, CDH1, EZH2, miR-200a, miR-200c, E-cadherin, ZEB1, ZEB2, JARID2	EMT		[24]
				A549	p53		↑Response to paclitaxel, ↓ proliferation, ↑apoptosis	[25]
		Down	46 resected tumor tissues (23 cisplatin-sensitive and 23 cisplatin-resistant)	A549, H1299,	miR-21-5p, SOX7		↓Proliferation, ↑apoptosis, ↑ response to cisplatin	[26]
			41 tumor tissues from advanced LAD patients	A549, A549/DDP	p53, Bcl-xl		↓cisplatin resistance, ↑apoptosis, ↓proliferation	[27]
			44 paired tissues	A549, SPC-A1, NCI-H1650, NCI-H358, NCI-H1299, NCI-H1975, SK-MES-1, 16HBE	p53		↓Proliferation, ↑apoptosis, ↓ invasion	[28]
			20 paired tissues	A549	Skp2, p27, miR-3163		↓cell growth	[15]
			40 paired tissues	H1299,	MYC		↓Proliferation, ↑apoptosis, ↓ migration	[29]
			72 paired tissues	BEAS-2B, A549, HCC823	MicroRNA-7-5p, Bcl-2, Bax, BRCA1		↑Apoptosis	[30]
Nasopharyngeal cancer			39 primary cancer samples and 22 noncancerous nasopharyngeal epithelia	C666-1, HK-1, NP69, NP361, NP460, xeno-666, xeno-2117, xeno-1915, xeno-99186, C15, C17	p53		↓Proliferation, ↓colony formation	[31]
Breast cancer		–	–	BT-549, MDA-MB-231, HF,	PRC2, EZH2	TGF-β signaling pathway		[32]
				MDA-MB-231, MCF7,	GRP78, IRE1, PERK, ATF6, CHOP, caspase-3, NF-κB, p53	NF-κB and p53 signaling	↓tumor growth, ↑apoptosis	[33]
		Down		MDA-MB-231, MCF-7, MCF-10A, HMEC-1,	SDF-1, VEGFA, VEGFB, PGF, bFGF, TGF-β1, Angiogenin, MMP-9	AKT pathways	↓cell growth, ↓ invasion, ↓ angiogenesis, ↓proliferation	[34]
			90 paired tissues	MDA-MB-231, MCF-7, SKBR3, MCF-10A,	MiR-421, E-cadherin,	EMT	↓Proliferation, ↓invasion	[34]
			207 paired tissues					[35]
			20 paired tissues	MCF-7, MDA-MB-231, MDA-MB-453, T47D, MCF-10A	miR-21,	PI3K/Akt pathway	↓tumor growth, ↓cell proliferation, ↓glycolysis, ↑ apoptosis	[36]
			20 paired tissues	MCF-7, MDA-MB-231, SKBR3, HEK 293T, MCF10A	SP3, DNMT1, miR-506, SP1,		↓Migration, ↓invasion	[37]
Tongue cancer	SCC	Down	76 paired tissues	HOK, SCC-15, CAL27	MiR-26a, DNMT3B		↓Proliferation, ↑apoptosis	[16]
Oral cancer	SCC	Down	83 paired tissues	SCC15, Cal27,		WNT/β-catenin signaling pathway	↓Proliferation, ↑apoptosis, ↓ migration, ↓metastasis	[38]
Esophageal cancer	SCC	Down	96 paired tissues	KYSE-410, HEEC, ECA-109, TE-1, TE-13	p53, MDM2		↓Proliferation, ↑apoptosis, ↓ metastasis	[39]
			28 paired tissues	EC109,	GRP78, IRE1, PERK, ATF6, CHOP, caspase-3	ER stress pathway	↓Proliferation, ↑ apoptosis	[40]
			143 paired tissues	TE1, TE13, Eca109, YES2, T.Tn, HEEpiC	miR-9, FOXO1, E-cadherin		↓Proliferation, ↓invasion	[41]

(*continued on next page*)

Table 1 (*continued*)

