

Consequences of Lymphotoxin- β Receptor Pathway Inhibition in Primate Lymphoid Organs

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The lymphotoxin- β receptor (LTBR) and herpes virus entry mediator (HVEM) signaling pathways are effectively inhibited by the receptor based Ig fusion protein, LTBR-Ig. Current clinical data indicate that this agent is effective in the treatment of rheumatoid arthritis. Disruption of LTBR/HVEM signaling will have multiple immunological consequences and presents a rather complex picture. The non-developmental components of LTBR/HVEM can be separated into at least three areas: a). effects on stromal/FDC networks and chemokine release with consequences for germinal center function, b). the dialog between activated T cells and mature dendritic cells, as well as DC homeostasis and c). control of addressin expression and possibly angiogenesis and lymphangiogenesis in the lymph nodes. The lymphotoxin system is also clearly involved in the development and maintenance of ectopic organized lymphoid tissues that can be observed in sites of chronic inflammation in most if not all autoimmune diseases. Here we will summarize the clinical findings and describe the impact of LTBR/HVEM inhibition on lymphoid architecture in monkeys to provide some guidance as to what can be expected in man. The data will be discussed in the context of a model for LTBR-Ig in autoimmune disease where treatment eliminates ectopic lymphoid tissues and restores reactive draining lymph nodes to a more quiescent state. As such, this immunomodulatory strategy represents a rather different approach to the treatment of autoimmune disease.

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