

# **Cellular Interactions Occurring in the Hilar Lymph Node Mediate the Development of Tolerance in an Ovalbumin - Induced Murine Model of Allergic Airway Disease**

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In a biphasic, ovalbumin (OVA)-induced murine asthma model where allergic airway disease (AAD) is followed by resolution and the development of local inhalational tolerance (LIT), transforming growth factor (TGF)- $\beta$  expressing CD5<sup>+</sup> B cells were selectively expanded locally in hilar lymph nodes (HLN) of LIT mice. When adoptively transferred, CD5<sup>+</sup> B cells isolated from HLN of LIT mice but not CD5<sup>-</sup> B cells inhibited airway eosinophilia, in this OVA model. These CD5<sup>+</sup> regulatory B cells (Breg) and CD4<sup>+</sup> Foxp3<sup>+</sup> T cells demonstrated similar increases in expression of chemokine receptors (CXCR4 and CXCR5) and localized in HLN B cell zones of LIT mice. LIT HLN CD5<sup>+</sup> B cells, but not LIT HLN CD5<sup>-</sup> B cells, induced expression of Foxp3 in CD4<sup>+</sup> CD25<sup>-</sup> T cells *in vitro*. In the mesenteric lymph node (MLN), the frequencies of Foxp3<sup>+</sup> Tregs, CD5<sup>+</sup> B cells and OVA-specific CD8<sup>+</sup> T cells do not increase at AAD or LIT. Further, Foxp3<sup>+</sup> Tregs did not localize in the MLN B cell zones of LIT mice. Thus, the expansion and preferential localization of regulatory cells in B cell zones occurs only in the HLN and is not observed in other mucosal sites such as the MLN. Studies with transgenic mice (HEL mice) expressing B cell receptor specific to the antigen- hen egg lysozyme (HEL) demonstrated that AAD develops normally in these mice in response to the OVA antigen. Also, there was the induction of LIT in the HEL mice and the LIT HLN B cells from these mice induced expression of Foxp3 in CD4<sup>+</sup> CD25<sup>-</sup> T cells *in vitro* similar to wild-type mice. Thus, Bregs are induced normally in the HLN upon chronic daily antigen exposure in an antigen non-specific manner.