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METTL16 in human diseases: What should we do next?

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Abstract:	METTL16 is a class-I methyltransferase that is responsible for depositing a vertebrate-conserved SAM site. Since 2017, there has been a growing body of research focused on METTL16, particularly in the field of structural studies. However, the role of METTL16 in cell biogenesis and human diseases has not been extensively studied, with limited understanding of its function in disease pathology. Recent studies have highlighted the complex and sometimes contradictory role that METTL16 plays in various diseases. In this work, we aim to provide a comprehensive summary of the current research on METTL16 in human diseases.

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Dear Editors,

We would like to submit the enclosed manuscript entitled “METTL16 in human diseases: What should we do next?”, which we wish to be considered for publication in “Open Medicine”. No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication. I would like to declare no behalf of my co-authors that the work described was new discovery that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

In this work, we review the role of METTL16 in various diseases. METTL16 is a class-I methyltransferase that deposits a conserved SAM site in vertebrates. Since 2017, numerous studies have focused on the structure of METTL16. However, its function in cell biogenesis and human diseases remains largely unexplored. Current research suggests that METTL16 plays a complex and sometimes contradictory role in many diseases. Our review aims to provide a theoretical basis and direction for the study of METTL16 in clinical diseases and to attract interest in this important molecule. We hope it’s suitable for Open Medicine.

We deeply appreciate your consideration of our manuscript, and we look forward to receive comments from the reviewers. If you have any queries, please contact me(yszh500@163.com).

Thank you and best regards.

Yours sincerely,

Hui Zhang

METTL16 in human diseases: What should we do next?

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Keywords: METTL16, m6A methyltransferase, human diseases, RNAs, cancers.

Abstract

METTL16 is a class-I methyltransferase that is responsible for depositing a vertebrate-conserved SAM site. Since 2017, there has been a growing body of research focused on METTL16, particularly in the field of structural studies. However, the role of METTL16 in cell biogenesis and human diseases has not been extensively studied, with limited understanding of its function in disease pathology. Recent studies have highlighted the complex and sometimes contradictory role that METTL16 plays in various diseases. In this work, we aim to provide a comprehensive summary of the current research on METTL16 in human diseases.

Introduction

m6A modification is considered the most prevalent RNA modification in mammalian cells, emerging in both coding RNAs and non-coding RNAs[1-5]. This epi-transcriptional modification is known to promote the initiation and progression of many human diseases[6-8]. As is widely understood, m6A modification is regulated by writers, readers, and erasers, and exerts its effects by influencing RNA splicing, stability, transcription, translation, and decay[8-13]. To date, many m6A writers, such as METTL3, METTL14, WTAP, KIAA1429, RBM15, have been thoroughly investigated, while the role of METTL16 in this process remains poorly understood.

METTL16 belongs to the class-I methyltransferase family, which has a vertebrate conserved S-adenosylmethionine (SAM) site [14-16]. Structural studies over the past few decades have confirmed that METTL16 consists of 562 amino acids, involving to 7 beta-strands in the Rossmann fold. The quaternary structure of METTL16 is formed by an N-terminal methyltransferase domain (MTD) and two C-terminal vertebrate-conserved regions (VCRs), the MTD and the two VCRs are flanked by two disordered regions[14, 17, 18]. Accumulated studies have shown that METTL16 can exist as both a homodimer and a monomer [17, 19], and is found in both the cytoplasm and nucleus [15]. METTL16 directly binds to target RNA that possesses a specific sequence and stem-loop structure, and also binds directly to the translation initiation complex (TIC) to regulate translation[5, 17, 20-22]. Studies have shown that METTL16 is closely related to almost all types of RNAs, as well as many RNA regulators and effectors[23-25] .Other studies have determined that METTL16 is also involved in maintaining SAM homeostasis[17, 20]. Particularly, METTL16 can directly interact with ribosomal RNA to enhance translation, which distinguishes it from other METTL members such as METTL3 [22].

Numerous studies have highlighted the significance of METTL16 in various cellular functions and human diseases, though investigations have been relatively limited in past decades. In this work, we have summarized the current achievements in METTL16 studies related to human diseases, as illustrated in **Figure 1**. We anticipate

that METTL16 will be a key area of focus in future studies on human diseases.

METTL16 in Cancers

m6A modification and its associated regulated factors, including METTL3/METTL14, YTHDC, FTO, and ALKBH5 etc, have been widely researched for their roles in various types of cancer. However, the investigation of METTL16 in cancer is limited and there are only a few reports available to date.

