ROLE OF TLR4 IN INNATE IMMUNE RESPONSES AND DISEASE PATHOGENESIS TO HUMAN METAPNEUMOVIRUS INFECTION

TS Velayutham, D Kolli, RP Garofalo, A Casola

Department of Pediatrics, University of Texas Medical Branch, Galveston, Texas

Human metapneumovirus (hMPV), described for the first time in 2001, has become one of the main viral pathogens responsible for acute respiratory tract infections in children, elderly and immunocompromised patients. The mammalian Toll-like receptors (TLR) were identified as critical regulators of innate immunity to a variety of microbes, including bacteria and fungi. Respiratory syncytial virus (RSV) fusion protein has been shown to activate TLR4, but their role in other viral infections, such as hMPV, has been largely unexplored. In this study, we examine the in vivo innate immune response to hMPV in TLR4-deficient (C57BL/10ScNJ) and wild-type (C57BL/10SnSnJ) mice, to address the role of TLR4 in the innate immune response to infection with this respiratory virus. Our results demonstrate that mice lacking TLR4 loose significantly less body weight compared to wild type mice. Further, consistent with bodyweight loss, TLR4 deficient mice show better pulmonary function demonstrated by reduced airway obstruction and airway hyperresponsiveness. When inflammatory mediators were measured in bronchoalveolar lavage fluid on different days post-infection, significantly lower levels of proinflammatory cytokines (IL-1b, IL-6, TNF-alpha), immunomodulatory cytokines (GM-CSF, IL-12 p40, IL-17) and chemokines (MCP-1, MIP-1alpha) were detected in the TLR4 deficient mice compared to the wild type. These results indicate that TLR4 is important for activation of the innate immune response to hMPV infection, however it can also contribute to disease pathogenesis.