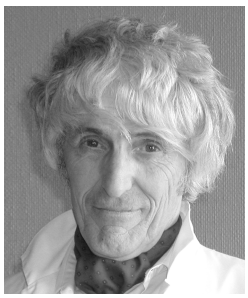
Editorial



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 crosstalk[1].

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) response[2], whereas TLR-9 are sequestered away from the plasma membrane of B and plasmocytoid 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 production[3]. Interestingly, CpG dsDNA promotes autoantibody, engages TLR-9, and activates antigen receptors (B cell receptors) on B lymphocytes[4] or Fc-gamma (Fcγ) receptors on pDC[5].

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 analyses[6]. 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 quantitative[8]. 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 Korean[9], British[10], or American[7] 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 SLE[11], mammalian nucleic acids acquire the capacity to substitute for exogenous nucleic acids with respect to TLR-9[12].

The genuine mechanisms might be much more complex than originally thought[13]. 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 cells[14] 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.

PIERRE YOUINOU, MD, DSc,
Head, Department of Immunopathology;
Professor of Immunology,
Brest University Medical School,
CHU, BP 824,
Brest, F 29206 France.
E-mail: youinou@univ-brest.fr

See Association study of Toll-like receptors, *page 1708*

ACKNOWLEDGMENT

Special thanks to Simone Forest, who typed the manuscript.

REFERENCES

1. Marshak-Rothstein A. Toll-like receptors in systemic autoimmune disease. Nat Rev Immunol 2006;6:823-35.
2. Hayashi F, Smith KD, Ozinsky A, et al. The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. Nature 2001;410:1099-103.
3. Ishii KJ, Akira S. Innate immune recognition of, and regulation by, DNA. Trends Immunol 2006;27:525-32.
4. Viglianti GA, Lau CM, Hanley TM, Miko BA, Shlomchik MJ, Marshak-Rothstein A. Activation of autoreactive B cells by CpG dsDNA. Immunity 2003;19:837-47.
5. Means TK, Latz E, Hayashi F, Murali MR, Golenbock DT, Luster AD. Human lupus autoantibody-DNA complexes activate DCs through cooperation of CD32 and TLR9. J Clin Invest 2005;115:407-17.
6. Hawn TR, Wu H, Grossman JM, Hahn BH, Tsao BP, Aderem A. A stop codon polymorphism of Toll-like receptor 5 is associated with resistance to systemic lupus erythematosus. Proc Natl Acad Sci USA 2005;102:10593-7.
7. Demirci FYK, Manzi S, Ramsey-Goldman R, et al. Association study of Toll-like receptors 5 and 9 polymorphisms in systemic lupus erythematosus. J Rheumatol 2007;34:1708-11.
8. Migita K, Miyashita T, Maeda Y, et al. Toll-like receptor expression in lupus peripheral blood mononuclear cells. J Rheumatol 2007;34:493-500.
9. Hur JW, Shin HD, Park BL, Kim LH, Kim SY, Bae SC. Association study of Toll-like receptor 9 gene polymorphism in Korean patients with systemic lupus erythematosus. Tissue Antigens 2005; 65:266-70.
10. De Jager PL, Richardson A, Vyse TJ, Rioux JD. Genetic variation in Toll-like receptor 9 and susceptibility to systemic lupus erythematosus. Arthritis Rheum 2006;54:1279-82.
11. Gaipl US, Voll RE, Sheriff A, Franz S, Kalden JR, Herrmann M. Impaired clearance of dying cells in systemic lupus erythematosus. Autoimmun Rev 2005;4:189-94.
12. Barrat FJ, Meeker T, Gregorio J, et al. Nucleic acids of mammalian origin can act as endogenous ligands for Toll-like receptors and may promote systemic lupus erythematosus. J Exp Med 2005;202:1131-9.
13. Sun CM, Deriaud E, Leclerc C, Lo-Man R. Upon TLR9 signaling, CD5+ B cells control the IL-12-dependent Th1-priming capacity of neonatal DCs. Immunity 2005;22:467-77.
14. Mizoguchi A, Bhan AK. A case for regulatory B cells. J Immunol 2006;176:705-10.