PROGRESS REPORT for Mizutani Foundation Research Grant

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FINAL PROGRESS REPORT

(a) Abstract:

Effective humoral immunity is reliant on the efficient recruitment of circulating naive B cells from the blood into peripheral lymph nodes (LN) and the timely transition from antigen-inexperienced B cells to high affinity antibody (Ab)-producing cells. Knowledge of the endogenous mechanistic factor(s) coordinating activation and/or differentiation activities within LN is still incomplete. Recent studies on circulating and LN-resident naïve B cells highlight a remarkably strong binding activity to the potent immunoregulator, galectin (Gal)-9, and associated susceptibility to Gal-9-mediated inhibition of B cell receptor (BCR) activation and related BCR signaling, indicating that Gal-9 could function as a critical negative regulator of B cell activity. However, the spatial and functional influence of Gal-9 on naïve B cell action is still ill-defined. In this grant, we performed immunohistochemical analyses of Gal-9 in human lymph node and tonsil tissues illustrating that high endothelial and post-capillary venules express a strikingly high amount of Gal-9. As a consequence of high expression of vascular endothelial cell (EC) Gal-9 and of Gal-9 ligand on naïve B cells, cell adhesion assays indicated that Gal-9 is capable bridging ECs and B cells. Further, RNAseq analysis revealed that incubations of human naïve B cell isolates with Gal-9, including EC-derived Gal-9, caused significant upregulation of several molecular programs capable of globally regulating B cell function, signaling and membrane rigidity. These results implicate vascular Gal-9 as a major endogenous effector controlling B cell responsiveness, a feature potentially needed to avert autoimmunity.