RNAi can be an antiviral immunity in mammals

Subject Code: H19

With the support by the National Natural Science Foundation of China, a collaborative study by the research groups led by Prof. Zhou Xi (**周溪**) from the State Key Laboratory of Virology, Wuhan Institute of Virology, Chinese Academy of Sciences and Prof. Qin Chengfeng (**秦成峰**) from Beijing Institute of Microbiology and Epidemiology demonstrates that RNAi can be induced and suppressed by human enterovirus 71 (HEV71), and function as antiviral immunity in mammals, which was published in *Immunity* (2017, 46: 992—1004).

RNAi is an evolutionarily conserved post-transcriptional gene silencing mechanism in eukaryotes, and has been well recognized as an antiviral immunity in fungi, plants, and invertebrates. In the process of antiviral RNAi, viral dsRNA replicative intermediates generated during RNA virus replication are recognized and processed by Dicer into siRNAs. These virus-derived siRNAs (vsiRNAs) are then transferred into RNA-induced silencing complex (RISC), to direct the cleavage of cognate viral RNAs. However, whether RNAi can function as an antiviral defense in mammals, particularly in differentiated mammalian somatic cells, remains unclear for decades.

HEV71 infection in infants and young children causes hand-foot-and-mouth disease and severe neurological manifestations, and has emerged as one of the major global threats to public health. In this work, Zhou and colleagues identified the nonstructural protein 3A of HEV71 as the viral suppressor of RNAi that inhibits vsiRNA biogenesis. When the RNAi suppression activity of 3A was impaired, the 3A-mutant viruses effectively triggered RNAi response in both mammalian cells and mice, producing abundant vsiRNAs. These vsiRNAs are Dicer-dependently produced from viral dsRNA, loaded into RISC, and fully active to degrade cognate viral RNAs. The 3A-deficient mutants of HEV71 are significantly restricted in human somatic cells and mice, while Dicer deficiency successfully restored HEV71 infection independently of type I interferon response.

These findings highlight that RNAi can indeed function as antiviral immunity in mammals. And it uncovers for the first time the detailed mechanism by which a human RNA virus evades antiviral RNAi both *in vitro* and *in vivo*. More studies are needed to understand how many other mammalian viruses interact with host RNAi pathway, and how the findings in this study can lead to the development of novel antiviral drugs or immunotherapies.

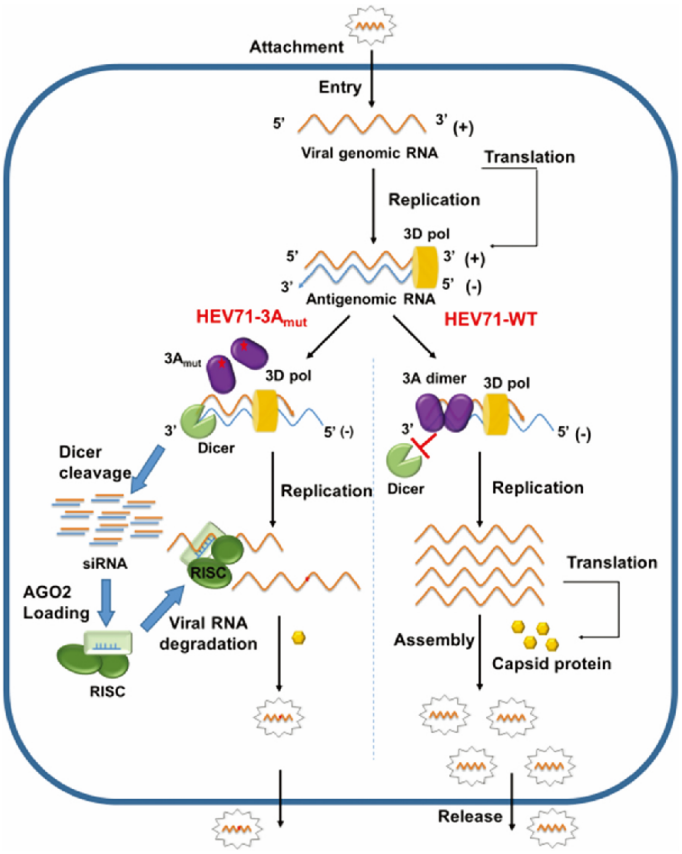

Figure HEV71 suppresses antiviral RNAi.