Minireview *Highlight article*

The role of mediator complex subunit 19 in human diseases

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Impact statement

Mediator is an important part of the transcriptional mechanism in eukaryotes. It interacts with RNAP II and participates in the process between different proteins. *MED19* is an important member of the mediator family. As a tumor-related gene, it plays an important role in cell proliferation, transcriptional regulation, and apoptosis. It is closely related to the occurrence and development of lung cancer and other tumors. Additionally, *MED19* is also related to lipid metabolism and the pathogenesis of coronavirus disease 2019 (COVID-19). This review summarizes the role of *MED19* in tumor progression, fat metabolism, drug therapy, as well as COVID-19, to provide a new idea for disease diagnosis and treatment.

Abstract

Mediator is an evolutionarily conserved multi-protein complex that mediates the interaction between different proteins as a basic linker in the transcription mechanism of eukaryotes. It interacts with RNA polymerase II and participates in the process of gene expression. Mediator complex subunit 19 or regulation by oxygen 3, or lung cancer metastasis-related protein 1 is located at the head of the mediator complex; it is a multi-protein co-activator that induces the transcription of RNA polymerase II by DNA transcription factors. It is a tumor-related gene that plays an important role in transcriptional regulation, cell proliferation, and apoptosis and is closely related to the occurrence and development of the cancers of the lung, bladder, skin, etc. Here, we used the structure of mediator complex subunit 19 to review its role in tumor progression, fat metabolism, drug therapy, as well as the novel coronavirus, which has attracted much attention at present, suggesting that mediator complex subunit 19 has broad application in the occurrence and development of clinical diseases. As a tumor-related gene, the role and mechanism of mediator complex subunit 19 in the regulation of tumor growth could be of great significance for the diagnosis, prognosis, and treatment of mediator complex subunit 19 -related tumors.

Keywords: Mediator complex subunit 19, tumor, fat metabolism, novel coronavirus

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Introduction

Mediator complex is a multi-protein co-activator complex found in yeast composed of 25 subunits. Mediator is composed of four modules, including head, middle, tail and kinase modules, which are ubiquitously expressed and conserved. It acts as a link between DNA-binding activator and RNAP II transcription mechanisms, and is thus vital for transcriptional regulation, as well as cell proliferation and differentiation. The structure and function of the mediator complex are highly conserved between yeast and human. The first mammalian mediator to be isolated was thyroid receptor-associated protein (TRAP), and its two main types were TRAP with suppressor of RNA polymerase B 8–11 (Srb8-11) and TRAP without Srb8-11 components.[1] Each module domain of the Mediator complex is known to be directly targeted by sequence-specific regulatory systems.[2] For example, studies have shown that the *MED17/TRAP80* subunit of the Drosophila mediator, a homolog of the Head domain subunit *Srb4*, directly interacts with Drosophila heat-shock factor (HSF). The mediator complex acts as a functional bridge in the process of eukaryotic transcription and RNAP II mechanism.[3] By interacting with transcription factors via binding to the enhancers and promoter elements, the mediator complex transmits regulatory signals from DNA binding transcription factors to RNAP II, stimulating the assembly of the pre-initiation complex and phosphorylation of the pol II C-terminal domain (CTD), thus, activating pol II transcription. Several transcriptional regulatory factors in eukaryotic cells are known to interact with the protein subunits and domains of the mediator complex, change their conformations through protein–protein interactions, promote pol II

aggregation in the initiation sequence of transcriptional genes and form the pre-elongation complex (PEC), and then regulate gene transcription.[4,5] Along with affecting transcriptional initiation and elongation, the mediator complex also plays a role in chromatin modification and RNA modification.[6] It has been found that the binding of mediator complex to pol II is reversible;[7] it binds tightly to the hypo-phosphorylated pol IIa subtype, but very weakly to the hyper-phosphorylated pol IIo. The functions of RNAP II-related factors in transcriptional elongation and cell cycle regulation suggest that it might be associated with the malignant phenotype. Studies have shown that the recruitment of mediators precedes the study of pol II, proving that it can independently exit without RNAP *in vivo*.[8–10] The mediator complex is generally considered to be a transcriptional co-activator; however, in some cases, it might act as a co-repressor.[11]

