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Principal Investigator: Linda G. Baum
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Progress Report:

a) Abstract

Dendritic cells (DCs) are antigen-presenting cells that can either stimulate (immunogenic DCs, iDCs) or inhibit (tolerogenic DCs, tDCs) adaptive immune responses. Dendritic cells reside in tissues; monocytes that traffic from the blood into tissues are stimulated by inflammatory factors in the tissues to differentiate into immature DCs, and the immature DCs mature into immunogenic or tolerogenic DCs depending on additional cytokine and antigen stimuli in the tissue environment. To generate a productive and appropriate adaptive immune response, DCs must migrate from inflamed tissue across lymphatic endothelium into the lymphatic vasculature and then traffic to regional lymph nodes. However, the processes that regulate DC migration across lymphatic endothelium are ill defined. We previously found that **galectin-1**, a member of the galectin family of carbohydrate binding proteins that is expressed by vascular endothelial cells, can regulate DC migration. The current project was based on our observation that galectin-1 is also expressed by lymphatic endothelial cells, and that galectin-1 differentially regulates migration of iDCs and tDCs.

The **objectives** of this proposal were to 1) identify the glycoprotein receptors on inflammatory and tolerogenic dendritic cells that are recognized by galectin-1 and characterize modification of these glycoprotein receptors by glycosyltransferases that can create or mask glycan ligands for galectin-1; 2) determine the roles of the glycoprotein receptors and ST6Gal1 in galectin-1 regulation of DC migration *in vitro*; 3) examine an *in vivo* murine model of lymphedema in wildtype and galectin-1 null mice, as well as primary human lymphedema tissue samples. The **methods** used included flow cytometry, *in vitro* and *in vivo* cell migration assays, histology and immunohistochemistry, immunoprecipitation, modification of gene expression by siRNA, and confocal microscopy. The **results** include 1) identification of CD43 as the primary cell surface receptor for galectin-1 on immunogenic and tolerogenic DCs and determination that the C2GnT1 transferase is responsible for preferential modification of CD43 on iDCs vs. tDCs; 2) demonstration that modification of CD43 by C2GnT1 is responsible for the differential effect of galectin-1 on regulating iDC vs. tDC migration *in vitro*; and 3) determination that induction of lymphedema in galectin-1 null mice results in greater tissue damage, edema and inflammation compared to wildtype mice.