The Expression and Prognostic Significance of METTL16 in Cancer

METTL16 has been identified as a potential gene involved in the initiation and progression of cancer. However, its expression varies across different tumor types and is associated with different outcomes. In some cases, it has been identified highly expressed and associated with poor outcomes.For example, Wang et al. reported that METTL16 is highly expressed in gastric cancer and predicts worse survival in patients. The underlying molecular mechanism mainly involves METTL16 functioning as an m6A methyltransferase to promote cancer cell proliferation[26]. A clinical cohort study containing 66 hepatocellular carcinoma (HCC) tissues and 21 adjacent normal tissues determined that higher METTL16 expression group displayed a worse clinic outcomes [27]. Additionally, bioimformatics analyses have shown that METTL16 is overexpressed in esophageal cancer [28],colorectal cancer[29],and perdicts poor survival in HCC, CRC, endocrine system tumors, glioma, melanoma, soft-tissue sarcomas, and breast cancer[22, 29-34]. While in other cases ,there also have been reported that METTL16 is underexpression in endometrial cancer[35], urothelial carcinoma [36]and breast cancer[30]. In patients with pediatric neuroblastoma, Zhang et al. found that METTL16 could affect the overall survival (OS) and disease-free survival (DFS) of patients[37].What's more , In a RAS-related gene score of esophageal squamous cell carcinoma, METTL16 was found upregulated in the lower score group and predicted a better prognosis[38]. In a study to investigated m6A associated genes between patients with TP53 wild-type and mutation groups, METTL16 exhibited divergent expression between groups[39].

METTL16 showed divergent expression in cancers ,even in the same cancer ,it has

been found different expression in different studies ,the underlying reasons should be further studies. Usually ,METTL16 leads to a bad prognosis,however the effects on cancer prognosis can be modulated by other genes. These findings suggest that its role in cancer is complex and context-dependent. Recent studies uncovered that METTL16 can function as both a m6A dependent way or non-dependent way ,both as a writer and a reader,both in cytoplasm or in nuclnear,both regulate splice or translation ,all of which showed a fantastic of METTL16 .however,limit studies in specifical cancers was conducted,Further research is needed to elucidate the molecular mechanisms underlying these effects and to explore the potential of METTL16 as a therapeutic target for cancer treatment.

METTL16 Gene Mutation in Cancer

The identification of mutations in genes that diverged may play a significant role in understanding individual differences and recognizing diverse clinicopathological characteristics. Various studies have revealed that the METTL16 gene mutation is widespread in several types of cancer. In high microsatellite instability (MSI-H) colorectal cancers, METTL16 contains frameshift mutations that are not present in normal tissues[40]. An analysis of METTL16 CNVs using bioinformatics has shown that CNVs of this gene are common in cancers and can influence gene expression, leading to a worse prognosis. In more than 60% of sarcoma patients and 62.16% of HCC samples, METTL16 CNVs were present[34]. Furthermore, anti-tumor drugs have been associated with METTL16 mutation, and a study on methotrexate revealed that drug sensitivity to melanoma was linked to METTL16 mutations[33]. However, experimental validation and clinical data were lacking,indicating the need for further research in this area. Overall, the current study of METTL16 Gene Mutation showed the importance of gene mutations in cancers and the need for further research to develop effective treatment options for patients with cancer.

METTL16 and LncRNA

The LncRNA MALAT1 has an ENE+A structure and an METTL16 recognition sequence, allowing it to interact directly with METTL16[24]. Studies have shown that MALAT1 can both facilitate and suppress cancer development and is common in

various cancers[41, 42]. An analysis of 89 pathways in 64 different cancers has revealed the presence of MALAT1[43]. Additionally, MALAT1 can interact with microRNA and cancer drugs[44, 45]. These studies highlights the significant associations of LncRNA MALAT1 or microRNA with METTL16, which has been shown to play a crucial role in regulating cellular signals and promoting cancer development.Another LncRNA, named lncRNA RAB11B-AS1, has recently been found to directly bind to METTL16, promoting cancer development in an m6A-dependent manner by decreasing LncRNA stability[46]. These findings suggest that METTL16 interacts with LncRNA and miRNA to regulate cellular signals and contribute to cancer development. However, further experiments are necessary to fully understand the role of METTL16 and RNAs in cancer.

METTL16 and DNA Damage Response (DDR)

DNA damage response (DDR) has been linked to the development of tumors. Studies have shown that during the early stages of DDR, there is a significant increase in N6-adenosine methylation in RNA following UV-micro-irradiation. In later stages, small RNAs ,including snRNAs and snoRNAs ,in the vicinity of DNA lesions were found to be methylated, and it was determined that METTL16 is the sole methyltransferase responsible for this process[47]. These findings suggest that METTL16 may play a critical role in cancer development related to DDR. However, the precise mechanism by which METTL16 contributes to DDR remains unknown.