Cancer type	Sub-type	Expression pattern	Numbers of clinical samples (tissues, serum, *etc.*)	Assessed cell line	Targets/Regulators	Signaling Pathways	Function	Ref.
Gastric cancer		Down	72 paired tissues	SGC7901, AGS, MGC803, MKN45, BGC823, GES-1	p53		↓Proliferation, ↑apoptosis	[17]
			30 gastric cancer tissues and 30 normal tissues	AGS, NCI-N87, SGC-7901, MKN-45, TMK-1, GES-1	miR-21	EMT	↓Invasion, ↓migration, ↓cell mobility, ↓tumor growth, ↓ metastasis	[42]
			82 paired tissues				↓lymph node metastasis	[42]
			30 paired tissues	MKN74, MKN45, SGC7901, AGS, GES-1	MiR-21	MEG3/miR-21 axis	↓Proliferation, ↓ metastasis	[43]
			31 paired tissues	SGC7901, BGC823, MKN45, HGC27, GES-1		p53 signaling pathway	↓Proliferation, ↓ metastasis	[44]
			50 paired tissues	MGC-803, HGC-27, MKN-45, SGC-7901, BGC-823, AGS	miR-181 family, Bcl-2		↓Proliferation, ↓migration, ↓ invasion, ↑apoptosis	[45]
			75 tumor samples and 75 normal tissues	SGC-7901, MKN45, HEK-293 T, GES-1	MiR-141, E2F3		↓Proliferation, ↓cell cycle progression, ↑apoptosis, ↓cell growth	[46]
			134 paired tissues	MKN45, SGC7901, BGC823, AGS	miR-770		↓Proliferation, ↓ invasion	[47]
			52 gastric cancer samples	SGC-7901, BGC-823 GES-1	miR-148a, DNMT-1		↓Proliferation	[48]
			50 paired tissues					[49]
Colon cancer		Down	62 paired tissues	HCT-116, DLD-1			↓Proliferation	[50]
			80 oxaliplatin-responding tissues and 80 non-responding tissues + serum samples from 70 patients showing response to oxaliplatin and 70 showing no response	HT29, SW480			↓Chemoresistance to oxaliplatin, ↑apoptosis	[40]
			61 paired tissues	RKO, SW1116, HT29, HCT116, LoVo, SW620, SW480, 293 T	Clusterin	Vitamin D Signaling	↓Proliferation, ↓ tumor growth, ↓ migration, ↓metastasis	[51]
			84 paired tissues	NCM460, SW480, HT29, HCT116, HT29/OXA, HCT116/OXA	miR-141, PDCD4		↓oxaliplatin resistance	[52]
			84 paired tissues + Serum samples 34 healthy controls and CRC patients	Hs 698.T, Hs 255.T, SNU-C1,	SPHK1, TGF-β1		↓ Proliferation, ↑apoptosis	[53]
		Up	Plasma samples of 58 cancer patients and 56 healthy individuals					[22]
Pancreas cancer	PNET	–	–	MIN6-4 N, Vec-4 N, M27-4 N,	c-MET, EZH2, HGF,		↓Proliferation	[54]
			–	HEK293, CCL-153, EC-304, BON1, QGP-1,	Cyclin E1, CDK1, Cyclin D1, CDK4, caspase-3, caspase-9, Bcl-2, miR-183, BRI3	p38/ERK/AKT and Wnt/β-Catenin	↓Metastasis, ↓cell viability, ↑ apoptosis, ↓migration, ↓invasion, ↓cells growth	[55]
				PANC-1, SW1990	p53		↓Proliferation, ↑chemo-response to fenofibrate	[56]
		Down	30 paired tissues	PANC-1	PI3K, AKT, Bcl-2, Bax, Cyclin D1, p53, MMP-2, MMP-9	PI3K/AKT/Bcl-2/Bax/ Cyclin D1/p53 and PI3K/AKT/MMP-2/ MMP-9	↓Proliferation, ↑apoptosis, ↓ invasion	[47]
			25 paired tissues	SW 1990, COLO357, MIA PaCa-2, T3M4, AsPC-1, BxPC-3, CAPAN-1 PANC-1, hTERT-HPNE	Snail	EMT	↓Proliferation, ↓migration, ↓ invasion, ↓chemoresistance	[57]

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Table 1 (*continued*)

