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Distinct Antiviral Pathway for ZFP36-Like Family Members Against Flavivirus Infection

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Abstract : The human zinc finger protein 36-like protein family, containing zinc finger protein 36-like 1 (ZFP36L1) and zinc finger protein 36-like 2 (ZFP36L2), belongs to CCCH-type zinc-finger protein identified as an RNA-binding protein that participates in controlling posttranscriptional regulation via RNA decay pathways. Recently, we demonstrated that human ZFP36L1 showed potent antiviral activity against flavivirus Infection by both 5´-3´ XRN1 and 3´-5´RNA-exosome RNA decay pathways (Journal of Virology 2022 Jan 12;96(1): e0166521). However, another zinc finger protein 36-like protein member, ZFP36L2, in the host defense response against flaviviruses has yet to be addressed. Here, we also demonstrate that ZFP36L2 functions as a host innate defender against flaviviruses, including Japanese encephalitis virus (JEV) and dengue virus (DENV). Overexpression of ZFP36L2 reduced JEV and DENV infection, and ZFP36L2 knockdown significantly promoted viral replication. Distinct from the antiviral mechanism of ZFP36L1, ZFP36L2 inhibits flavivirus infection by only a 5´-3´ XRN1-mediated RNA decay pathway but not the 3´-5´RNA-exosome RNA decay pathway. Human ZFP36L1 and ZFP36L2 can restrict flavivirus replication by directly binding and destabilizing viral RNA. Thus, for the first time, human zinc finger protein 36-like family members, ZFP36L1 and ZFP36L2, are identified as host antiviral factors that can bind and degrade flavivirus viral RNA by diverse antiviral mechanisms.

Keywords : ZFP36L1, ZFP36L2, 5'-3' exonuclease XRN1, antiviral mechansim
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