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"Sending the right signals: Integrating B cell homeostasis and selection"

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The primacy of BLyS family ligands and receptors in governing B lymphocyte homeostasis has become increasingly clear in recent years. This family consists of two ligands, BLyS (also known as BAFF) and APRIL; and three receptors, BR3 (also known as BAFFr), TACI and BCMA. BLyS can bind to all three receptors, but interacts most strongly with BR3. In contrast, APRIL can interact only with TACI and BCMA. Interclonal competition for BLyS-BR3 interactions determines the size of naïve B cell pools, and can regulate the stringency of selection applied as B cells complete maturation. This relationship between BCR and BR3 signaling suggests integrative mechanisms likely connect the signaling systems of these two receptors. Mounting evidence suggests that cross talk between the two major NFk-B pathways ma mediate this interdependence, whereby BCR signaling generates critical substrate for the BAFFr signaling cascade. These findings suggest a model that mechanistically integrates anergic elimination, positive selection for effective BCR specificities, and the maintenance of primary B cell numbers.

Antigen experienced B cells differ from naïve B cells in their BLyS receptor expression patterns, suggesting they occupy independently regulated homeostatic niches. Further, localized sources of BLyS and APRIL may afford anatomic compartmentalization of these subsets, based on BLyS family ligand-receptor preferences. Thus, activated B cells and short lived antibody forming cells appear strongly biased towards TACI expression; whereas long lived plasma cells may rely primarily on BCMA signaling in an APRIL-rich environment provided by the bone marrow mileiu.

REFERENCES

1. Miller JP, Stadanlick JE, Cancro MP: Space, selection, and surveillance: setting boundaries with BLyS. *J Immunol* 2006, 176:6405-6410.
2. Treml LS, Crowley JE, Cancro MP: BLyS receptor signatures resolve homeostatically independent compartments among naive and antigen-experienced B cells. *Semin Immunol* 2006, 18:297-304.
3. Treml LS, Carlesso G, Hoek KL, Stadanlick JE, Kambayashi T, Bram RJ, Cancro MP, Khan WN: TLR stimulation modifies BLyS receptor expression in follicular and marginal zone B cells. *J Immunol* 2007, 178:7531-7539.