Cancer type	Sub-type	Expression pattern	Numbers of clinical samples (tissues, serum, *etc.*)	Assessed cell line	Targets/Regulators	Signaling Pathways	Function	Ref.
Liver cancer		–	–	HepG2, HuH-7	miR-29a, miR-185, DNMT1, 3A, 3B,		↑Chemo-response to DNMT1, 3A and 3B	[58]
				HepG2, Huh-7, HEK293	p53, caspase-3, MDM2, cyclin D1, ILF3		↓Cell growth, ↑apoptosis	[59]
				HepG2	NF-κB, p53, GRP78, IRE1, PERK, ATF6, CHOP, caspase-3, Bay11-7082	ER stress pathway	↓Proliferation, ↑apoptosis	[59]
				Hep3B	miR122, PKM2, β-catenin, PTEN, GSK3β, CyclinD1, C-Myc		↓Cell growth	[51]
				SMMC-7721, Huh-7, MHCC97H, HCCLM3, L02	PKM2	EMT	Interaction with Arsenic trioxide	[60]
		Down		HCC Huh-7, SMMC-7721, HepG2, 7402, L02	miR-664, ADH4, NF-κB		↓Proliferation, ↓colony formation	[61]
			72 paired tissues	HepG2, SNU423, SMMC-7721, MHCC97H, 97 L, Hep3B, L02	p53, UHRF1, DNMT1		↓Proliferation, ↑apoptosis	[62]
			23 paired tissues	HepG2, SK-Hep–1, HEK293, HCT116,	p53		↓Growth, ↓proliferation, ↑ apoptosis	[63]
			46 paired tissues	HepG2, Hep3B, MHCC97H, SMCC-7721, L02	miR-26a, DNMT3B		↓Proliferation, ↓ migration, ↓ invasion, ↓metastasis	[64]
			72 paired tissues	THLE-3, SMMC-7721, Hep3B, BEL-7402, LM3	AP1G1	PI3K/AKT Pathway	↓Proliferation, ↓invasion	[65]
Gallbladder cancer		Down	84 paired tissues	GBC-SD, QBC939	p53, cyclin D1, caspase 3		↓Proliferation, ↑apoptosis	[66]
			50 paired tissues	NOZ, GBC-SD, SGC-996, EH-GB1, OCUG-1, H69,	EZH2, LATS2	EMT	Proliferation, ↑apoptosis, ↓ invasion, ↓tumorigenesis	[67]
Cervical cancer		–	–	Hela	PI3K, AKT, MMP-2, MMP-9, Bcl-2, Bax, P21		↓Proliferation, ↑ apoptosis, ↓ invasion	[68]
		Down	18 paired tissues	HeLa, C-33A, HCC94			↓Proliferation, ↑apoptosis	69]
			108 paired tissues	HeLa, CaSki	miR-21-5p, p53, caspase 3		↓Proliferation, ↑apoptosis, ↓ tumor growth	[70]
			72 paired tissues	HeLa, CaSki			↓Proliferation	[71]
			20 normal cervical epithelium tissue samples, 20 cervical intraepithelial neoplasia tissue samples, 20 cervical squamous cell carcinoma tissue samples	HcerEpic, C-33A, C4-1, Caski, SiHa, Hela	Rac1	Rac1 pathway, EMT	↓Migration, ↓invasion, ↓cell survival, ↓proliferation	[72]
Endometrial cancer		Down	30 paired tissues	HEC-1A, KLE	Notch1, Hes1	Notch signaling pathway	↓Proliferation, ↓tumor growth	[73]
			63 tumor samples and 19 normal endometrial tissue specimens	Ishikawa, HEC-1B	PI3K, m-TOR, P70S6K, VEGFA, BCL-XL		↓Cell viability, ↓migration, ↓ invasion, ↓tumor growth	[74]
Ovarian cancer		–	–	SKOV-3, CAOV-3, OVCAR-3, HO-8910, A2780	PTEN		↓Proliferation, ↑apoptosis, ↓ invasion, ↓migration	[75]
				OVCAR-3, SKOV3, A2780, A2780cp	miR-214		↑Chemo-response to curcumin	[76]
	EOC	Down	20 normal ovaries and 20 EOCs tissues	OVCAR3, SKOV3, HP8910, ES-2	p53		↓Proliferation, apoptosis	[77]
Pituitary cancer		–	–	PDFS	p53		↓Tumor growth	[78]
		Down	14 clinically nonfunctioning tumors and 3 normal tissues					[79]
			38 human pituitary tumor tissues and 88 normal tissues		GADD45γ			[80]
			44 human pituitary adenomas tissues and 10 normal tissues		DLK1			[81]
Kidney cancer	–	Down	29 paired tissues	786-0, SN12, 293 T	Bcl-2, procaspase-9		↑Apoptosis, ↓cell viability	[82]
	CCRCC		72 paired tissues	HK-2, A-498, 786-O	MiR-7, RASL11B		↑Apoptosis, ↓proliferation, ↓ migration, ↓invasion	[83]

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Table 1 (*continued*)

