Clinical and Experimental Medicine (2025) 25:3
https://doi.org/10.1007/s10238-024-01506-w

RESEARCH

Analysis of METTL14 expression in pancreatic cancer and adjacent tissues and its prognostic value for patient outcomes

Siyu Meng[1] · Cong Wang[2]

Received: 4 May 2024 / Accepted: 16 October 2024

Abstract

This study aims to analyze the differential expression of METTL14 in pancreatic cancer (PC) tissues and adjacent normal tissues, and its correlation with clinical outcomes. According to the inclusion and exclusion criteria, a total of 80 patients diagnosed in our hospital from January 2021 to January 2023 were chosen as research subjects. RTQ-PCR has detected the mRNA level expression of METTL14 in cancer and para-cancerous tissues. Immunohistochemistry was used to detect the protein expression of METTL14 in cancer and para-cancerous tissues. To compare the relationship between METTL14 expression and clinicopathological parameters in different PC patients. Kaplan–Meier survival analysis of the relationship between METTL14 expression in PC tissues and patient survival prognosis. The Multifactor COX model evaluates factors affecting the prognosis of PC. The expression level of METTL14 mRNA in PC tissues was 5.51 ± 0.35 (kDa), and the positive rate of METTL14 protein expression in PC tissues of all patients was 73.75 (59/80). Tumor location ($P = 0.012$), tumor differentiation degree ($P = 0.028$), tumor AJCC stage ($P = 0.000$), and lymph node metastasis ($P = 0.000$) were significantly related to the positive rate of METTL14 protein expression in PC tissue. Follow-up results showed that among 80 patients, 63 died. The three-year survival rate of the METTL14 positive group was 13.56% (8/59), and the three-year survival rate of the negative group was 42.86% (9/21). The difference in the three-year survival rate between METTL14 positive and negative expression groups was statistically significant ($P = 0.031$). Multivariate COX regression analysis results showed that METTL14 was positive (OR 2.797, 95% CI 1.233–5.877), tumor AJCC stage II–III (OR 1.628, 95% CI 1.435–3.859) and lymph node metastasis (OR 1.733, 95% CI 1.122–2.372) were substantive risk factors for poor prognosis in patients with PC. METTL14 expression increases in PC tissue, which is related to tumor AJCC stage, tumor differentiation, and lymph node metastasis, and can be evaluated in the survival prognosis of patients with PC.

Keywords Pancreatic cancer · Methyltransferase 14 (METTL14) · Prognosis · Tumor AJCC stage · Tumor differentiation · Lymph node metastasis

Introduction

Pancreatic cancer (PC) is one of the most lethal cancers in the world, and the overall five-year survival rate of PC patients is only 11% [1]. In 2020, there were 496,000 new cases of pancreatic cancer worldwide, ranking 12th among malignant tumors, and 466,000 deaths, ranking seventh. The number of deaths and the number of incidences were almost equal [2]. Due to the tumor biological characteristics of PC, which progresses rapidly and is easy to metastasize, as well as the anatomical characteristics of the pancreas, which is deep in location and has many adjacent organs, the surgical resection rate is only 20%. Surgery is currently the only possible cure for PC. In addition, the biological characteristics of PC tumors determine their high recurrence rate and low sensitivity to chemotherapy and radiotherapy. The five-year survival rate of patients after RO resection is only 25% [3]. Most patients are already in the intermediate and paramount stages when confirmed. At the same time, PC is not sensitive to radiotherapy and chemotherapy and

✉ Cong Wang
CongWang1@yeah.net

[1] Department of Radiology, Shengjing Hospital of China Medical University, Shenyang 110000, China

[2] Department of General Surgery, Shengjing Hospital Affiliated to China Medical University Shenbei Campus, No. 16 Puhe Avenue, Shenbei New District, Shenyang 110000, Liaoning Province, China

Published online: 11 November 2024

is one of the main lethal tumors. Because the prognosis of PC is extremely poor, despite years of arduous exploration in the diagnosis and treatment of PC, its survival rate has not been significantly improved [4]. It is generally believed that genetic factors, smoking, excessive drinking, high-fat diet, and excessive body mass index are the main risk factors for PC. In addition, chronic pancreatitis, diabetes, etc. are also concerning the occurrence of PC. Although some progress has been made in the treatment of PC, the results of treatment are not satisfactory [5]. The poor prognosis of PC patients is due to their high malignancy, advanced stage at diagnosis, and lack of effective treatments. Therefore, we need to fully understand the molecular mechanisms of PC occurrence and development, and find new molecular therapeutic targets, which is very meaningful to improve the prognosis of PC patients.

