humans.[32,34] Thus, CD19 expression appears to be tightly controlled.

CD19 is part of a multimolecular complex (Fig. 1) that involves various intracellular signaling pathways.[17] When expressed on the cell surface, CD19 interacts non-covalently with cell-surface CD21, a receptor for complement clevage fragments generated during complement activation.[35] In addition, CD19 interacts with CD81, a broadly expressed member of the tetraspans family of cell-surface molecules that are involved in multiple diverse signaling pathways.[36,37] Recently, CD81-deficient mice have revealed that CD81 expression is important for optimal cell-surface CD19 expression. The major hallmark of CD81-deficiency is decreased CD19 expression and signaling in B cells.[38–40] CD81 associates with another widely-expressed cell-surface molecule termed Leu-13.[41–43] Although the functional significance of this multimolecular complex on the cell surface is not understood, it is envisioned that CD19 and its associated CD81/Leu-13 molecules provide a signaling function for informing B cells of complement activation in the microenvironment.

Two different models for CD19 complex function/signaling have been proposed (Fig. 2). CD19 can function as a costimulatory molecule for the augmentation of B cell proliferation *in vitro*.[22,44] This has led to the suggestion that the CD21/CD19 complex serves as a costimulatory molecule for BCR signals when C3d fragments covalently bound to antigen coligates the CD21/CD19 complex with the BCR.[45] In this context, CD19 and BCR signaling would be upregulated when antigen-specific B cells encounter antigen-C3d complexes *in vivo*.

CD19 also functions as an intrinsic response-regulator,[22] as revealed in studies of mice that lack or overexpress CD19.[46–48] Changing CD19 expression levels in gene-targeted or transgenic mice significantly alters peripheral B cell numbers and their function. In CD19-deficient mice, B cells develop normally, but fail to expand in the periphery and spleen. CD19-deficient B cells are hypo-responsive to most transmembrane signals, including BCR ligation and mitogens, which leads to significant deficiencies in proliferation, clonal expansion and differentiation.[24,32,46,49,50] Although CD19-deficient B cells express cytoplasmic signal-

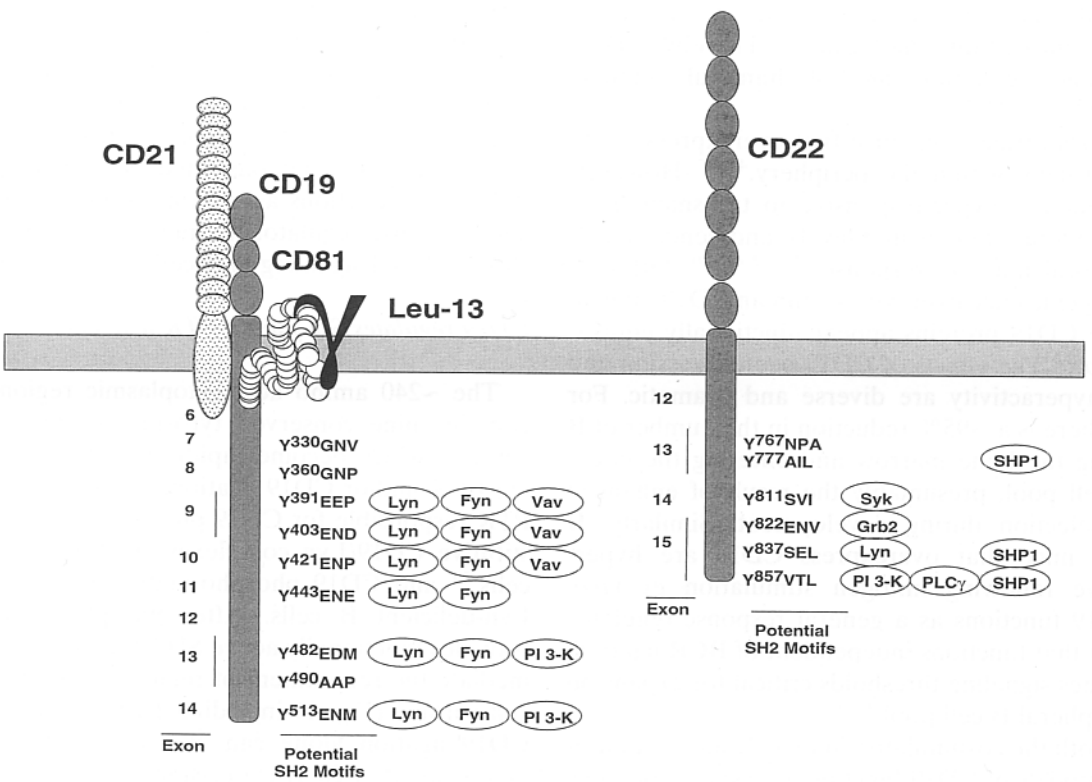

Fig. 1 Model of CD19 and CD22 structure (shaded) and associations with other signaling molecules. Y designates sites of potential tyrosine phosphorylation in the cytoplasmic domains of human CD19 and CD22. Amino acid positions are as described.[22,70]