Cancer type	Sub-type	Expression pattern	Numbers of clinical samples (tissues, serum, *etc.*)	Assessed cell line	Targets/Regulators	Signaling Pathways	Function	Ref.
Bladder cancer		Down	31 paired tissues	T24			↓Autophagy, ↑apoptosis, ↓ proliferation	[84]
			21 paired tissues	T24, 5637	p53, MMP2, MMP9, caspase-3, bax		↓Migration, ↓invasion, ↑chemo-response to cisplatin	[85]
			45 paired tissues	5637, RT4, RT-112, T-24, SV-HUC-1	Mir-96, TPM1, Bax, Bcl-2, Cyclin D1		↓Proliferation, ↑apoptosis, ↓ tumor growth	[75]
			27 paired tissues	UMUC3, T24T	c-Myc, c-Jun, PHLPP2, MAPK, miR-27a		↓Invasion	[86]
Prostate cancer		Down	21 paired tissues	PC3, DU145, HepG2	Bcl-2, Bax, caspase 3, Cyclin D1		↓Proliferation, ↑apoptosis, ↓cell viability, ↓tumorigenesis	[87]
			85 paired tissues	PC-3, DU145, VCaP, 22RV1, WPMY-1,	miR-9-5p, QKI-5		↓Proliferation, ↓migration, ↓ invasion, ↑apoptosis, ↓ tumor growth	[88]
Osteosarcoma		–	–	MG63, HOS	EWSAT1		↓Proliferation, ↓metastasis, ↓ migration, ↓invasion, ↓cell growth	[89]
		Up		MG63, 143B, G292, hFOB1.19, OS-732, SaOS,	miR-127, ZEB1	JNK and Wnt signaling pathways	↑cell viability, ↑ migration, ↑ invasion, ↓apoptosis, ↑metastasis, ↑cell growth	[18]
		Down	–	MG63, U2OS, hFOB 1 .19	Notch1, Hes1,TGF-β, *N*-cadheren, E-cadheren		↓Proliferation, ↓migration, ↓cell growth, ↓metastasis	[19]
			–	hFOB 1.19, U-2 OS,	miR-664a		↓Migration	[20]
			64 paired tissues					[21]
Retinoblastoma		Down	63 paired tissues	Weri-Rb1, Y79		Wnt/β-catenin	↓Proliferation, ↑ apoptosis	[90]
Melanoma		Down	42 paired tissues	A375, WM35, SK-MEL-5, SK-MEL-2, HEMa-LP	CYLD, miR-499-5p, *N*-Cadherin, Cyclin D1, E-cadherin		↓Proliferation, ↑apoptosis, ↓ metastasis, ↓invasion, ↓ migration, ↓ tumorigenesis	[91]
Thyroid cancer	PTC	Down	16 metastatic tissues *versus* matched group of non-metastatic tissues	TPC-1, HTH83, 293 T	Rac1		↓Cell migration, ↓ invasion	[92]
			20 paired tissues	FTC-133, TPC-1, 293 T,	miR-182		↑Apoptosis, ↓proliferation, ↑ radiosensitivity of ^{131}I, ↓cell viability	[83]
Glioma		–	–	U87			↑Apoptosis, ↑autophagy, ↓ cisplatin resistance	[93]
				U251	Sirt7, Bax, caspase-3/-9, Beclin-1, p62, LC3-II/LC3-I	PI3K/AKT and mTOR signaling pathways	↓Proliferation, ↓migration, ↑ apoptosis, ↑autophagy, ↓tumor formation	[94]
		Down	17 paired tissues	U251, U87	p53		↓Proliferation, ↑apoptosis	[95]
			71 glioma tumor tissues and 12 normal brain tissues	U251, U87, A172	DNMT1, p53,		↓Proliferation, ↑apoptosis, ↓ colony formation	[96]
			40 paired tissues	NHAs, U87, U251	miR-19a, PTEN,		↓Migration, ↓invasion, ↓ proliferation, ↑Apoptosis, ↓ tumorigenesis	[97]
			30 paired tissues	U-251, M059J	miR-93, caspase-3, caspase-9	PI3K/AKT pathway	↓Cell growth, ↓proliferation, ↑ apoptosis,	[76]
			54 surgically resected glioma tissues and 10 non-tumor brain samples	U87, U251, NHA		Wnt/β-catenin signaling	↓Proliferation, ↓cell growth	[98]
			79 paired tissues	U251, NHA,			↓Proliferation, ↑apoptosis, autophagy	[99]