The occurrence of PC is premeditated to be a multi-step progressive process relate to genomic changes and epigenetic dysregulation [6, 7]. At the genomic level, the progression of PC is caused by the activation of a series of inactivation of oncogenes and tumor suppressor genes. For example, the mutational inactivation of KRAS and inactivation of some tumor suppressor genes p53, CDNK2A/p16, DPC4/SMAD4, and BRCA2 [8, 9]. KRAS is a G protein family that is mutated in more than 90% of PCs and can activate the downstream RAF-MEK-ERK tertiary kinase cascade. It can induce the occurrence of PC and promote the evolution of PC in both in vivo and in vitro models [10–12]. The literature has reported that a variety of molecular mechanisms can promote the activation of the RAS-MAPK signaling pathway, such as point mutations and microRNA [13, 14]. Inhibitors targeting KRAS and its key downstream signaling pathways, such as targeting Raf, MEK, and PI3K, have been developed and have shown effective anti-cancer activity [15, 16]. Literature reports that the RAS-MAPK signaling pathway is activated in 76% of lung cancer cases, suggesting that the activation of the miR-activated RAS-MAPK signaling pathway may be related to the development of lung cancer [17]. Last few years, post-transcriptional regulatory events, such as RNA methylation, have attracted more and more attention from researchers and have become a new mechanism for regulating tumorigenesis [18]. In mammalian messenger RNA, N6-methyladenine is the most common internal RNA modification [19]. 6-methyladenine is transferred from the methyl group to the sixth nitrogen atom on adenine by the methyltransferase complex METTL3, METTL14, and WTAP [20]. At the same time, it can also be oxidized by demethylases FTO and ALKBH5 [21]. m6A-modified RNA is specifically recognized by YTHDF1, YTHDF2, and YTHDF3 proteins in cells and regulates the downstream functions of RNA. In mammals, 6-methyladenine modification is involved in multiple physiological processes, such as regulating the self-renewal and circadian clock of mouse embryonic stem cells [22]. Studies have shown that 6-methyladenine can regulate processes such as messenger RNA shearing, nuclear export, protein translation, and degradation. Last few years, it has been published in the literature that RNA methylation regulates the development and occurrence of solid tumors. In the liver cancer cell line HepG2, in vitro experiments confirmed that knocking out METTL3 in the cell line can induce apoptosis of liver cancer cells [23]. A study reported that the reduced expression abundance of methylated RNA in liver cancer is related to the reduced methylase METTL14. In vivo and in vitro experiments confirmed that gene knockout of METTL14 can significantly inhibit the metastasis and invasion of liver cancer cells [24]. The RAS-MEK signaling pathway, which plays a pivotal role in the regulation of cell proliferation and survival, has been shown to be frequently dysregulated in pancreatic cancer. This pathway may interact with epigenetic modulators such as METTL14, influencing tumorigenesis. However, the expression abundance, role, and regulatory mechanism of 6-methyladenine in PC are still unknown.

In recent years, studies have found that METTL14 expression was upregulated in malignant tumors such as colorectal cancer [25]. and gastric cancer [26]. It can promote N6-methyladenosine (m6A) modification of non-coding RNAXIST, enhance tumor cell proliferation and metastasis, and participate in the formation of drug resistance to radiotherapy and chemotherapy, which is intimately related to the poor prognosis of tumor patients. But, there are still few reports on the expression and clinical meaning of METTL14 in PC. Therefore, this study used real-time fluorescence quantitative PCR and immunohistochemistry to detect the expression of METTL14 in PC tissues at the mRNA level and protein level respectively, and explored the clinical significance of both.

Methods and materials

Research object

80 patients with PC diagnosed in our hospital from January 2021 to January 2023 were chosen as the subjects of this study. There were 48 male cases and 32 female cases, aged 42–76 (63.51 ± 6.08) years old. Tumor AJCC staging was carried out according to the seventh version of the American Joint Committee of Cancer staging criteria in 2009: 35 cases were in stage I, 41 cases in stage II, and four cases in stage III. The degree of tumor differentiation: 53 cases were moderately differentiated and 27 cases were poorly differentiated. Tumor diameter: ≤ 4 cm in 51 cases and > 4 cm in 29 cases; tumor location: pancreatic head in 55 cases and pancreatic body and tail in 25 cases; in 39 cases lymph node metastasis (Table 1).

