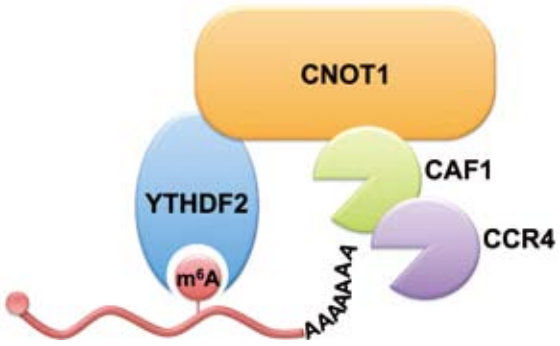
Mechanism of YTHDF2-mediated Degradation of M^{6}A-containing RNAs

Methylation at the *N6* position of adenosine (m^{6}A), which is a reversible process with important biological implications, is the most abundant internal modification within protein-coding and long noncoding RNAs in eukaryotes. YT521-B homology domain family (YTHDF) proteins are the readers of m^{6}A, the binding of which results in the alteration of the translation efficiency and stability of m^{6}A-containing RNAs. However, the underlying mechanism is poorly understood.

A team of researchers led by Prof. WU Ligang from the Institute of Biochemistry and Cell Biology (SIBCB), Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS), filled the gap by uncovering the mechanism of YTHDF2-mediated degradation of m^{6}A-containing RNAs in mammalian cells, and reported online in late August their discovery in *Nature Communications*.

The researchers used a pulse-chase system to monitor the decay of RNAs. They found that both m^{6}A modification and binding of YTHDF2 can destabilized RNA by hastening deadenylation (shortening of the poly(A) tail) as the initial step. Next they screened for interactions between YTHDF2 and components of the potential cellular deadenylase complexes. The results drew their attention to CCR4-NOT, a nine-subunit complex containing two deadenylase subunits (CAF1 and CCR4) and a large scaffold subunit, CNOT1. Dominant-negative assay confirmed that CAF1 and CCR4 are the ribonucleases responsible for the YTHDF2-mediated deadenylation. Further study showed that YTHDF2 recruited the CCR4-NOT complex through a direct interaction between the YTHDF2 N-terminal region and the SH domain of the CNOT1 subunit; and that this recruitment was essential for the deadenylation and decay of m^{6}A-containing RNAs.



YTHDF2 binds to the m^{6}A modification on RNA and recruits the CCR4-NOT deadenylase complex through direct interaction with CNOT1, thus promoting the deadenylation and decay of RNA. (Image provided by Prof. WU Ligang's lab)

Unveiling the mechanism of YTHDF2-mediated degradation of m^{6}A-containing RNAs in mammalian cells, this study might help further the understanding of RNA modifications on regulation of gene expression.

This work was conducted in collaboration with Prof. MA Jinbiao's lab of the School of Life Sciences, Fudan University.

Titled "YTHDF2 destabilizes m^{6}A-containing RNA through direct recruitment of the CCR4-NOT deadenylase complex", this has been published online in *Nature Communications* on August 25, 2016.

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