INFECTIOUS 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

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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 HEL^{2x} autoreactive model, knock-in B cells (Taki *et al.*, 1993) express a B cell receptor highly specific for Hen-Egg Lysozyme (HEL) that recognizes HEL^{2x} 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 HEL^{2x} 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.

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