The role of Toll-like receptor 3 in viral encephalitis

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The spectrum of diseases of childhood caused by enterovirus 71 (EV71) is broad, ranging from asymptomatic infection or self-limited hand-foot-and-mouth diseases (HFMD) to life-threatening encephalitis, however, the molecular mechanisms underlying these different clinical presentations remain unknown. We hypothesized that severe EV71 infection in children might reflect an intrinsic host single gene defect of anti-viral immunity. We searched for mutations in Toll-like receptor 3 (TLR3), which have been previously found in children with herpes simplex encephalitis (HSE) in young patients with severe EV71 infection. We sequenced TLR3 and tested the impact of the mutation found. We tested dermal fibroblasts from our patient and other patients with known genetic defect in TLR3 or related genes, for their response to both poly(I:C) stimulation and EV71 infection. We found that three children were heterozygous for the TLR3 mutations, which are shown to have severe impact on the TLR3 function. One patient's fibroblasts with heterozygous mutation had impaired but not abolished response to TLR3 agonist poly(I:C). We also showed that TLR3 was crucial in cellular defense against EV71 infection, as TLR3-deficient or TLR3 heterozygous mutation fibroblasts were highly vulnerable to EV71 infection. In Summary, our results demonstrated that TLR3 deficiency may underlie severe EV71 infection and TLR3 signaling is crucial in human immunity against EV71. Children with severe EV71 infection should be tested for inborn errors of TLR3 immunity.