Table 1 Basic characteristics

Characteristic	Category	Number of cases ($n=80$)	Percentage (%)
Gender	Male	48	60
	Female	32	40
AJCC Stage	I	35	43.75
	II	41	51.25
	III	4	5
Tumor differentiation	Moderately differentiated	53	66.25
	Poorly differentiated	27	33.75
Tumor diameter	≤ 2 cm	27	33.75
	2–4 cm	24	30.00
	> 4 cm	29	36.25
Tumor location	Pancreatic head	55	68.75
	Pancreatic body and tail	25	31.25
Lymph node metastasis	Yes	39	48.75
	No	41	51.25
Age (years)	42–50	35	43.75
	51–60	21	26.25
	61–70	17	21.25
	> 70	7	8.75

Inclusion and exclusion criteria

Inclusion criteria: (a) There is no adjuvant treatment for tumors before surgery, and postoperative pathological examination confirms PC; (b) Initial diagnosis and treatment; (c) Clinical follow-up data are complete with a minimum follow-up duration of 12 months; (d) Age between 18 and 75 years. Exclusion criteria: (a) received anti-tumor treatment before surgery; (b) complicated by other types of tumors; (c) complicated by autoimmune system diseases. This study was approved by the patient's informed signature and officially recognized by the ethics committee of our hospital.

Instruments and reagents

Narodrop1000 micro-volume spectrophotometer (Nanodrop Company, USA); reverse transcription kit (Beijing Quanshijin Company, Cat. No. 11141ES10); METTL14 and GAPDH primers were synthesized by Sangon Company; PCR Master Mix (Japanese TAKARA Company, Cat. No. RR320A); METTL14 monoclonal antibody (Abcam Company, Cat. No. ab220030); SP-9000 immunohistochemistry kit (Beijing Zhongshan Jinqiao Company); CX31 microscope (Olympus Company, Japan).

The PCR primers used for the amplification of the target genes were designed based on sequences obtained from the NCBI database.

Fluorescence quantitative PCR detection

Use the Trizol method to extract RNA from cancer tissues and adjacent tissues, and detect the $A_{260\ nm}/A_{280\ nm}$ of RNA between 1.8 and 2.0. Reverse transcription into cDNA followed by fluorescence quantitative polymerase chain reaction. Primer sequence METTL14: upstream: 5′-AAAAGT TGACGCCGCATTCT-3′, downstream 5′- ACACTCCAG CTGGGCGACGAAAACCCUAA-3′. The reaction system totaled 20 μl, including 1 μl each upstream and downstream primer, 2 μl cDNA, 10 μl SYBR Green, and 6 μl DEPC water. The conditions were: 95 °C for 5 min, denaturation at 95 °C for 25 s, annealing at 60 °C for 30 s, extension at 70 °C for 15 s, and a total of 35 cycles of denaturation, annealing, and enlarge. The expression of METTL14 mRNA was expressed using the $2^{-\Delta\Delta Ct}$ value method.

Immunohistochemical testing

Cancer and paracancerous tissues were fixed overnight with 10 g/dl neutral formaldehyde, embedded in paraffin, sectioned, and stained according to conventional immunohistochemical staining procedures. The slides were mounted in neutral resin, and METTL14 protein staining was observed under a 200× microscope and immunohistochemical staining was scored (staining intensity score multiplied by stained area). The staining area is divided into 0 points: area ≤ 25%, 1 point: area 25–50%, and 2 points: area ≥ 50%.

An immunohistochemistry staining score < 2 was classified as negative, and a score ≥ 2 was classified as positive.

Statistical analysis

The data in this research were analyzed by SPSS 26.0 software, including counting data and measurement data. The former is represented by "[*n* (%)]" and "χ^2" is used for testing, and the latter is represented by mean ± standard deviation ($\_x \pm s$) and takes "*t*" to carry out the test. Count data were expressed as rates, and chi-square tests were used for comparisons between groups. Survival analysis used the Kaplan–Meier method (Log-rank test). Multifactor COX regression analysis of factors affecting survival and prognosis of PC. If $P < 0.05$, it can be confirmed that the data difference is significant.

Result

Expression of METTL14 mRNA and protein in PC and adjacent tissues

The expression level of METTL14 mRNA in tissues of PC was 5.51 ± 0.35 (kDa), and the positive rate of METTL14 protein expression in PC tissues of all patients was 73.75 (59/80) (Table 2).

Table 2 Expression of METTL14 mRNA and protein in PC and adjacent tissues

Pancreatic cancer	METTL14	
	mRNA (kDa)	Protein (%)
Paracancerous tissue	5.51 ± 0.35	59/80 (73.75)

The relationship between METTL14 protein expression and clinicopathological characteristics

The results of our analysis demonstrated that tumor location, tumor differentiation, tumor AJCC stage, and lymph node metastasis were significantly related to the positive rate of METTL14 protein expression in PC tissues (all $P < 0.05$) (Table 3 and Fig. 1).

