NIPAH VIRUS MATRIX PROTEIN TARGETS THE E3-UBIQUITIN LIGASE TRIM6 TO INHIBIT THE IKKE KINASE-MEDIATED TYPE-I IFN ANTIVIRAL RESPONSE

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Type-I interferons (IFN-I) are important antiviral cytokines that require activation of multiple signaling components including the IκB kinase epsilon (IKKe). We recently showed that the E3-ubiquitin ligase TRIM6 catalyzes the synthesis of unanchored K48-linked polyubiquitin chains, which are not covalently attached to any protein, and activate IKKe for induction of IFN-I mediated antiviral responses. For efficient replication, viruses have developed mechanisms to evade innate immune responses. Nipah virus (NiV), a highly pathogenic member of the paramyxoviridae family, with viral proteins demonstrating IFN antagonist functions. Here we report that NiV matrix protein, which is important for virus assembly and budding, can also inhibit IFN-I responses. We show here that the NiV Matrix protein interacts with TRIM6 and promotes its degradation. Consequently, NiV-M expression results in reduced levels of unanchored K48-linked polyubiquitin chains associated with IKKe leading to impaired IKKe oligomerization, IKKe autophosphorylation and subsequent reduced IFN-mediated responses. This IFN antagonist function could be mapped to a conserved lysine residue (K258) on the nuclear localization signal of paramyxovirus Matrix proteins. Consistent with this, the Matrix protein of Ghana, Hendra and New Castle disease viruses were also able to inhibit IFN beta induction. Live Nipah virus infection reduced the levels of endogenous TRIM6 protein expression, whereas a recombinant Nipah virus lacking the M protein did not significantly affect TRIM6 cellular levels. We report here a new paramyxovirus protein with IFN antagonist function and a novel mechanism of viral innate immune evasion by targeting TRIM6 and unanchored polyubiquitin chains. These findings provide a new potential target for therapeutic interventions.