INFECTIONOUS AGENTS AND B CELL TOLERANCE BREAKDOWN

S. Jung 1,2, A. Kern 3, A.S. Korganow 1,4
1 CNRS UPR 9021 “Therapeutic Immunology and Chemistry”, “B cell tolerance and autoimmunity” team, Molecular and Cellular Biology Institute (IBMC), Strasbourg, France
2 Section 5703 “Biological Sciences”, Faculty of Dentistry, University of Strasbourg, France, s.jung@unistra.fr
3 EA 4438 “Physiopathology and Translational Medicine”, Faculty of Medicine, University of Strasbourg, aurelie.kern@etu.unistra.fr
4 “Department of Internal Medicine and Clinical Immunology”, NHC, Strasbourg and Faculty of Medicine, University of Strasbourg, korganow@unistra.fr

Keywords
Autoimmunity, B cells, bacterial infection, tolerance, transgenic mouse models.

Abstract
The role of infectious agents in autoimmune diseases genesis is still a matter of debate. Several observations have suggested that autoimmune diseases may be initiated or worsened by infections (review by Kivity et al., 2009). However, there is no clear understanding of the underlying mechanisms. In particular, autoantibody production during infections could be the result of the non specific activation of “natural” autoreactive B cells that produce only low-affinity antibodies (Lacroix-Desmazes et al., 1998). A relevant hypothesis making the link between infections and autoimmune diseases could be the progressive genesis of more affine autoreactive B cells that could be involved in different pathogenic conditions. The major purpose of our work is therefore to study the breakdown of B cell tolerance and the ability for autoreactive B cells, especially low reactive B cells, to engage in an affinity maturation process during infections.

We have created a new autoreactive B cell model allowing a relevant study of affinity maturation process. In this intermediate affinity SW HEL X HEL2x autoreactive model, knock-in B cells (Taki et al., 1993) express a B cell receptor highly specific for Hen-Egg Lysozyme (HEL) that recognizes HEL2x mutated auto-antigen with intermediate affinity (Phan et al., 2003; SW HEL model). Phenotypic analysis revealed that these autoreactive B cells are in a state of partial tolerance compared to the high affinity model (Phan et al., 2003; SW HEL X ML5 model) characterized by a strong anergy of HEL positive B cells.

Experimental infections were performed with Borrelia burgdorferi, a Gram-negative spirochete, leading to sustained lymph nodes polyclonal B cell activation and hypergammaglobulinemia (Soulas et al., 2005). In SW HEL X HEL2x infected mice, in the presence of their auto-antigen, intermediate affinity autoreactive B cells are able to proliferate, to be activated, to enter into lymph nodes germinal centers and to produce IgM and IgG autoantibodies, although in low amounts. Moreover, IgG auto-antibodies in infected mice appear somatically mutated in the auto-antigen recognizing area. These data are consistent with a partial tolerance breakdown and the next experimental step will consist in checking the long-term survival of such activated autoreactive B cells and the impact of the observed mutations.

Acknowledgements
We thank R. Brink who provided us the SW HEL and ML5 mice and the HEL2x cDNA (Garvan Institute of Medical Research, Sydney, Australia). We thank B. Jaulhac for experimental infections and housing of infected animals (Bacteriology Institute, Strasbourg). We thank M.C. Birling for help in HEL2x transgenic mouse generation (Mouse Clinic Institute, IGBMC, Illkirch). We thank C. Ebel for B cells sorting (IGBMC, Illkirch).

References