Neuroimmune axis: ADAR-mediated RNA editing plays a role in molecular evolution of West Nile Virus

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Since 2015 - when the link between Zika Virus (ZIKV) and fetal microcephaly was discovered, resulting in thousands of infants born with neurodevelopmental defects – invertebrate-transmitted arboviruses, including mosquito-transmitted flaviviruses, had been in the spotlight. Our recent work (Piontkivska et al. 2017) has shown that RNA editing, specifically, adenosine to inosine deamination catalyzed by members of the adenosine deaminases acting on RNA (ADAR) gene family, plays a role in molecular evolution of ZIKV, likely as part of interferon-regulated antiviral response. However, because of ADARs' dual role in the neural transcriptome diversification, ADAR-mediated editing also has the potential to influence expression and function of key host neural proteins (Piontkivska et al. 2019). This in turn may explain the breadth and severity of neurological symptoms associated with many arboviral infections, including that of West Nile Virus (WNV). Here we use publicly available sequences of complete WNV polyproteins to examine the footprints of ADAR editing. Our results indicate that similarly to ZIKV genomes, WNV genomes reflect the signature of ADAR editing as one of the evolutionary forces acting on the viral genome, e.g., as manifested by the higher proportion of ADAR-resistant sites among conserved sites as compared to that among the sites harboring nucleotide polymorphisms. These results further expand our prior findings about ADAR editing serving as a mutation and evolutionary force of RNA viruses, and offers insights into potential mechanisms behind viral neurotoxicity and neurodegeneration stemming from neuroinvasive flaviviral infections.