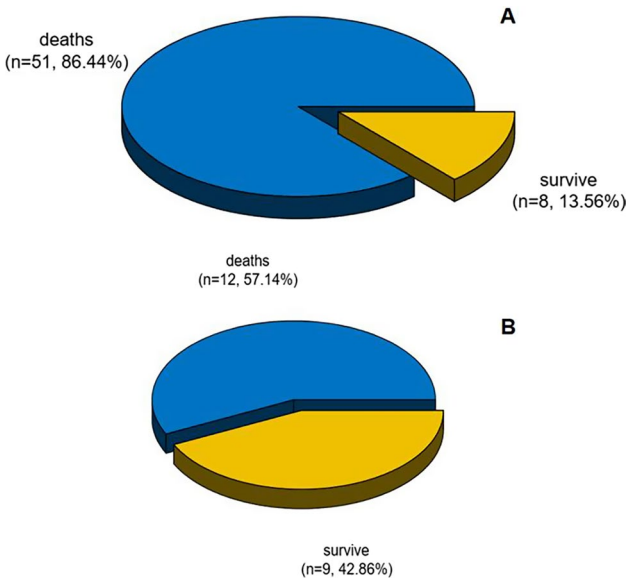

Fig. 1 Tumor location, tumor differentiation degree, tumor AJCC stage, and METTL14 protein expression in lymph node metastasis

Table 3 Relationship between METTL14 protein expression and clinicopathological characteristics [*n* (%)]

Category		*n*	METTL14 positive	*t*	*P*
Gender	Male	48	37 (77.08)	0.689	0.4078
	Female	32	22 (68.75)		
Age	≤ 60	36	25 (69.44)	0.627	0.429
	> 60	44	34 (77.27)		
Tumor diameter (cm)	≤ 4	51	34 (66.67)	3.646	0.056
	> 4	29	25 (86.21)		
Tumor location	Head of the pancreas	55	36 (65.45)	6.256	0.012
	Body and tail of the pancreas	25	23 (92.00)		
Degree of tumor differentiation	High, moderate differentiation	53	35 (66.04)	4.825	0.028
	Low differentiation	27	24 (88.89)		
Tumor AJCC staging	I	35	19 (54.29)	12.177	0.000
	II–III	45	40 (88.89)		
Lymph node metastasis	Had	39	38 (97.44)	22.053	0.000
	No	41	21 (51.22)		

Table 4 Three-year survival rate of METTL14 positive and negative expression groups

METTL14	Deaths	Three-year survival rate
Positive ($n=59$)	51	13.56 (8/59)
Negative ($n=21$)	12	42.86 (9/21)
p	0.031	

Effect of METTL14 protein expression on survival prognosis of patients with PC

We followed up on all patients for 2–36 months, and no one was lost to follow-up. Among 80 patients, 63 died. The three-year survival rate of the METTL14 positive expression was 13.56% (8/59), and the three-year survival rate of the negative expression was 42.86% (9/21) (Table 4 and Fig. 2). The difference in three-year survival rates between METTL14 positive and negative expression groups was significant ($P=0.031$).

Analysis of factors affecting the prognosis of patients with PC

Multivariate COX regression analysis results (Table 5) showed that METTL14 positivity, tumor AJCC stage II–III, and lymph node metastasis were substantive risk factors for poor prognosis in patients with PC.

