REVIEW

CD19 and CD22 Regulate a B Lymphocyte Signal Transduction Pathway That Contributes to Autoimmunity

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Abstract. The fate of B lymphocytes is dependent on intrinsic and B cell antigen receptor (BCR)-induced signals. These signals are modified and interpreted by other cell-surface molecules such as CD19 and CD22 that govern mature B cell activation. This review assesses our current understanding of how CD19 and CD22 regulate B lymphocyte signaling and how alterations in these response-regulators contribute to autoimmunity in mice and humans. We propose that CD19 functions as a specialized adapter protein that regulates B lymphocyte signaling and autoantibody production. Overexpression of CD19 by B cells in systemic sclerosis patients correlates with autoantibody production and transgenic mice that overexpress CD19 produce similar autoantibodies. CD19 establishes a novel Src-family kinase activation loop that regulates basal signal transduction thresholds in resting B cells and amplifies Src-family kinase activation following BCR ligation. Reciprocally, CD22 is a potent regulator of CD19 function. These observations provide insight into how CD19 and CD22 govern the molecular ordering and intensity of signals transduced in B cells that may contribute to autoimmunity. (Keio J Med 49 (1): 1–13, March 2000)

Key words: B lymphocyte, autoimmunity, CD19, CD22, signal transduction

Introduction

The fate of B lymphocytes is dependent on basal and B cell antigen receptor (BCR)-induced signals. The BCR complex is comprised of membrane immunoglobulin (Ig) noncovalently associated with disulfide-liked CD79a/CD79b (Igα/Igβ) heterodimers. Membrane Ig mediates ligand binding, while CD79a and CD79b contain immunoreceptor tyrosine-based activation motif (ITAM) sequences that function as signal transducing elements. BCR engagement activates signaling pathways through two distinct classes of non-receptor protein tyrosine kinases (PTKs) including Syk and the Src-family members, Lyn, Fyn, Blk, and Lck.[1–4] Src-family PTKs associate with the BCR complex in resting B cells and become activated upon BCR ligation.[5] Activated Src-family PTKs, primarily Lyn, phosphorylate tyrosine residues within ITAMs of CD79a/CD79b, which results in the recruitment of Syk through its Src homology 2 (SH2) domains.[6]

Lyn, the predominant Src-family member in B cells, has a crucial initiating role in BCR signaling. However, Lyn is also essential for feedback regulation since it phosphorylates immunoreceptor tyrosine-based inhibitory motifs (ITIM) within negative regulatory molecules.[5,7–10] In addition, regulation of Src-family PTK's catalytic activity is mediated by phosphorylation of two different tyrosine residues, which reciprocally regulate kinase activity.[11,12] PTK function is also regulated by "cross-talk" between PTKs, protein tyrosine phosphatases, and interactions with intracellular regulatory and adapter proteins.[13,14] PTK activation in turn propagates multiple downstream signaling events including tyrosine phosphorylation of important transmembrane receptors, phosphoinositide turnover and intracellular calcium ($[Ca^{++}]_i$) increases through the activation of phospholipase C-γ2 (PLC-γ2). PTK activity also influences the activation of mitogen-activated protein kinases (MAPKs), including the extracellular signal-regulated kinase (ERK), c-jun N-terminal kinase

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