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Aberration of MDA5-mediated signaling causes autoimmune disorder

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Abstract

RIG-I-like receptors recognize viral RNA in infected cells and trigger antiviral immune responses such as induction of type I interferons (IFNs) and inflammatory cytokines. Type I IFNs play a central role in antiviral innate immunity, although it is implicated that excessive type I IFNs cause autoimmunity including systemic lupus erythematosus (SLE). We incidentally obtained mutant mice, harboring MDA5 mutation generated by N-ethyl-N-nitrosourea(ENU) mutagenesis. These mice spontaneously developed lupus-like nephritis and autoimmunity without viral infection. Heterozygotes displayed chronic inflammation in kidney, skin, liver and salivary glands and anti-double stranded DNA antibodies were detected in sera. Inflammation was totally dependent on adaptor molecule, IPS-1 which suggests that MDA5-dependent signaling is the key for the chronic inflammation. In addition, intercrossing the mutant mice with type I IFN receptor-deficient mice improved clinical manifestation. These findings lead to new insights into pathogenesis regarding type I IFN and autoimmunity.