COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Lncrna Snhg15 Positively Regulates Inflammatory Response To Venezuelan Equine Encephalitis Virus Infection In Primary Mouse Astrocytes

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Venezuelan equine encephalitis virus (VEEV) is an enveloped positive-sense RNA virus in the alphavirus genus of the Togaviridea family. VEEV poses a significant threat by causing encephalitis in both humans and equids. VEEV is naturally transmitted by mosquitoes and has been responsible for several outbreaks in Central and South America, affecting hundreds of thousands of individuals. Besides the natural route of transmission, VEEV can also spread via aerosol and has been previously weaponized. Despite the significance of VEEV as a natural pathogen and a potential biological threat, there is a gap in our knowledge about VEEV-host cell interaction, evident by the lack of an FDA-approved vaccine or treatment available for human use. In recent years, non-coding RNAs have emerged as critical regulatory factors affecting different cellular pathways. In particular, long non-coding RNAs (lncRNAs) have been identified as regulators of antiviral pathways during various viral infections. Despite extensive efforts to understand the function of lncRNAs in different contexts, their role in regulating VEEV infection remains unknown. Here we report differential expression of several lncRNAs in primary mouse astrocytes and neurons after infection with non-pathogenic (TC-83) but not pathogenic (TrD) VEEV, suggesting the potential protective role of these lncRNAs during VEEV infection. We further demonstrated that siRNA suppression of five lncRNAs increased VEEV TC-83 replication, among which knockdown of lncRNA Small nucleolar RNA host gene 15 (Snhg15) increased VEEV TC-83 replication by more than 10-fold. To further expand our investigation into Snhg15 function during VEEV TC-83 infection, we compared gene expression in TC-83-infected primary mouse astrocytes with or without knockdown of Snhg15. Our RNA-seq results showed decreased expression of proinflammatory cytokines and chemokines after Snhg15 knockdown in TC-83-infected primary mouse astrocytes. KEGG pathway analysis further confirmed significant suppression of antiviral signaling pathways, such as TLR, MAPK, and NF-kB signaling pathways, responsible for production of inflammatory cytokines and chemokines during TC-83 infection after Snhg15 knockdown in these cells. These results suggest that Snhg15 acts as a positive regulator of the inflammatory response during VEEV infection. Further investigations are needed to unravel the mechanism by which Snhg15 regulates inflammatory response to VEEV infection. These findings have the potential to lead to the development of novel countermeasures to combat VEEV infection.

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