

Do Toll-like Receptors Contribute to the Pathogenesis of Lupus?



Flaws in the relationship between innate and adaptive immunity may favor the development of systemic lupus erythematosus (SLE), a disease of exceedingly complex pathogenesis. The former signaling pathway is triggered by microbial products, while the latter is shifted towards nuclear components. The pattern-recognition receptors (PRR), most particularly the Toll-like receptors (TLR), are now appreciated for their crucial role in this crosstalk¹.

In fact TLR have moved to center stage, as critical sensors of pathogen-associated molecular patterns. In particular, flagellated bacteria bind to TLR-5, which defend the cell surface, and mount a robust type I interferon (IFN) response², whereas TLR-9 are sequestered away from the plasma membrane of B and plasmacytoid dendritic cells (pDC), as an attempt to prevent undesirable activation of TLR-9. Although dedicated to unmethylated cytosine-phosphate-guanosine (CpG)-containing single-stranded DNA, these PRR are involved in anti-double-stranded (ds) DNA antibody production³. Interestingly, CpG dsDNA promotes autoantibody, engages TLR-9, and activates antigen receptors (B cell receptors) on B lymphocytes⁴ or Fc-gamma (Fcγ) receptors on pDC⁵.

This raises the issue as to whether structural variations of the TLR influence their function or reflect the clinical outcome of the disease. One step further, single nucleotide polymorphisms (SNP) may be sufficient to promote or resist SLE. Actually, every single nucleotide counts: for example, a stop codon in the TLR-5 gene has been implicated in vulnerability to pneumonia, and, unexpectedly, in protection from SLE. Such an association was established in a Caucasian SLE cohort using transmission-testing analyses⁶. One cannot exclude a linkage disequilibrium of SNP with nearby causative genes, because a case-control methodology failed to replicate this observation in a similar cohort of patients, as reported by Demirci and colleagues in this issue of *The Journal*⁷.

It is no surprise that nucleic acid-related PRR have also been suspected to play a role in SLE. Based on the high expression levels of TLR-9 in B lymphocytes, but not in

pDC, their involvement might be quantitative⁸. On the other hand, it might be qualitative and dependent on the diversity of the TLR-9 gene. Such genetic variations of a frontline receptor are most likely to produce an effect. No association of susceptibility to SLE has been found to date in Korean⁹, British¹⁰, or American⁷ patients. This occurrence locus should thus be extremely low.

Nonetheless, type I IFN act as efficient defence agents against microorganisms, and present as important factors in the pathogenesis of any autoimmune setting. Further, this awareness is coupled with the fact that, due to defective clearance of apoptotic cells in SLE¹¹, mammalian nucleic acids acquire the capacity to substitute for exogenous nucleic acids with respect to TLR-9¹².

The genuine mechanisms might be much more complex than originally thought¹³. There is indeed increasing evidence that TLR are activated by endogenous ligands, and therefore regulated through hitherto ignored mechanisms. In addition, TLR require coreceptors for microbial recognition. These include the B cell receptors, CD14, or Fc receptors. Even more important, after TLR-9 triggering, B cells produce high concentrations of interleukin 10 (IL-10), preventing optimal IL-12 secretion by pDC and the subsequent Th1 priming. Although both CD5-expressing and CD5-non-expressing B cells respond to CpG stimulation, only CD5-expressing B cells make IL-10. This is paradoxical and raises the possibility that activation of regulatory B cells¹⁴ might result from the engagement of TLR-9.

To conclude, there is an obvious need for further research in this field, before targeting TLR signaling in pDC and B lymphocytes as a therapy for SLE and various non-organ-specific autoimmune diseases.

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