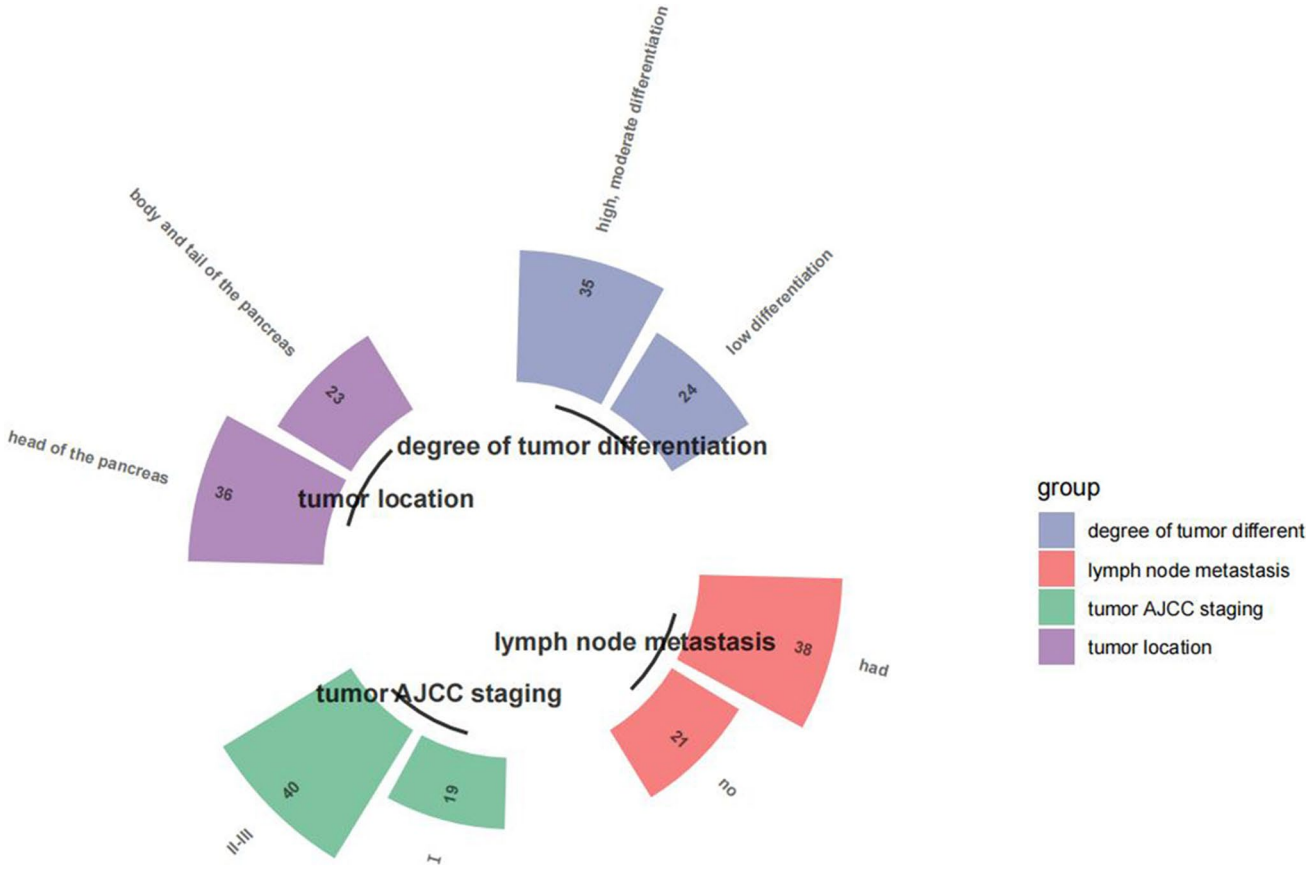

Fig. 2 Three-year survival rate of METTL14 expression groups. **A** Positive; **B** negative

Table 5 Multifactor COX proportional hazards regression model affecting the prognosis of patients with pancreatic cancer

category	β	SE	Wald χ^2	P	OR	95% CI
METTL14	0.946	0.405	5.526	0.012	2.797	1.233–5.877
Tumor AJCC staging	0.902	0.264	9.598	0.000	1.628	1.435–3.859
Lymph node metastasis	0.560	0.251	6.878	0.000	1.733	1.122–2.372

Discussion

PC is a highly detrimental digestive system tumor with an insidious onset, rapid disease progression, and extremely poor prognosis. Although the level of relevant medical diagnosis and treatment continues to advance, the five-year survival rate of PC is less than 10% [27]. In the early stages of PC, cancer cells can directly invade the tissues around the pancreas or metastasize to adjacent and distant organs through lymph and/or blood vessels. More than 80% of PC patients are in the paramount stage when confirmed. Therefore, patients with PC have rare opportunities for surgical treatment, and the tumor is insensitive to both chemotherapy and radiotherapy, resulting in poor prognosis for patients. Last several years, with the improvement of tumor molecular biology research, new therapeutic drugs, and strategies have been developed, such as immune checkpoint blockade therapy, tyrosine kinase inhibitor drug therapy, allowing tumor patients to obtain good clinical effects [28]. Consequently, it is of great implication to greatly explore the pathogenesis of PC and find new clinical treatment targets.

The chance and development of PC are related to abnormal epigenetic modifications, such as DNA or RNA methylation modifications, lactation modifications. m6A modification is the most common modification method among RNA post-transcriptional modifications. It is catalyzed by m6A methyltransferase, demethylase, and m6A-binding protein. It is widely involved in cell differentiation, cell stress, apoptosis, and other cellular activities [29]. METTL14 is a new m6A methyltransferase that can combine with METTL3 to form a heterodimer and participate in the regulation of RNA metabolism and other processes [30]. Last several years, it has been found that METTL14 is abnormally conveyed up-or down-regulated in malignant tumors such as colorectal cancer, and it accelerates the growth and irrupts of colorectal cancer cells by promoting the expression of high mobility gene group 4 mRNA [31, 32]. In this study, METTL14 expression was significantly increased in PC, suggesting that METTL14 may be involved in the tumorigenesis of PC. Previous studies have also confirmed that m6A modification is common in 70% of PCs, and METTL14 is the main methyltransferase in PCs [33]. Studies have shown that the CDC-like kinase 1/serine- and arginine-rich splicing factor five signaling axis in PC upregulates METTL14 protein expression by promoting the alternative splicing of METTL14 [34]. In addition, METTL14 expression in PC is integrated with adverse clinicopathological characteristics, suggesting that METTL14 expression is touched upon in promoting the malignant development of PC.