MED19, a subunit of the mediator complex, was first identified while screening heme-regulated mutants in the presence of the increased expression of cytochrome C-7 (*CYC7*) gene.[12] Due to its nuclear location, it is considered to be a transcriptional regulator. *MED19* is a component of the head module domain of the mediator complex, located at chromosome 11q 12.1, contains 949 nucleotides, and encodes a polypeptide containing 177 amino acids. It is widely expressed in eukaryotes. As a unique functional module in the mediator complex, *MED19* is involved in the transcriptional regulation of basic and heat shock genes; its mutation can lead to glucose repression and regulation of stress response.[13,14] As a co-activator of the DNA binding factor, *MED19* constitutes the head component of yeast RNAP II, which can be transcribed by RNAP II; it plays a key role in the activation and inhibition of the transcription system, and participates in the regulation of various biological behaviors, thus, promoting carcinogenesis. Its expression is closely related to the survival and prognosis of patients. MED19 participates in the regulation of developmental transcription through its homologous domain with Hox protein as a pol holo-enzyme "cofactor".[15] However, the absence of *MED19* leads to a relative decrease in the transcription of the mediator complex, resulting in a decreased ability of the *MED19* complex to bind RNAP II and the inability to enhance the phosphorylation of CTD through transcription factor IIH *(TFIIH)*.[13,14] As a member of the mediator, *MED19* plays a key role in the activation and inhibition of tumor signal transduction or transcriptional regulation and other developmental diseases. However, the specific mechanism of *MED19* in the occurrence and development of tumors and other diseases is unclear. Therefore, an in-depth understanding of the biological function of *MED19* and its mechanism of action in related diseases might be helpful in the identification of potential targets for clinical treatment.

MED19 and tumor

The human homologous gene of *MED19*, also known as lung cancer metastasis-related protein 1 (*LCMR1*), was cloned from lung large cell carcinoma in 2003.[16] *MED19* plays a key role in the malignant growth of tumors by regulating cell growth, differentiation, cell cycle, and apoptosis-related signal transduction pathways. Several studies have reported the elevated expression of *MED19* in the cancers of the lung, breast, liver, bladder, etc., and thus it plays a vital role in carcinogenesis. The Cancer Genome Atlas (TCGA) database also contains records of the aberrant expression of *MED19* in various tumor tissues, which was found to have a significant correlation with the survival and prognosis in patients with malignancies. The overall survival as well as the disease-free survival time of patients in the *MED19* high-level group was found to be significantly shorter than that in the low-level group. Table 1 shows the expression and function of *MED19* in tumors.

Effect of *MED19* on tumor cell proliferation

As an effective tumor-promoting factor, *MED19* is highly expressed in various tumor tissues. The elevated expression of *MED19* has been associated with the enhanced proliferation ability of tumor cells. Elevated expression of *MED19* has been shown to enhance the proliferation of breast cancer cells. Zhang *et al.* [17] found that the expression of *MED19* in breast cancer tissues was significantly higher than that in para-carcinoma tissues, which promoted the proliferation of breast cancer cells through the EGFR/MEK/ERK signaling pathway. Additionally, the inhibition of *MED19* expression reduced the *in vivo* malignant progression of breast cancer. However, other studies have shown that elevated expression of CBFA2 translocation partner 3/transcription factor 12 (*CBFA2T3/HEB, TCF-12*) could reverse the upregulated expression of *MED19*.[18] Additionally, several studies have reported that *MED19* plays a key role in the growth of the cancers of the lung, liver, prostate, etc. For non-small cell lung cancer, the overexpression of *MED19* has been shown to be significantly correlated with the clinical stage.[19] For hepatocellular carcinoma, *MED19* knockdown was shown to inhibit the cell proliferation, induce cell cycle arrest in the G0/G1 phase, and inhibit tumor formation.[20] Also, *MED19* is known to regulate androgen receptor-mediated transcription and proliferation, and thus impacts the survival rate and poor prognosis of men with prostate cancer.[21]

Effect of *MED19* on invasion and migration of tumor cell

Most malignant tumors are characterized by high mortality and early metastasis, which is also one of the primary reasons for the failure of tumor treatment. A study showed that *MED19* acted as an oncogene in osteosarcoma via the Cyclin D1/cyclin B1 regulatory pathway, thus promoting the growth and metastasis of osteosarcoma, and was related to prognosis.[22] De-methylation-activated *miR-570p-3p* inhibited *MED19* and autophagy-related protein 2 (*ATG2*) and participated in the anti-metastasis effect of metformin on human osteosarcoma.[23,24] Another study on melanoma, a highly metastatic and fatal form of skin cancer, showed that expression of Tspan8 protein was directly proportional

Table1. Expression and function of MED19 in tumors.

