34.Epicutaneous application of the TLR7 agonist leads to development of lupus glomerulonephritis in wild-type mice

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Systemic lupus erythematosus (SLE) is the prototypical autoimmune disease characterized by formation of a variety of autoantibodies and development of skin rash and internal involvements such as glomerulonephritis. Although the underlying etiology still remains unknown, the genetic predisposition and environmental factors together contribute to the initiation of SLE. It has been thought that aberration of adaptive immunity associated with immunological tolerance and resulting B cell hyperactivation leads to production of autoantibodies against chromatin and ribonucleoproteins. In contrast, recent studies have demonstrated that innate immunity including TLR signaling plays an essential role in the development of SLE. Previous studies demonstrated that disease in lupus-prone mice was dependent on the presence of TLR7, and that treatment of them with a TLR7 agonist aggravated lupus nephritis. Here we report that repeated topical treatment of wild-type mice with a TLR7 agonist imiquimod (IMQ) resulted in generation of autoantibodies and glomerulonephritis. Wild-type mice of FVB/N strain, regardless of sex, which were topically applied by IMQ onto the ear pinna three times weekly, showed anti-double strand DNA antibodies in the sera from 4 weeks, increased creatinine levels, and glomerulonephritis by 8 weeks, and finally died by 10 weeks of the treatment. Direct immunofluorecence examination of the glomeruli revealed deposits of IgG and IgM autoantibodies. Wild-type mice from other strains including C57BL/6 and BALB/c also developed autoantibodies and glomerulonephritis following epicutaneous IMQ treatment, suggesting that repeated TLR7 stimulation via skin lead to lupus-like disease in wild-type mice beyond the genetic background. Collectively, these results suggested that cutaneous perturbation by TLR7 agonists such as RNA viruses might be implicated in the onset of SLE.