Studies have reported that METTL14 in PC modifies PMP22-related p53 effector mRNA through m6A, thereby enhancing the proliferation, invasion, and metastasis capabilities of PC tumor cells [34]. In addition, increased expression of METTL14 can promote epithelial-mesenchymal transition in tumor cells, and the expression of mesenchymal phenotype N-cadherin is increased. However, epithelial phenotypes such as down-regulation of E-cadherin expression enhance the invasion and metastasis capabilities of tumor cells, pushing tumor lymphatic metastasis, and leading to an increase in tumor stage [35]. Therefore, the expression of METTL14 in PC facilitates the tumor to make headway in PC. We followed up on patients with PC and found that patients with positive expression of METTL14 had a poor survival prognosis. It is a substantive risk factor that influences the poor survival prognosis of patients with PC, indicating that METTL14 may be a new tumor marker related to the prognosis of PC. Based on this analysis, PC tumor cells with positive expression of METTL14 have more significant malignant biological behaviors such as proliferation and invasion. Patients with higher AJCC stages demonstrated a significantly increased likelihood of lymph node metastasis, highlighting the aggressive nature of their disease. In addition, upregulation of METTL14 expression can also enhance the development of revolt to cisplatin treatment in non-small cell lung cancer by activating the expression of RNA-binding protein 24/axis development inhibitory factor, leading to poor patient prognosis. Therefore, clinicians can evaluate the clinical prognosis of patients with PC based on the expression of METTL14, and actively provide diagnosis and treatment to improve the patient's prognosis.

In short, this study found that METTL14 expression was added in PC, and their expression is related to tumor AJCC stage, tumor differentiation, and lymph node metastasis. And jointly participate in promoting the tumor progression of PC, and are new tumor markers related to the prognosis of PC patients. Yet, the case of patients included in this study was limited, and no in-depth experimental research was conducted on the specific mechanisms of action of the two in PC, which needs to be further explored in the future.

Acknowledgements We would like to acknowledge the hard and dedicated work of all the staff that implemented the intervention and evaluation components of the study.

Author contributions MSY and WC conceived the idea and conceptualized the study. MSY collected the data. MSY and WC analyzed the data. MSY and WC drafted the manuscript, then MSY reviewed the manuscript. All authors read and approved the final draft.

Funding No external funding received to conduct this study.