Others

METTL16 has been reported to affect cell differentiation and protein translation. Studies have shown that the level of METTL16 is negatively associated with tumor cell differentiation and that the m6A level decreases with better differentiation[48]. METTL16 can regulate protein translation and aggravate cancer development by directly binding to the translation initiation complex (TIC) [22].

METTL16 in other diseases

Recent studies have shed light on the potential involvement of METTL16 in non-cancerous diseases across various human systems. In the respiratory system, research

has shown that exposure to PM2.5 induces pulmonary vessel damage in a m6A-dependent manner through METTL16, providing new insights into the mechanisms of chronic obstructive pulmonary disease (COPD) and cancer[49]. Additionally, In a mouse model of acute respiratory distress syndrome (ARDS) induced by LPS, researchers observed a gradual increase in m6A levels over 6 hours, followed by a decrease. During this process, the METTL16 protein increased consecutively, while METTL16 mRNA decreased after LPS induction. The differences between METTL16 mRNA and protein expression warrant further investigation[50]. In the spinal system, studies have shown that the expression of METTL16 differs between human degenerative nucleus pulposus and control groups, and METTL16/MAT2A axis aggravates apoptosis of Nucleus Pulposus Cells by regulating splicing, maturation, and degradation of MAT2A pre-mRNA[51]. In the endocrine system, a cross-sectional study for people of Middle Eastern descent revealed an association between METTL16 and diabetic nephropathy (DN) [52]. Additionally, in the reproductive system, research found that although the m6A level of pregnancy was elevated consistently, METTL16 was lower in patients with infertility and recrudescence abortion[53]. Finally, studies suggest METTL16 may also play a role in cardiovascular and hematological systems, with low expression in immature RBCs of Hb cs thalassemia versus healthy controls[54] and contributing to mouse cardiomyocytes [55].Moreover, METTL16 was identified to play a role in erythropoiesis through the repair of DDR[56]. Overall, these findings highlight the potential involvement of METTL16 in various non-cancerous diseases, emphasizing the wide roles of METTL16 in human disease ,indicating the need for further research to elucidate the mechanisms of action and potential therapeutic applications.

Discussion And Conclusion

METTL16 plays a vital role in cellular biogenesis and is associated with various human diseases. Studies have found that METTL16 knockdown can cause a significant decrease in the installation of m6A/A [17], and can even lead to embryonic lethality in mice. [19]. While there is significant evidence that METTL16 is involved in both cancer

and non-cancer diseases, the role that it plays is complex, with numerous paradoxes and contradictions. For example, METTL16 can be located in both the cytoplasm and nucleus, can function as both a writer and a reader, and can have both higher and lower levels of expression even in one disease of two studies. Additionally, it can exert its effects in multiple ways, such as directly binding to TIC or regulating target RNA splicing, stability, and more. It can function as both a promoter and suppressor of diseases, making it challenging to determine its overall effect. Moving forward, further research is needed to answer critical questions, such as how METTL16 influences human diseases, the mechanisms by which it exerts its effects, and whether its role varies depending on the cell type, disease, or individual.

The importance of understanding the role of METTL16 in diseases cannot be understated, as it has the potential to become a target for therapeutic intervention. However, as the evidence surrounding its function is complex and sometimes contradictory, it is essential to conduct further studies to determine the full extent of its role in various diseases. In particular, future studies could focus on the identification of METTL16 substrates and the development of small molecule inhibitors that can modulate METTL16 activity in a disease-specific manner. A more in-depth understanding of how METTL16 functions at the molecular level and how it contributes to disease development and progression could pave the way for more effective treatments and therapies.

Abbrevation:

GC: Gastric cancer

CRC: Colorectal cancer

HCC: Hepatocellular carcinoma

Glimo: Glioma

COPD: Chronic obstructive pulmonary disease

UC: Urothelial carcinoma

DN: Diabetic nephropathy

EC: Esophageal cancer

Declarations：

Ethics approval and consent to participate

Not applicable

Consent for publication

all authors approved for publication

Availability of data and material

The datasets used in the current study are available from the corresponding author or the first author on reasonable request

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Mingliang Lu,Huizhang and Mengqi Yin took responsibility for the integrity of the work as a whole, from inception to published article. Mingliang Lu, Hua Huang and Gongfang Zhao gave support and indication. Hui Zhang wrote the paper.

all authors approved the final version of the manuscript

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Figure1 The schema of METTL16 in diseases.

Figure

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