ABSTRACT

Chikungunya virus (CHIKV) has received global attention due to the series of large-scale outbreaks in different parts of the world. The appearance of many unusual severe manifestations e.g. neurological disorders and death were reported in post resurgence epidemics with implication of novel East Central South African (ECSA) genotype with E1:A226V mutation. The molecular mechanism of CHIKV neuropathogenesis is not yet understood. In this study, the neuropathogenesis of CHIKV with & without E1:A226 V mutation was elucidated in cell based and BALB/c mice model. The 226V (mutant) strain was more replication competent in Human (SHSY-5Y) & mouse (N2a) neuronal cells as compared to A226 (non mutant) strain. Besides, the 226V strain showed relatively less induction of antiviral genes i.e. IFN-β, OAS-3, MX-2, ISG-15 and TLR 3 as compared to A226 strain. The mutant strain replicated in mice brain with peak titer of 10^4 on 6 dpi. There was significant up regulation of TLR3, TRAF-6, TICAM-1, MCP-1, CXCL-10, IL-6, IL-4, ISG-15, IFN-β & OAS-3 genes that ultimately resulted in virus clearance from brain by day 9–10 suggesting activation of innate immune pathway. It is also elucidated that pretreatment of mice with Poly I: C caused reduction of CHIKV titer and offered 100% protection of animals. The protection was mediated by an increased induction of TLR3, IFN-β and antiviral genes in mice brain. Proteomic analysis revealed main processes altered during the course of CHIKV infection were those that involves in the process of apoptosis, lipid metabolism and translation process.

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