Use of Inhibitors of the Lymphotoxin/LIGHT Axis to Manipulate Lymphoid Microenvironments and the Consequences for Immune Responses

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Much of the efficiency of the immune system is attributed to the high degree of spatial/temporal organization in the secondary lymphoid organs. Signaling through the lymphotoxin-beta receptor (LTBR) is a key element in the maintenance of this organized microenvironement. Much of this regulation may center on the specialized stromal reticular networks in the lymphoid organs and the maintenance of their fully differentiated status. Current thinking relies heavily on the paradigm provided by LT control of the BLC/CXCR5 chemokine axis and the orchestration of follicular B cell positioning. Likewise the splenic marginal zone is under LT control and this microenvironment may be critical for the generation of autoreactive B cells. In epithelial cells, activation of LTBR can be a stimulus as effective as TNF for the induction of the synthesis of the CXCR3 ligands, IP-10, MIG and ITAC. This activity indicates that effector phase responses may also be influenced by the LT system. Thus, LT system has the potential to have an impact at multiple points in the immune response and therefore effects of LT inhibition have been difficult to dissect. Because of the well-characterized developmental defects that accompany mice deficient in the LT pathway and the accompanying difficulty in experimental interpretation, we have explored for several years the *in vivo* effects of LTBR-Ig as a LT pathway inhibitor. This inhibitor was remarkably effective at blocking the development of disease in various rodent models of autoimmune disease and arresting progression in several cases of established disease. Curiously, some of these models were purely T cell based and it has been an enigma as to why this agent was so effective. Two systems will be addressed, the role of the marginal zone microenvironment on autoreactive B cell development in BAFF-tg mice and the impact of LTBR-Ig on T cell responses. The effect of LTBR-Ig on in vivo T cell expansion was examined using Ova-TCR Tg mice and in the pathological setting of murine and rat EAE models. In our working model, disruption of some aspect of the microenvironment leads to the generation of a suppressed state. The potential effects at both the initiating and effector phases of the immune response suggest that LT inhibition may be a novel approach to the treatment of immunological disease.

Dohi, T., Rennert, P., Fujihashi, K., Kiyono, H., Shirai, Y., Kawamura, YI., Browning, JL., and JR. McGhee (2001) "Elimination of colonic patches with lymphotoxin-beta receptor-Ig prevents Th2 -type colitis" J. Immunol. 167, 2781

Mackay, F., Woodcock, S. A, Lawton, P., Ambrose, C., Baetscher, M., Schneider, P., Tschopp, J. and J. L. Browning (1999) Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations" J. Exp. Med. 190, 1697-1710

Mackay, F. and Browning, J. L. (1998) "Turning off follicular dendritic cells" Nature 395, 26-27

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