Tumor types	Expression and meaning	Mechanism of action	References
Lung cancer	MED19 is highly expressed in lung cancer tissues and is involved in cell proliferation, cycle regulation, and apoptosis	MED19 interacts with DEK to inhibit apoptosis of lung cancer cells; is related to the p53 pathway, regulates the apoptotic pathway by transcribing the pro-apoptotic gene *Bax* and the anti-apoptotic gene *Mcl-1*	31, 32
Prostate cancer	Elevated expression of MED19 promotes the proliferation of prostate cancer cells	The downregulated expression of MED19 induces apoptosis by upregulating the expression of the apoptotic protein Caspase 7 and pro-apoptotic protein Bid	37
Osteosarcoma	The upregulated expression of MED19 is involved in the growth and proliferation of osteosarcoma cells and is related to prognosis	As the target of miR-570-3p, LCMR1 participates in the anti-metastasis effect of metformin on human osteosarcoma, resulting in the downregulated expression of Cyclin D1 and Cyclin B1. It induces apoptosis by promoting the expression of Caspase-3 and poly ADP-ribose polymerase (PARP).	22, 64
Melanoma	MED19 regulates Tspan8-mediated melanoma invasion in melanoma	LCMR1 transcription activates the endogenous expression of Tspan8; LCMR1 regulates the adhesion and invasion of melanoma in a Tspan8-dependent manner in vitro.	26
Laryngeal cancer	MED19 expression is upregulated in laryngeal cancer cells and involved in cancer cell apoptosis	MED19 gene knockdown induces the apoptosis of laryngeal cancer cells by activating Caspase-3, -9 and Apaf-1.	39
Bladder rothelial carcinoma	Elevated expression of MED19 promotes the metastasis and invasiveness of bladder cancer	MED19 promotes bone metastasis and invasion of bladder urothelial carcinoma through bone morphogenetic protein 2 (BMP2)	3
Breast cancer	Elevated expression of MED19 promotes the proliferation of breast cancer cells	MED19 targets miR-101-3P/miR-422a, promotes breast cancer progression by regulating the EGFR/MEK/ERK signaling pathway; it participates in chemotherapy resistance of breast cancer through HMBG1-mediated autophagy and promotes cell proliferation by regulating CBFA2T3/HEB expression	17, 18, 41
Colorectal cancer	MED19 is highly expressed in colorectal cancer tissues and promotes the proliferation of colorectal cancer cells	SP1-induced lncRNA Linc00339 promotes the onset of CRC through miR-378a-3p/MED19 axis. MiR-214 mediated expression of MED19 inhibits the proliferation, invasion, and migration of CRC cells.	24, 29

to the progression and invasiveness of melanoma.[25] Agasse *et al.* [26] found that *MED19* was a key regulator of Tspan8-mediated melanoma invasion via RNA interference, and it positively regulated the expression of endogenous Tspan8. *MED19* transcription can activate endogenous Tspan8 expression and regulate the adhesion and invasion of melanoma in a Tspan8-dependent manner. Additionally, some studies reported that the expression of *MED19* was positively correlated to the expression of bone morphogenetic protein 2 (*BMP2*) in bone metastasis and invasion of bladder urothelial carcinoma.[3] Yuan *et al.* found that *MED19* knockdown inhibited the proliferation and migration of bladder cancer cell by downregulating the activity of *WNT/β-catenin* (WNT family member/*β-catenin*) signal pathway.[27]

Epithelial-mesenchymal transformation (EMT), a basic process involved in embryonic development, is also known to play a key role in the malignant transformations. EMT is known to promote tumor cell invasion and metastasis to distant sites. Therefore, an in-depth analysis of the relationship between *MED19* and key molecules involved in EMT would be helpful to clarify the mechanism of tumor cell invasion or metastasis. In breast cancer, *MED19* was found to promote invasion, migration, and EMT of cancer cells via the EGFR/MEK/ERK signaling pathway.[17] For prostate cancer cells, the downregulation of *MED19* inhibited the proliferation, migration, and invasion cancer cells, as well as the expression of EMT-related genes, such as *P27, E-cadherin, N-cadherin, Vimentin, Snail1*, and *Snail2*.[28] Recent studies have found that *MED19* promotes the EMT process by activating the activity of *WNT/β-catenin* signaling pathway, thus inhibiting the proliferation and migration of colorectal cancer cells,[29] which is of great significance in exploring the influence of *MED19* on tumorigenesis and metastasis.

