The RNA helicase DDX46 inhibits innate immunity by entrapping m^{6}A-demethylated antiviral transcripts in the nucleus

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Cao Xuetao (**曹雪涛**) at the National Key Laboratory of Medical Molecular Biology & Department of Immunology, Chinese Academy of Medical Sciences, and the National Key Laboratory of Medical Immunology, Second Military Medical University, recently reported that RNA helicase DDX46 is an important negative regulator of antiviral response, which was published in *Nature Immunology* (2017, 18: 1094—1103.).

Type I interferon (IFN) plays critical roles in innate defense against viral infection. However, previous studies of the molecular regulation of IFN production focused mainly on the cytosolic regulators of innate signaling. The roles of nuclear factors, especially epigenetic regulators, in the regulation of IFN production are still largely unknown. Most members of the DEAD-box (DDX) family are located in the nucleus and control nearly every aspect of RNA metabolism. Whether these factors participate in the regulation of IFN production needs further investigation.

Our group performed the iCLIP-seq and found that DDX46 bound *Mavs*, *Traf3* and *Traf6* transcripts, which encode signaling molecules in the innate antiviral pathway, via their conserved CCGGUU element. Further investigation showed that, upon viral infection, DDX46 recruited ALKBH5, an 'eraser' of the RNA modification N6-methyladenosine (m^{6}A), via DDX46's DEAD helicase domain, and then demethylated those m^{6}A-modified antiviral transcripts. It consequently enforced their retention in the nucleus and therefore suppressed their translation and downstream IFN production. Importantly, we also confirmed that DDX46 suppressed antiviral innate immune response *in vivo*. Thus, DDX46 inhibits antiviral innate response by entrapping selected antiviral transcripts in the nucleus by erasing their m^{6}A methylation, which is a modification normally required for mRNA export from nucleus to cytoplasm and translation.

These findings may provide new insight into the roles of m^{6}A RNA modification in the regulation of innate immune response and inflammation, and may provide potential targets for the control of viral infection and infectious diseases.

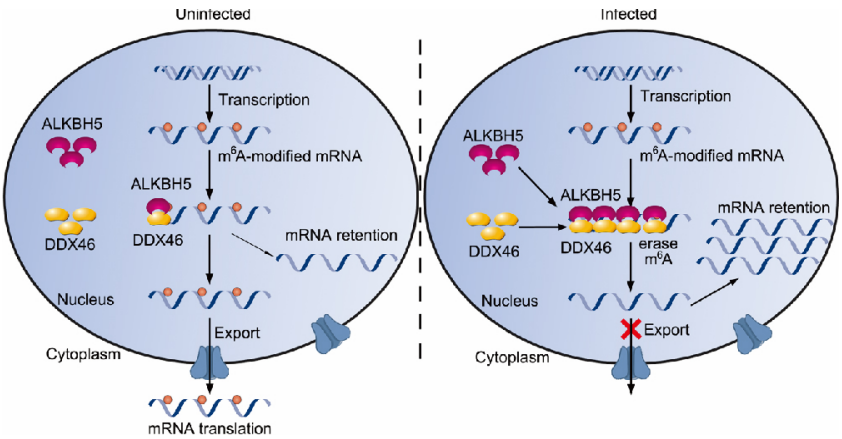

Figure Working model for the mechanism of RNA helicase DDX46 which recruits m^{6}A eraser ALKBH5 to inhibit antiviral innate immune response by entrapping m^{6}A-demethylated antiviral transcripts in the nucleus.