It takes two: Cellular cross talk in germinal center initiation and evolution

Radhika Goenka¹, Lisa G. Barnett¹, Andrew H. Matthews¹, Jean L. Scholz¹, Patrick J. O’Neill¹, Jonathan S. Silver¹, William Stohl³, Christopher A. Hunter², Terri M. Laufer¹, and Michael P. Cancro¹.

Univ. of Pennsylvania Schools of ¹Medicine and ²Veterinary Medicine, Philadelphia, PA; and ³Univ. of Southern California Keck School of Medicine, Los Angeles, CA

The BLyS family of ligands and receptors governs survival and differentiation within B cell subsets. This family includes two ligands, BLyS (also termed BAFF) and APRIL; as well as three receptors, BR3 (also termed BAFFr), TACI, and BCMA. B cells in the transitional and mature, pre-immune B lineage subsets rely on BLyS signals via the BR3 receptor for survival.

In contrast to pre-immune pools, B cells in recently activated and antigen-experienced subsets shift their BLyS receptor profiles and ligand reliance. Short-lived antibody-forming cells adopt a TACI dominated BLyS receptor signature, whereas germinal center (GC) B cells profoundly down-regulate TACI but retain BR3. This process of TACI downregulation, as well as other key aspects of GC B cell status, relies on IL21 produced by TFH, which in turn depends on cognate B cell antigen presentation. The lack of TACI on GC B cells leads to a paucity of retained BLyS in the GC, such that the sole local source of BLyS in the GC is the TFH cell. Moreover, BLyS expression by GC TFH is crucial for appropriate GC evolution, since efficient affinity maturation fails in mixed chimeras where only the T cells are BLyS deficient.

Based on these observations, we propose a mechanism whereby cognate B-TFH interactions are required to establish GC status in recently activated T and B cells; and subsequently limit BLyS-mediated GC B cell survival, thereby fostering the competitive selection underlying affinity maturation.

Background references:


The 50th Midwinter Conference of Immunologists, January 22-25, 2011, Pacific Grove, California USA