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Table 1 (*continued*)

Cancer type	Sub-type	Expression pattern	Numbers of clinical samples (tissues, serum, *etc.*)	Assessed cell line	Targets/Regulators	Signaling Pathways	Function	Ref.
Leukemia	CML	Down	68 patients with CML (imatinib-sensitive and imatinib-resistant)	K562,	miR-21, MRP1, MDR1, ABCG2		↓Proliferation, ↑apoptosis, ↑ chemo-response to imatinib	[100]
			BM samples of 40 CML patients and 10 healthy donors	KCL22, K562	mi-R21, Bax, bcl-2, MMP-2, MMP-9, LSD1, MDM2, EZH2, PTEN, DNMT1, MYC, AKT, KLF4, SFRP2		↓Proliferation, ↑apoptosis	[101]
			BM samples of 60 CML patients and 10 healthy donors	KCL22, K562, DNMT1, DNMT3B, MBD2, MECP2, HDAC1	miR-147, DNMT1, JAK2, TYK2, STAT3, HDAC1, DNMT3B, MBD2, MECP2	JAK/STAT Pathway	↑Chemo-response to Chidamide, ↓Proliferation, ↑apoptosis	[37]
	AML		BM of 42 samples from AML patients and CD34+ cells derived from 15 potential donors for allogeneic bone marrow transplantation		p53, WT1, TET2		↓Tumor growth	[102]
			Blood samples from 57 patients with AML and 57 healthy volunteers	THP-1, HL-60, CCL-240, CRL-1582	miR-184		↓Proliferation, ↓invasion, ↓ metastasis	[103]
Lymphoma	T-LBL	–	–	Jurkat, SUP-T1	p-glycoprotein	EMT, PI3K/mTOR signaling pathway	↓Cell growth, ↓invasion, ↓ migration, ↑sensitivity to chemotherapeutic agents	[104]
		Down	50 human T-LBL tissues and 38 adjacent normal tissues	CCRF-CEM, Jurkat, SUP-T1, H9	miR-214, AIFM2		↓cell growth, ↑ apoptosis, ↓ proliferation	[105]
Multiple myeloma			–	ARP-1, LP-1	miR-181, HOXA11		↓tumor growth	[103]

Abbreviations: NSCLC: non-small cell lung cancer, LAD: lung adenocarcinoma, PTC: papillary thyroid carcinoma, PNET: primitive neuroectodermal tumor, EOC: epithelial ovarian cancer, T-LBL: T-cell acute lymphoblastic lymphoma, AML: acute myeloid leukemia, CML: chronic myeloid leukemia, ccRCC: clear cell renal cell carcinoma, SCC: squamous cell carcinoma, CRC: colorectal cancer, BM: bone marrow, ↓: decrease, ↑: increase, paired samples: tumor and adjacent normal tissues of a same patient.

Table 2
Summary of selected studies reporting diagnostic/prognostic value of *MEG3* expression in cancers.

Sample origin	Sample number	Area under curve	Sensitivity	Specificity	Kaplan-Meier analysis	Univariate cox regression	Multivariate cox regression	Ref.
Cervical cancer	72 paired tissues	For discrimination between tumors < 4 cm and tumors ≥4 cm: 0.705 As a biomarker for lymph node metastasis: 0.716	For discrimination between tumors < 4 cm and tumors ≥4 cm: 56.1%, As a biomarker for lymph node metastasis: 70.5%	For discrimination between tumors < 4 cm and tumors ≥4 cm: 80.6% As a biomarker for lymph node metastasis: 67.9%	*MEG3* expression level was associated with RFS and OS.	*MEG3* expression was prognostic factor for RFS.	*MEG3* expression was independent prognostic marker for RFS.	[71]
Colorectal cancer	Serum samples from 316 patients	0.784	72.86%	61.43%	Low *MEG3* expression was associated with poor OS and RFS.	*MEG3* expression level was independent prognostic factor for OS of patients receiving oxaliplatin.	*MEG3* expression level was independent prognostic factor for OS of patients receiving oxaliplatin.	[108]
	371 colorectal cancer patient	–	–	–	Patients with higher *MEG3* expression have better DFS.		*MEG3* is an independent prognostic factor for the DFS.	[51]
Oral squamous cell carcinoma	45 paired tissues	0.84	–	–	–	–	–	[109]
Epithelial ovarian carcinoma	95 ovarian cancer samples, 8 normal samples, 17 benign tissues	benign tumor *vs.* ovarian cancer: 0.72 normal *vs.* ovarian cancer: 0.76	–	–	–	–	–	[110]
Breast cancer	40 paired tissues	0.67	–	–	–	–	–	[111]
	207 paired tissues	–	–	–	Patients with low *MEG3* expression had poor OS rate and PFS.	–	*MEG3* expression was an independent poor prognostic factor for 5-year OS and 5-year PFS.	[112]
Osteosarcoma	64 paired tissues	–	–	–	Patients with low lncRNA *MEG3* expression had a shorter OS.	*MEG3* expression was associated with OS.	*MEG3* expression was independent prognostic factor.	[21]
Glioma	79 paired tissues	–	–	–	The OS rates in patients with low *MEG3*expression were lower than patients with high *MEG3* expression.	Low level of *MEG3* expression was the leading variable for prognosis.	Low level of *MEG3* was correlated with poor prognosis.	[113]
Gallbladder cancer	50 paired tissues	–	–	–	Patients with low *MEG3* levels had a shorter survival than those with high levels.	Low *MEG3* was prognostic factor.	Low *MEG3* expression was an independent prognostic factor.	[67]

