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Mechanism for METTL6-Mediated m3C RNA Methylation in Terms of its Structure

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ABSTRACT

RNA modifications are critical in mediating how RNAs perform biological functions. Despite being less common, 3-methylcytidine (m3C) is discovered to be widely present in tRNAs, rRNAs, and mRNAs. A m3C methyltransferases for tRNAs, including transfer, is human METTL6 (UGA). In the presence of S-adenosyl-L-methionine, we were able to solve the structure of human METTL6, and an enzyme assay revealed that recombinant human METTL6 is active towards transfer (UGA). A putative tRNA binding area on the surface of METTL6 was identified by structural analysis, which also revealed the specific interactions between S-adenosyl-L-methionine and METTL6. In the near future, the design of effective METTL6 inhibitors will undoubtedly become clearer as a result of structural study that is accompanied by biochemical enzyme testing.

Keywords: Plant Biology, biochemistry,METTL6

INTRODUCTION

Numerous RNA modifications, such as localization, splicing, translation, and turnover, have been found to often occur inside practically all types of RNAs to mediate there in vivo functions [1,2]. The most popular kind is methylation of RNA. The two most common internal RNA modifications, N6-adenosine (m6A) and 5-methylcytosine (m5C) are specifically linked to the post-transcriptional control of gene expression in higher eukaryotes [1,3,4].

Some RNA modifications are known to be installed and deleted by RNA methyl Transferase ("writers") and Demethylases ("erasers"), similarly to covalent changes on proteins and DNAs. Some RNA alterations may be able to function biologically by being recognized by particular elements, or "readers," that are referred to as such. For instance, YTH domain proteins act as m6A reader proteins whereas *METTL14-METTL3* [5-7], *METTL5-TRMT112* [8, 9], and *METTL16* [10]. are recognized as m6A methyl transferase and *ALKBH5* and FTO function as demethylases [9,10], Other RNA methylation marks, such as 3-methylcytidine (m3C), are far less common than m6A and, until very recently, their biochemistry was not well known [5, 6]. This is in contrast to m6A, which may be found in a range of RNA types.

It has been discovered that m3C, which was first discovered to be a particular alteration inside rRNAs and tRNAs [7, 8], also occurs in mammalian mRNAs to control RNA fates [8]. Trm140 and Trm140/Trm141, which catalyse the m3C methylation on the tRNAs of *Saccharomyces pombe and S. cerevisiae*, respectively, were discovered to function as the mammalian tRNA m3C methyl transferase. To be more precise, *METTL2* adds m3C to tRNA Thr(UGU) and tRNA Arg(CCU), while *METTL6* catalyses' the m3C32 of tRNA Ser(AGA/UGA) found in is acceptors [6, 9]. Mettl6 deficiency has been shown to affect pluripotency and slow the proliferation of tumors cells [9], making it a possible target for pharmaceutical companies for developing inhibitors. However, due to a paucity of structural knowledge, it is still unclear how *METTL6* detects and catalyses' its tRNA substrates. Here, using the co-factor S-Adenosyl methionine (SAM), we were able to solve the crystal structure of human *METTL6* and discovered that it dis-plays a non-traditional Rossmann fold with seven beta strands. It was determined by the biochemistry enzyme test that METTL6 is a functional methyltransferases for transfer (UGA). As a result, our biochemistry and structural studies shed light on the inhibitor design for this m3C methyltransferases in addition to the catalytic mechanism of *METTL6.*

MATERIALS AND METHODS

Expression and purification of proteins In order to transform *E. coli BL21*, a cDNA fragment encoding the complete human

METTL6 (residues 1 to 284) was sub cloned into the pET28-MHL vector (DE3). After being induced by 1 mM (final concentration) isopropyl—D-1-thiogalactopyranoside, the recombinant protein was overexpressed at 16°C for 18 hours (IPTG). The cells were then suspended in a solution containing 20 mM Tris-HCl (pH 7.5), 400 mM NaCl, and lysed by centrifugation at 3600 g, 4°C, for 15 minutes.

RESULTS AND DISCUSSION

METTL6's identification as the transfer (UGA) m3C methyltransferases in earlier research served as inspiration. To examine the catalytic activity of human *METTL6* towards transfer (UGA) in vitro, we generated full-length recombinant human METTL6 protein through cloning, expression, and purification. We acquired two sets of kcat and KM values by employing the MTase-GloTM Methyltransferases assay, one for tRNASER (UGA) and the other for SAM. The transfer kcat/KM values (UGA).

Data Availability

The *RCSB* protein data bank has accession number 7F1E for the coordinates and structural elements of the structure of *METTL6* bound with SAM.

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