in vivo *20*: 621-628 (2006)

A High Dose of an Idiotype Generates High Levels of Ab2s

SNEZANA ZIVANCEVIC-SIMONOVIC[1], MARIJANA STOJANOVIC[2], ALEKSANDRA INIC-KANADA[2], IRENA ZIVKOVIC[2], TATJANA ODRLJIN[2,3] and LJILJANA DIMITRIJEVIC[2]

[1]Institute of Pathophysiology, School of Medicine, University of Kragujevac, Svetozara Markovica 69, 34 000 Kragujevac;
[2]Institute of Immunology and Virology – Torlak, Department of Research and Development, Vojvode Stepe 458, 11152 Belgrade, Serbia and Montenegro;
[3]Research Information, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, U.S.A.

Abstract. *Background: Network perturbations have been reported in autoimmune processes which could cause polyclonal cell activation. Materials and Methods: Hyper-immunization was achieved by the injection of 3 mg of human monoclonal IgM DJ into BALB/c mice. Indirect ELISA was performed to detect induced antibody specificities. Competitive ELISAs were carried out on sera to detect the idiotypes expressed in first (Ab1) and second (Ab2) antibodies in sequence. Results: In the sera of hyper-immunized mice, the concentrations of Ab1 and Ab2 were respectively five and ten times higher than in the sera of normo-immunized mice. Polyclonal lymphocyte activation was demonstrated by an increase in antibodies specific for antigens (cytochrome C) not related to the immunizing antigen, elevated levels of IgM antibodies specific for the immunogen and elevated levels of Ab2s of the IgM isotype. Conclusion: These findings are indicative of antigen-dependent network perturbation being a causative factor in polyclonal lymphocyte activation.*

It is the established view that two organizations coexist within the immune system, the clonal (1) organization and the network (2-4) organization. However, the dividing line between these two is by no means clearly defined or easy to draw. Historically, studies of idiotypes and anti-idiotypic antibodies have been criticized for propounding a clonal theory of immune response (5-7) which allows for no points of commonality with the network theory of immune response (defined as the outcome of interactions between various idiotypes). Whilst monoclonality is the main characteristic of the components of the cellular and humoral immune systems, network studies should include the quantitative measurements of the mutual interactions of its monoclonal counterparts (8).

Because of the variability of the V regions of Abs or T-cell receptors (TCRs), there is still no experimental data to confirm Jerne's hypothesis of a network-regulated immune system. However, the introduction of mathematical modeling (9-12) to network research should facilitate the design of meaningful network experiments. According to the Weisbuch-Boer-Pelerson model (13), immunization-induced perturbations of the immune system may give rise to an immune response, either as a result of percolation (filtration of an idiotypic signal through the network) (14), or through a localized idiotypic memory (15). According to this model, percolation (16) implies polyclonal B-cell activation, or the sequential stimulation of a potentially unlimited number of clones; the network, thus, functions at a higher level because of the activation of multiple idiotypic clonalities. Models of diseases generated by immunization with idiotypes (17, 18) indicated that the intense activation of an idiotypic network (either by polyclonal cell activation or by molecular mimicry) may result in the deregulation of the immune system and in the production of various pathogenic auto-antibodies.

Polyclonal B-cell activation usually precedes an antigen-specific response (19), so that the majority of antibodies specific for auto-antigens detected after polyclonal B-cell activation have low affinities. Lymphocytes with receptors of higher affinities do not respond to polyclonal activation, because they have already been selected by exposure to self-antigen (20) during ontogenesis. Polyclonal lymphocyte activation may be consequential to the loss of appropriate CD4+ T-cell control or to direct stimulation by microbial agents (21). Polyclonal T-cell activation generates effector T-cells capable of providing protection against a range of antigenic variants (viruses), but may simultaneously induce the switching of non-autoreactive T-cells to differentiated T-cell progeny, specific for self-derived, low affinity ligands (22). This T-cell cross-reactivity forms the basis of the molecular mimicry

Correspondence to: Snezana Zivancevic-Simonovic, MD, Ph.D., Institute of Pathophysiology, School of Medicine, University of Kragujevac, Svetozara Markovica 69, 34 000 Kragujevac, Serbia and Montenegro. Tel: + 381 34 370 137, Fax: + 381 34 306 800, e-mail: simonov@eunet.yu

Key Words: Network, Ab1s, Ab2s, polyclonal activation.