Abbreviations: OS: overall survival, RFS: recurrence-free survival, PFS: progression-free survival, DFS: disease-free survival.

Table 3
MEG3 polymorphisms and their association with cancer risk or therapeutic response.

Cancer type	Number of cases	*MEG3* variant associated with		Ref.
		Cancer risk/phenotype modifier	Therapeutic response	
Colon cancer	518 cases and 527 control	The rs7158663 AA genotype, but not the heterozygote genotype, confers risk of cancer.		[114]
Nasopharyngeal cancer	505 newly diagnosed cases		The rs10132552 CT genotype was associated with better response to chemoradiotherapy.	[118]
Neuroblastoma	392 neuroblastoma children and 783 controls	The rs4081134 AG/AA genotypes are associated with early disease onset and high clinical stage.		[115]
Lung cancer	526 lung cancer patients and 526 healthy controls	The rs4081134 AA genotype was associated with risk of lung cancer.		[116]
Oral squamous cell carcinoma	444 patients and 984 cancer-free controls	The rs11160608 CC genotype was associated with cancer risk especially among drinkers.		[117]

2. Discussion

MEG3 is a tumor suppressor lncRNA which modulates expression of p53 and some of its targets [2]. Although the bulk of evidence indicates remarkable role of *MEG3* in up-regulation of p53 transcription and induction of accumulation of p53 protein [2], a single study in endothelial cells has shown that *MEG3* knock down triggers DNA damage, induces p53 signaling and up-regulates the expression of p53 target genes [10]. However, the same study has indicated that *MEG3* expression is up-regulated in endothelial cells following p53 activation [10]. Further studies are needed to resolve this discrepancy.

MEG3 also contributes in the regulation of several cancer-related pathways such as TGF-β, PI3K/AKT, Notch, mTOR and Wnt/ β-catenin pathways. *MEG3* expression is activated by Wilms' tumor 1 (WT1) whose dysregulation contributes in carcinogenesis process [102]. Preliminary results have indicated the possibility of application of serum levels or methylation status of this lncRNA in cancer diagnosis. Notably, some SNPs within this gene have been associated with risk of diverse cancers. In the prevailing concept, *MEG3* down-regulation is associated with the increased risk of cancer. However, the luciferase assay has shown higher activity of a cancer-associated allele (rs11160608 C allele) in a single study [117]. Consequently, future studies are needed to clarify the mechanism by which this risk allele contributes in cancer risk.

Notably, expression levels of this lncRNA correlates with response of cancer cells to chemotherapeutic agents. In non-small cell lung cancer cells, *MEG3* increases cisplatin sensitivity through modulating miR-21-5p/SOX7 axis [26]. Assessment of clinical samples has shown associations between decreased level of *MEG3* and poor responses to cisplatin-based chemotherapy. Low levels of this lncRNA in clinical samples were accompanied by low p53 protein levels and high Bcl-xl protein levels [27].

Taken together, the results of *in vitro* studies as well as clinical assays indicate that *MEG3* has a pivotal role in the abrogation of carcinogenesis. Consequently, strategies for induction of its expression might be effective in treatment of cancer. As epigenetic mechanisms are implicated in the down-regulation of its expression in tumor tissues, epigenetic-therapies are putative methods for induction of *MEG3* expression and reprograming of cancer cells.

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