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Toll-like Receptors in the Pathogenesis of Systemic Lupus Erythematosus (SLE): Melissa W. BOULE1, Courtney BROUGHTON2, Christina LAUP3, Elizabeth A. LEADBETTER2, Ann MARSHAK-ROTHSTEIN4, Ian R. RIFKIN1
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Toll-like receptors (TLRs) function to stimulate the innate immune system response to pathogens. However, certain TLRs can also recognize self-antigens released from stressed or damaged host tissues, and such self-recognition can potentially promote the development of autoimmune disease. We have previously shown that self-antigen (chromatin)-containing immune complexes (IC) activate IgG2a-specific neutrophil factor (transgenic B cells in vitro by a mechanism involving sequential engagement of the B cell antigen receptor and TLR9. Dendritic cells also express TLR9, and dendritic cell activation by nucleic acid-containing IgG complexes is implicated in SLE pathogenesis. We therefore examined the effect of chromatin-containing IC on murine dendritic cell activation in vitro, and found that these IC are indeed able to activate murine myeloid dendritic cells. Activation occurs by two distinct pathways, involving dual engagement of the IgG Fc receptor FcγRII on TLR9, while the other pathway is TLR9-independent. Each pathway elicits distinct cytokine patterns. The data establish a role for self-antigen in dendritic cell activation and explains how the innate immune system might drive the adaptive immune response in SLE. To evaluate the contribution of TLR9s to the development of SLE in vivo, we determined the effect of MyD88-deficiency in a murine lupus model, and also treated MRL-lpr/lpr mice with a TLR9 inhibitor. In both cases, autoantibody production was inhibited, pointing to an important role for TLR9 in the development of SLE in vivo.

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The NOD Family of Proteins: Their Role in Innate Immunity and Inflammatory Disease: Gabriel NUNEZ1, Yasunori OGURA1, Mathias CHAMAILLARD1, Tatsushi TANABE1, Theresa DOWDS4, Naohiro INOHARA1 (1Department of Pathology and Comprehensive Cancer Center, University of Michigan, Ann Arbor, USA)

NODs are members of a family of cytosolic proteins with homology to plant disease resistance (R) gene products. R proteins control the defense response of plant cells to invading pathogens. We have identified 24 NOD genes in the human genome. NODs including NOD1 and NOD2 contain variable N-terminal effector domains, a centrally located nucleotide-binding oligomerization domain (NOD) and C-terminal leucine-rich repeats (LRRs). Mutation in three NOD proteins (NOD2, Cryopyrin and CIITA) are associated with inflammatory disease or immunodeficiency. NOD1 and NOD2 recognize conserved but distinct structural motifs in bacterial peptidoglycan through their LRRs and induce the activation of NF-kappaB. Activation of NF-kappaB through NOD1 and NOD2 is mediated through RICK, a serine/threonine kinase that interacts with the RIK kinase (IKK) complex. Mutation and genetic variation in the LRRs of NOD2 are associated with susceptibility to Crohn’s disease, a common inflammatory disease of the bowel. NOD2 variants associated with disease are deficient in NF-kappaB activation induced by bacterial components. NOD2 expression is enhanced by proinflammatory cytokines and bacterial components via NF-kB, a mechanism which may contribute to the amplification of the innate immune response. Systematic mutational analyses revealed a general mechanism for recognition of pathogens by the LRRs of NOD2. Our data indicate that NODs including NOD1 and NOD2 function as intracellular receptors for microbial components leading to the activation of a cellular response against the pathogen. NOD2 mediates the host response to bacterial muropeptides derived from peptidoglycan, an activity that is important for protection against Crohn’s disease.