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METTL14 promotes prostate tumorigenesis by inhibiting THBS1 via an m6A-YTHDF2-dependent mechanism

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N6-methyladenine (m6A) is the most predominant RNA modification, which has been shown to be related to many types of cancers. However, understanding of its role in prostate cancer (PCa) is largely unknown. Here, we report an upregulation of METTL14 that was correlated with poor prognosis in PCa patients. Functionally, knocking down METTL14 inhibited tumor proliferation both in vitro and in vivo. Mechanically, RNA-seq and MeRIP-seq analyses identified THBS1 as the downstream target of METTL14 in PCa. METTL14 downregulated THBS1 expression in an m6A-dependent manner, which resulted in the recruitment of YTHDF2 to recognize and degrade Thrombospondin 1 (THBS1) mRNA. Thus, our findings revealed that METTL14 acted as an oncogene by inhibiting THBS1 expression via an m6A-YTHDF2-dependent manner. METTL14 could be a potential prognosis marker and a therapeutic target.

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INTRODUCTION

Prostate cancer (PCa) is the most common male cancer and represents the sixth cause of cancer death in men worldwide [1, 2]. Nowadays, for patients with advanced PCa, androgen deprivation therapy (ADT) has been the primary therapy for decades of years. Despite the initial response to androgen deprivation therapy (ADT), the majority of patients relapse with a poor prognosis stage of castration-resistant prostate cancer (CRPC). Patients with CRPC cannot be cured currently and the mortality remains high [3, 4]. Thus, understanding of the mechanisms underlying PCa progression is essential for molecular diagnosis and targeted therapy.

Traditionally, epigenetic regulations consist of diverse modifications on DNA and histone, which are a series of reversible biological processes regulating gene expression without changing the genome sequences [5]. Previous studies have found that many epigenetic regulators on DNA and histone methylation have important effects on PCa progression [6]. These studies have provided a novel epigenetic view for exploring promising targeted therapies for PCa. Apart from these regulators on DNA or histone, in recent years, accumulating studies have focused on RNA modification, especially methyladenine (m6A) modification, which is the most prevalent post-transcriptional alteration [7, 8]. As a dynamic and reversible process, m6A modification is installed to RNA by m6A methyltransferases(writers), including methyltransferase-like 3 (METTL3) [9], methyltransferase-like14 (METTL14) [10], and Wilms tumor 1 associated protein (WTAP) [11], and removed by alkylation repair homolog protein(ALKBH5) and Fat mass and obesity-associated protein (FTO), which both act as m6A demethylases (erasers) [12]. Besides, there are some proteins, called m6A readers, exerting their functions in recruiting and binding to m6A sites, like YTH domain-containing family protein 1/2/3(YTHDF1/2/3) and insulin-like growth factor 2 mRNA binding proteins 1/2/3 (IGF2BP1/2/3) [12]. The alterations of these m6A effectors have been implicated in many types of cancers, such as lung cancer [13], hepatocarcinoma [14], and colorectal cancer [15]. It has been previously shown that METTL3 drives migratory and invasive capacities of PCa cells via mediating m6A modification of USP4 mRNA in a YTHDF2-dependent manner [16]. METTL14, as the indispensable allosteric activator of METTL3, has been shown to play an important role in tumor progression in many types of cancers [17–19]. However, the biological significance of METTL14 in PCa has not been elucidated.

In this study, we report that METTL14 promoted the progression of PCa and identified Thrombospondin 1 (THBS1), an endogenous inhibitor of angiogenesis [20], as its downstream target. Moreover, a member of m6A readers, YTHDF2, was recruited for THBS1 mRNA decay. Collectively, our investigation proposes that METTL14 may be a novel prognosis marker and a potential therapeutic target for PCa.

RESULTS

Upregulation of METTL14 is correlated with poor prognosis of PCa patients

To quantify METTL14 expression in PCa patients, we performed IHC staining on a tissue microarray containing prostate tumor tissue specimens ($n = 49$) and adjacent normal prostate tissue specimens ($n = 11$). The staining results indicated that METTL14 was highly expressed in PCa tissues compared to the normal ones

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