MED19 is involved in cell cycle regulation and apoptosis

Apoptosis is defined as programmed cell death, which helps in maintaining the stability of the internal environment, and is vital for various life activities. As an apoptosis inhibitor, *MED19* plays an important role in the regulation of tumor cell cycle, apoptosis, as well as the process of gene transcription. The downregulation of *MED19* has been shown to result in cell cycle arrest (G0/G1 phase), thus inhibiting tumorigenesis in pancreatic cancer, prostate cancer, bone cancer, etc. Additionally, studies have shown the association between *MED19*-mediated apoptosis and the *p53* pathway. As a key tumor suppressor gene, *p53*

has been strongly correlated to the development of cancers in humans.[30] In the process of apoptosis, *p53* interacts with *MED19*-related genes, such as *Bax* and *Mcl* in a *p53*-dependent manner.[31]

XU *et al.*[32] found that the interaction between *MED19* and *DEK* Proto-oncogene (*DEK*) inhibited apoptosis in lung cancer cells.[32] Originally, the *DEK* gene was found in t(6:9) chromosome translocation in patients with a subtype of acute myeloid leukemia (AML); thus, human *DEK* protein has long been associated with cancer.[33] The cellular functions of *DEK* include apoptosis, inhibition of tumor cell growth, and transcription factors via pol II.[34–36] *MED19* gene knockdown has also been shown to induce apoptosis through Caspase-7, Caspase-8, and Caspase-9 pathways as well as increase the activity of Caspase-3.[37,38] During this process, caspase gets activated mainly via mitochondria and death receptors. *MED19*, as an oncogene of laryngeal cancer, has been shown to induce apoptosis of laryngeal cancer cells by activating apoptotic proteases, Caspase, and Apaf-1 [39.]

Treatment of *MED19* in tumors

Drug therapy is the most commonly used therapy for the treatment of tumors. In non-small cell lung cancer, the knockdown of *MED19* gene has been shown to arrest the cell cycle in G0/G1 phase, resulting in their increased sensitivity to the anticancer drug cisplatin to induce apoptosis.[40] Additionally, studies have shown that Vemurafenib can inhibit the expression of *MED19* and Tspan8, which are known to play a positive role in the treatment of melanoma.[26] During the treatment of breast cancer, *MED19* mediates autophagy of breast cancer cells through high mobility group protein B1 (*HMGB1*), thus increasing the sensitivity of adriamycin (ADM).[41] Metformin has been shown to cause di-methylation of DNA and reduce tumor progression. In 2019, cancer cell published an article in which researchers found that the use of metformin during fasting could significantly inhibit tumor growth, migration, and invasion.[42] Bao *et al.*[23] also found that metformin induced autophagy and indirectly inhibited the invasion of osteosarcoma cells. *MED19*, as the initiator of metformin-induced metastasis inhibition and autophagy reduction, could indirectly inhibit the migration and invasion of osteosarcoma cells, targeted by *miR-570-3p*. Studies have found [38] that *miR-4778-3p* regulates the radiation sensitivity of cervical cancer by targeting the expression of downstream genes nuclear receptor subfamily 2 group C member 2 (*NR2C2*) and *MED19* during the radiotherapy of cervical cancer, and reduces the viability, proliferation, and migration of radiation-resistant cervical cancer cells.

MED19 is involved in fat metabolism

Obesity, mainly caused by excessive adipose tissue, is defined as an increase in body mass index (BMI). Excessive obesity can lead to metabolic disorders, changes in related hormones, as well as some subclinical symptoms. Obesity causes many pathophysiological changes and is closely related to the occurrence and development of tumors. Obesity is an independent risk factor for malignant tumors and is closely related to the poor prognosis in the cancers of the liver, breast, pancreas, etc..[43–46] Currently, researchers are interested in examining the role of obesity in the occurrence, growth, and progression of tumors. Tumor-related genes are known to cause abnormal fat metabolism and their complex interactions, which help in the identification of new therapeutic targets.

Abnormal fat metabolism has been shown to cause various clinical diseases. White fat is known to store excess fat in the body, leading to obesity, while brown fat is responsible for breaking down the white adipose tissue that causes obesity, converting it into CO_2, H_2O, and energy, speeding up the body metabolism and promoting the consumption of white fat. The latest research has shown that *MED19* regulates the formation of fat and the maintenance of white fat mass by mediating peroxisome proliferator-activated receptor γ(*PPAR-*γ).[47] The downregulated expression of *MED19* is known to inhibit the formation of white fat but does not inhibit the formation of brown fat. *MED19* interacts with *PPAR-*γ and connects *PPAR-*γ to RNAP II. As a key promoting factor, *MED19* is involved in adipose tissue metabolism. Additionally, it has been shown that *MED19* directly binds to the GATA binding factor (*GATA*) transcription factors and regulates *GATA*-driven genes together with *MED1 in vivo.*[48] The expression of *GATA2/GATA3* has been shown to partially promote the differentiation of adipocyte precursors through *PPAR-*γ; the *GATA* factors are expressed in white adipose tissue but not in brown adipose tissue. However, further studies are required to explore whether *MED19* and *GATA* are involved in mediating *PPAR-*γ regulation of adipose dystrophy, obesity, and other diseases, as well as the specific mechanism of *MED19* in tumorigenesis and other diseases caused by abnormal fat metabolism. Additionally, there is evidence that the mediator complex plays a pathogenic role in cardiovascular disease, with metabolic syndrome as the main manifestation.[49] The mediator subunit is co-immunoprecipitated with the nuclear receptors (NRS) and is involved in adipogenesis and glucose homeostasis.

