Mosquito salivary protein promotes flavivirus transmission

With the support by the National Natural Science Foundation of China, the research team led by Prof. Cheng Gong (程功) at Tsinghua-Peking Center for Life Sciences, School of Medicine, Tsinghua University, identified a key mosquito salivary protein related to flavivirus transmission, which was published in *Nature Communications* (2020, 11: 260).

Mosquito-borne flaviviruses, such as Zika (ZIKV) and dengue (DENV) virus, cause hundreds of millions of infection cases every year and act as the etiological agents of human hemorrhagic fever, meningitis and encephalitis. Understanding the mechanisms of flavivirus transmission by mosquitoes will provide novel strategies to decrease disease burden in nature.

Mosquito-borne flaviviruses maintain a lifecycle between mosquitoes and susceptible hosts, in which the viral transmission from an infected mosquito to a host is an essential process for the viral survival. Numerous studies have demonstrated that mosquito saliva can facilitate the viral transmission. However, the roles of mosquito salivary proteins in flavivirus infection remain to be comprehensively investigated. Dr. Cheng' group screened the salivary proteins in the *Aedes aegypti* saliva, and found that a saliva protein AaVA-1 promotes DENV and ZIKV infection in human monocyte-lineage immune cells. Subsequently, inoculation of AaVA-1 with ZIKV into the AG6 mice ($ifnar1^{-/-}$ $ifngr1^{-/-}$) augmented ZIKV viremia and accelerated animal death, and the AG6 mice bitten by the ZIKV-infected AaVA-1-silenced mosquitoes presented a lower viremia and survived longer. The mechanism study elucidated that AaVA-1 interacted with a host negative regulator of autophagy named leucine-rich pentatricopeptide repeat-containing protein (LRPPRC), which is a dominant negative binder of Beclin-1. Through competitive binding to LRPPRC, AaVA-1 released host Beclin-1 from the LRPPRC-mediated sequestration, thereby enabling the initialization of the downstream autophagic signaling. Activation of autophagy is essential to the flavivirus replication in human cells.

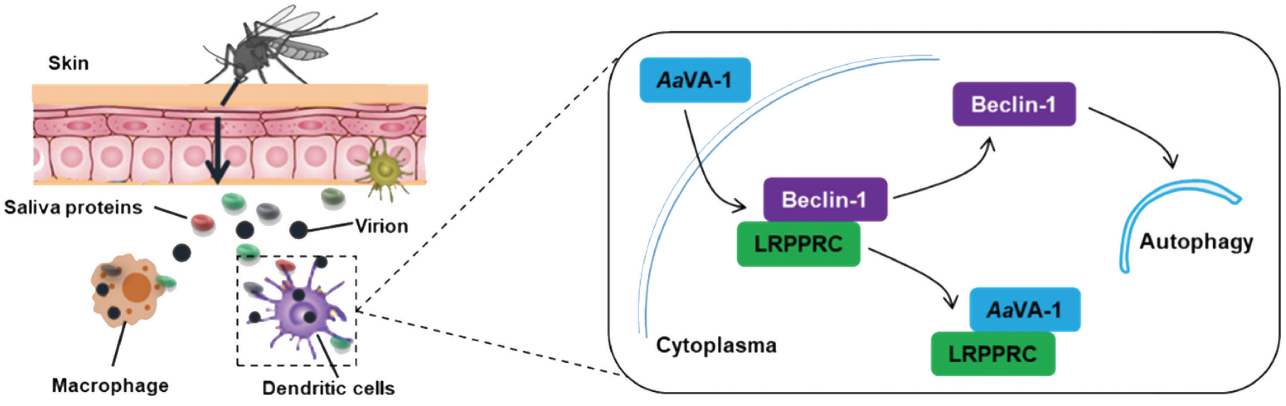

Figure Schematic representation of AaVA-1-mediated activation of autophagy.

Their study sheds light on the role of mosquito salivary protein-mediated autophagy activation in facilitating the flaviviral transmission. The study provides a deeper insight into the molecular basis of flavivirus transmission in nature, and could offer potential therapeutic targets for prevention of flavivirus dissemination.