Data availability All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and consent to participate This study was approved by the patient's informed signature and officially recognized by the ethics committee of China Medical University Affiliated Shengjing Hospital Shenbei Campus. This study was conducted in accordance with the declaration of Helsinki.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7–33. https://doi.org/10.3322/caac.21708.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49. https://doi.org/10.3322/caac.21660.
3. Puckett Y, Garfield K. Pancreatic cancer. StatPearls. 2022. https://www.ncbi.nlm.nih.gov/books/NBK518996/.
4. Zhao BS, Roundtree IA, He C. Post-transcriptional gene regulation by mRNA modifications. Nat Rev Mol Cell Biol. 2016;18(1):31–42. https://doi.org/10.1038/nrm.2016.132.
5. Elliott BA, Ho HT, Ranganathan SV, Vangaveti S, Ilkayeva O, Assi HA, Choi AK, Agris PF, Holley CL. Modification of messenger RNA by 2′-omethylation regulates gene expression in vivo. Nat Commun. 2019. https://doi.org/10.1038/s41467-019-11375-7.
6. Wang P, Doxtader KA, Nam Y. Structural basis for cooperative function of Mettl3 and Mettl14 methyltransferases. Mol Cell. 2016;63(2):306–17. https://doi.org/10.1016/J.MOLCEL.2016.05.041.
7. Zhang C, Fu J, Zhou Y. A review in research progress concerning m6A methylation and immunoregulation. Front Immunol. 2019;10:423288. https://doi.org/10.3389/FIMMU.2019.00922/BIBTEX.
8. Liu J, Li K, Cai J, Zhang M, Zhang X, Xiong X, Meng H, Xu X, Huang Z, Peng J, Fan J, Yi C. Landscape and regulation of m6A and m6Am methylome across human and mouse tissues. Mol Cell. 2020;77(2):426-440.e6. https://doi.org/10.1016/J.MOLCEL.2019.09.032.
9. Liu J, Yue Y, Han D, Wang X, Ye F, Zhang L, Jia G, Miao Y, Zhike L, Deng X, Dai Q, Chen W, He C. A METTL3–METTL14 complex mediates mammalian nuclear RNA N6-adenosine methylation. Nat Chem Biol. 2013;10(2):93–5. https://doi.org/10.1038/nchembio.1432.
10. Boccaletto P, MacHnicka MA, Purta E, Pitkowski P, Baginski B, Wirecki TK, De Crécy-Lagard V, Ross R, Limbach PA, Kotter A, Helm M, Bujnicki JM. MODOMICS: a database of RNA modification pathways. 2017 update. Nucleic Acids Res. 2018;46(D1):D303–7. https://doi.org/10.1093/nar/gkx1030.
11. Linder B, Grozhik AV, Olarerin-George AO, Meydan C, Mason CE, Jaffrey SR. Single-nucleotide-resolution mapping of m6A and m6Am throughout the transcriptome. Nat Methods. 2015;12(8):767-U114. https://doi.org/10.1038/nmeth.3453.
12 Liu WW, Wang H, Zhu XY. Physio-pathological effects of N6-methyladenosine and its therapeutic implications in leukemia. Biomark Res. 2022;10(1):1–15. https://doi.org/10.1186/S40364-022-00410-3.
13. Mo W, Chen Z, Zhang X, Dai G, Ma D, Pan J, Zhang X, Wu G, Fan W. N6-methyladenosine demethylase FTO (fat mass and obesity-associated protein) as a novel mediator of statin effects in human endothelial cells. Arterioscler Thromb Vasc Biol. 2022;42(5):644–58. https://doi.org/10.1161/ATVBAHA.121.317295.
14. Wei J, Liu F, Lu Z, Fei Q, Ai Y, He PC, Shi H, Cui X, Su R, Klungland A, Jia G, Chen J, He C. Differential m6A, m6Am, and m1A demethylation mediated by FTO in the cell nucleus and cytoplasm. Mol Cell. 2018;71(6):973-985.e5. https://doi.org/10.1016/J.MOLCEL.2018.08.011.
15. Huang C, Chen W, Wang X. Studies on the fat mass and obesity-associated (FTO) gene and its impact on obesity-associated diseases. Genes Dis. 2023;10(6):2351–65. https://doi.org/10.1016/J.GENDIS.2022.04.014.
16. Ruud J, Alber J, Tokarska A, Engström Ruud L, Nolte H, Biglari N, Lippert R, Lautenschlager Ä, Cieślak PE, Szumiec Ł, Hess ME, Brönneke HS, Krüger M, Nissbrandt H, Korotkova T, Silberberg G, Rodriguez Parkitna J, Brüning JC. The fat mass and obesity-associated protein (FTO) regulates locomotor responses to novelty via D2R medium spiny neurons. Cell Rep. 2019;27(11):3182-3198.e9. https://doi.org/10.1016/J.CELREP.2019.05.037.
17. Gholamalizadeh M, Doaei S, Kalantari N, Mohammadi NK, Izadi P, Eini-Zinab H, Salonurmi T, Jarrahi AM, Rafieifar S, Janipoor R, Sadeghypor M, Tabesh GA, Goodarzi MO, Doaei S, Kalantari N, Mohammadi NK, Izadi P, Gholamalizadeh M, Eini-Zinab H, Goodarzi MO. Up-regulation of FTO gene expression was associated with increase in skeletal muscle mass in overweight male adolescents. Arch Med Sci. 2019;15(5):1133–7. https://doi.org/10.5114/AOMS.2019.87239.
18. Chang JY, Park JH, Park SE, Shon J, Park YJ. The fat mass- and obesity-associated (FTO) gene to obesity: lessons from mouse models. Obesity. 2018;26(11):1674–86. https://doi.org/10.1002/OBY.22301.
19. Qu J, Hou Y, Chen Q, Chen J, Li Y, Zhang E, Gu H, Xu R, Liu Y, Cao W, Zhang J, Cao L, He J, Cai Z. RNA demethylase ALKBH5 promotes tumorigenesis in multiple myeloma via TRAF1-mediated activation of NF-κB and MAPK signaling pathways. Oncogene. 2021;41(3):400–13. https://doi.org/10.1038/s41388-021-02095-8.
20. Jain S, Koziej L, Poulis P, Kaczmarczyk I, Gaik M, Rawski M, Ranjan N, Glatt S, Rodnina MV. Modulation of translational decoding by m6A modification of mRNA. Nat Commun. 2023;14(1):1–13. https://doi.org/10.1038/s41467-023-40422-7.
21. Shi H, Wang X, Lu Z, Zhao BS, Ma H, Hsu PJ, Liu C, He C. YTHDF3 facilitates translation and decay of N6-methyladenosine-modified RNA. Cell Res. 2017;27(3):315–28. https://doi.org/10.1038/CR.2017.15.
22. Zong X, Xiao X, Shen B, Jiang Q, Wang H, Lu Z, Wang F, Jin M, Min J, Wang F, Wang Y. The N6-methyladenosine RNA-binding protein YTHDF1 modulates the translation of TRAF6 to mediate the intestinal immune response. Nucleic Acids Res. 2021;49(10):5537–52. https://doi.org/10.1093/NAR/GKAB343.

