Anti-dsDNA, surface-expressed TLR4 and endosomal TLR9 cooperate to exacerbate lupus

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Systemic lupus erythematosus (SLE) is a complicated multifactorial autoimmune disease influenced by many genetic and environmental factors. The hallmark of systemic lupus erythematosus (SLE) is the presence of high levels of anti-double-stranded DNA autoantibody (anti-dsDNA) in sera. In addition, greater infection rates are found in SLE patients and higher morbidity and mortality usually come from bacterial infections. Deciphering interactions between the susceptibility genes and the environmental factors for lupus complex traits is challenging and has resulted in only limited success.

In the June issue of *Experimental Biology and Medicine* Lee et al, from National Yang-Ming University in Taiwan, studied the role of anti-double stranded DNA (anti-dsDNA) and the Toll-like receptors (TLRs), TLR4 and TLR9, in the pathogenesis of lupus. They prepared transgenic mice carrying the anti-dsDNA transgene and challenged these mice with TLR4 and TLR9 agonists. They demonstrate that in the anti-dsDNA transgenic mice TLR4 and TLR9 are cooperatively linked to Lupus progression.

"Since simultaneous activation of extracellular and intracellular pattern-recognition receptors (PRR) is able to trigger more intense host immune responses, it is really crucial to determine whether co-engagement of extracellular and intracellular PRRs may increase disease severity in lupus," said Dr. Kuang-Hui Sun, corresponding author. However, only

individual conditional knockout models were used in previous studies to study the roles of TLR4 or TLR9. In addition, intracellular nucleic acid-sensing TLR9 plays either stimulatory or protective roles in different murine lupus models. Therefore, Sun and colleagues injected the ligands of TLR4 and TLR9 into the anti-dsDNA transgenic mice as a new model to investigate whether anti-dsDNA and co-activation of extracellular TLR4 and endosomal TLR9 impacts the pathogenesis of lupus in normal background mice. Their data suggest that, in addition to anti-dsDNA, signaling pathways triggered by simultaneous activation of surface-expressed TLR4 and endosomal TLR9 can promote the progression of SLE. These results suggest that simultaneous targeting of anti-dsDNA, TLR4 and 9 may be a potential therapy for SLE.

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said "These studies in transgenic mice offer new concepts for affecting immune tolerance and reducing SLE disease progression as future therapeutics are developed."

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