MED19 and novel coronavirus

COVID-19, triggered by novel coronavirus 2019, has now become a global pandemic. Currently, COVID-19 is the world's biggest health threat, with more than 9.5 million infections and 480,000 death worldwide.[50] The WHO has named this new type of Coronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). SARS-COV-2 is the third large-scale outbreak related to coronavirus after SARS and Middle East respiratory syndrome-coronavirus (MERS-COV). The possible mechanisms of the damage include the interaction of virus and angiotensin-converting enzyme-2 (ACE2) in the host cells, cytokine storm-induced immune response disorders, and adverse drug reactions.[51–53] ACE2 is a functional receptor for the spike glycoprotein in SARS-COV, SARS-COV-2, and human coronavirus NL63 (HCoV-NL63). The efficiency of the binding of SARS-COV-2 to ACE2 is a key determinant of transmissibility.[54] Several studies have shown that the

binding affinity of SARS-COV-2 to ACE2 is higher than that of SARS-COV to ACE2[55–57.]

Apart from causing various respiratory diseases, COVID-19 has also been shown to cause extrapulmonary manifestations, including thrombotic complications, myocardial dysfunction, acute kidney injury, gastrointestinal symptoms, drug-induced liver injury, liver steatosis, hyperglycemia, and ketosis,[58] all of which might be risk factors for cancer. Studies have found that miRNA might affect the virus by interfering with virus replication, translation, and even by regulating the expression of the host.[59] Demirci *et al.* explored the role of miRNA in SARS-COV-2 infection by computer analysis and found that the virus potentially targeted host transcription, and the human mediator complexes *MED1, MED9, MED12L*, and *MED19* were also involved as the elements of basic transcription mechanism.[60] However, the specific role of *MED19* and other mediator complexes in COVID19 and its further pathogenic mechanism have not been further explored. Therefore, further studies are required to explore the effect of *MED19* on many complications caused by SARS-COV-2 infection.

MED19 and neurological disease

Ning *et al.*[61] found that *MED19* was a key component in the *RE1* silencing transcription factor (*REST;* also known as neuron restrictive silencer factor, *NRSF*) regulatory device.[61] *RE1* silencing transcription factor is known to recruit mediators through the *MED19* interface to promote epigenetic silencing of neurons in non-nerve cells. However, the specific function and mechanism of *MED19* in the process of neuronal gene expression are unclear. Therefore, further studies are required to explore the role of *MED19* in the regulation of epigenetic modification in the nervous system.

Conclusions

Thus, *MED19* is known to be closely related to the mechanism and development of cancer, and the elevated expression of *MED19* in tumor cells or tissues indicates a poor prognosis of patients. *MED19* has been shown to be involved in the process of tumor cell proliferation, invasion, migration, cell cycle regulation, and apoptosis,[62,63] indicating that *MED19* might be a potential target for tumor diagnosis, targeted therapy, and prognosis. However, until now, the role of *MED19* in tumor signaling pathway and its upstream and downstream target genes has not been fully elucidated. Additionally, *MED19*, as a necessary multi-protein co-activator for DNA transcription factor to induce RNAP II transcription, its role, and mechanism in tumor has not been further confirmed. Also, the mechanism of *MED19*, a risk factor for the occurrence and development of tumors caused by abnormal fat metabolism, needs to be further elucidated. Additionally, in connection with COVID-19, which has attracted worldwide attention, the latest research found that *MED19* could be used as a mechanistic element in the process of virus transcription, but its application value in the pathogenic mechanism and prognosis of the COVID-19 needs further analysis. It is believed that the continuous in-depth analysis of *MED19* might reveal its mechanism and clinical significance in tumorigenesis, which will provide a more reliable direction and means for cancer treatment. Additionally, *MED19* is expected to become a new therapeutic target for more diseases in the future.

AUTHORS' CONTRIBUTIONS

All authors participated in the design, interpretation, and analysis of the data and review of the manuscript; YTZ: wrote the article, PFQ, LLT, JGY: collected and analyzed the literature, YLZ: modified the article.

DECLARATION OF CONFLICTING INTERESTS

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