Regulation of Enterovirus 71 Infection by Tumor Suppressor WW Domain-containing Oxidoreductase

Pei-Shiuan Chen[1*], Shao-Han Liao[1], Li-Jin Hsu[1]

[1.] Department of Medical Laboratory Science and Biotechnology, National Cheng Kung University Medical College, Tainan, Taiwan

Background/Objective

WW domain-containing oxidoreductase, designated WWOX or murine WOX1, is a candidate tumor suppressor protein. WWOX has been suggested to be involved in many signaling pathways that regulate tumor suppression, cell death, embryonic development and neuronal diseases. Previous studies have suggested that WWOX is associated with cancer progression induced by Epstein-Barr virus and human T cell leukemia virus. However, whether WWOX controls the infection of mammalian cells by enterovirus 71 (EV71) is still unknown.

Method

In this study, we showed that EV71 infection induced upregulation of WWOX protein expression in human rhabdomyosarcoma (RD) and neuroblastoma SK-N-SH cells. To investigate the possible role of WWOX in EV71 infection, Wwox gene ablation in mice and lentiviral shRNA-mediated knockdown of WWOX expression in cell lines were used.

Result

Higher levels of EV71 RNA and VP2 protein expression were detected in WWOX-knockdown cells than the controls after EV71 infection, suggesting that WWOX may impede EV71 replication in cells. Associated with decreased resistance to EV71 infection, Wwox gene knockout mice exhibited higher mortality rates and clinical scores than did wild-type and heterozygous littermates after EV71 infection. Also, higher viral loads were detected in EV71-infected Wwox knockout mice at day 5 or 7 post-infection.

Conclusion

We have demonstrated that WWOX regulates EV71 infection both in vitro and in vivo. Our results have provided a possible link between WWOX function and the resistance to viral infection.