23. Deng X, Su R, Stanford S, Chen J. Critical enzymatic functions of FTO in obesity and cancer. Front Endocrinol. 2018;9:380335. https://doi.org/10.3389/FENDO.2018.00396/BIBTEX.
24. Darnell RR, Shengdong KE, Darnell JE. Pre-mRNA processing includes N6 methylation of adenosine residues that are retained in mRNA exons and the fallacy of "RNA epigenetics." RNA. 2018;24(3):262–7. https://doi.org/10.1261/RNA.065219.117.
25. Yang X, Zhang S, He C, Xue P, Zhang L, Zirui He L, Zang BF, Sun J, Zheng M. METTL14 suppresses proliferation and metastasis of colorectal cancer by down-regulating oncogenic long non-coding RNA XIST. Mol Cancer. 2020. https://doi.org/10.1186/s12943-020-1146-4.
26 Fan H-N, Chen Z-Y, Chen X-Y, Chen M, Yi Y-C, Zhu J-S, Zhang J. METTL14-mediated m6A modification of circORC5 suppresses gastric cancer progression by regulating miR-30c-2-3p/AKT1S1 axis. Mol Cancer. 2022. https://doi.org/10.1186/s12943-022-01521-z.
27. Chen L, Zhu Z, Ye S, Zheng M. The serum uric acid to serum creatinine ratio is an independent risk factor for diabetic kidney disease. Diabetes Metab Syndr Obes Targets Ther. 2022;15:3693. https://doi.org/10.2147/DMSO.S387426.
28. Yuan M, Abuduhaibaier S, Ren S, Zheng L, Yuan C. Characteristics of pancreatic ductal adenocarcinoma immune microenvironment and related immunotherapy strategies. Zhonghua Yi Xue Za Zhi. 2021;101(12):831–5. https://doi.org/10.3760/CMA.J.CN112137-20201027-02938.
29. Tang Y, Chen K, Song B, Ma J, Wu X, Xu Q, Wei Z, Su J, Liu G, Rong R, Lu Z, De Magalhães JP, Rigden DJ, Meng J. m6A-atlas: a comprehensive knowledgebase for unraveling the N6-methyladenosine (m6A) epitranscriptome. Nucleic Acids Res. 2021;49(D1):D134–43. https://doi.org/10.1093/NAR/GKAA692.
30. Yang Z, Yang S, Cui Y-H, Wei J, Shah P, Park G, Cui X, He C, He Y-Y. METTL14 facilitates global genome repair and suppresses skin tumorigenesis. Proc Natl Acad Sci. 2021. https://doi.org/10.1073/pnas.2025948118.
31. Chen X, Xu M, Xu X, Zeng K, Liu X, Pan B, Li C, Sun L, Qin J, Xu T, He B, Pan Y, Sun H, Wang S. METTL14-mediated N6-methyladenosine modification of SOX4 mRNA inhibits tumor metastasis in colorectal cancer. Mol Cancer. 2020. https://doi.org/10.1186/S12943-020-01220-7.
32 Fan HN, Chen ZY, Chen XY, Chen M, Yi YC, Zhu JS, Zhang J. METTL14-mediated m6A modification of circORC5 suppresses gastric cancer progression by regulating miR-30c-2–3p/AKT1S1 axis. Mol Cancer. 2022. https://doi.org/10.1186/S12943-022-01521-Z.
33. Chen S, Yang C, Wang ZW, Hu JF, Pan JJ, Liao CY, Zhang JQ, Chen JZ, Huang Y, Huang L, Zhan Q, Tian YF, Shen BY, Wang YD. CLK1/SRSF5 pathway induces aberrant exon skipping of METTL14 and cyclin L2 and promotes growth and metastasis of pancreatic cancer. J Hematol Oncol. 2021. https://doi.org/10.1186/S13045-021-01072-8.
34. Wang M, Liu J, Zhao Y, He R, Xu X, Guo X, Li X, Xu S, Miao J, Guo J, Zhang H, Gong J, Zhu F, Tian R, Shi C, Peng F, Feng Y, Yu S, Xie Y, Qin R. Upregulation of METTL14 mediates the elevation of PERP mRNA N6 adenosine methylation promoting the growth and metastasis of pancreatic cancer. Mol Cancer. 2020. https://doi.org/10.1186/S12943-020-01249-8.
35. Wen J, Zhang G, Meng Y, Zhang L, Jiang M, Yu Z. RNA m6A methyltransferase METTL3 promotes colorectal cancer cell proliferation and invasion by regulating snail expression. Oncol Lett. 2021. https://doi.org/10.3892/OL.2021.12972.