and BCR engagement increased Lyn's binding to CD19. PI 3-kinase is constitutively associated with CD19 at detectable levels in unstimulated B cells, but the amount of PI 3-kinase precipitated with CD19 increases more than 10-fold after BCR cross-linking. The relative timing of Lyn and PI 3-kinase associations with phosphorylated CD19 suggests that Lyn binding takes precedence over PI 3-kinase binding following Lyn's phosphorylation of CD19. Thus, CD19 amplification of Lyn kinase activity may influence subsequent PI 3-kinase binding to CD19 through Y^{482} and Y^{513} phosphorylation sites. Indeed, PI 3-kinase phosphorylation is impaired in CD19-deficient B cells following BCR ligation.[21]

While CD19 may function as an adapter molecule to facilitate PI 3-kinase mobilization to the cell surface, the biological significance of this event is yet to be realized. PI 3-kinase facilitates $[Ca^{++}]_i$ mobilization and activates the Akt protein kinase pathway.[77,78] Whether targeted deletion of the gene encoding the p85α subunit of PI 3-kinase affects $[Ca^{++}]_i$ mobilization has not been reported, although this genetic deletion results in an *Xid*-like immunodeficiency in mice.[79,80] Nonetheless, B cells from CD19-deficient mice generate near-normal $[Ca^{++}]_i$ responses following BCR engagement.[32,81] Wortmannin, a potent PI 3-kinase inhibitor, also has relatively small effects on BCR-induced $[Ca^{++}]_i$ mobilization in wild type B cells.[57] Wortmannin also inhibits $[Ca^{++}]_i$ responses generated by B cells from CD19-deficient mice (data not shown). Furthermore, the baseline *in vitro* activity of immunoprecipitated PI 3-kinase is ~50% higher in CD19-deficient B cells than in wild type B cells before activation (unpublished observations). Following BCR ligation, the relative increase in PI-3 kinase activity is much lower in CD19-deficient B cells than in wild type B cells, although PI 3-kinase activity remains higher in CD19-deficient B cells compared to wild type B cells. Similarly, CD19 expression is not required for the membrane localization of PI 3-kinase activity since Akt phosphorylation is not remarkably inhibited in CD19-deficient B cells while Wortmannin treatment blocks Akt activation (unpublished observations). Thus, while CD19 expression in a plasmacytoma cell line increases PI 3-kinase activation,[57] loss of CD19 expression does not block activation of the PI 3-kinase/Akt pathway following BCR ligation in primary B cells.

CD22

CD22 structure, expression, and function

CD22 is a 140,000 M_r cell-surface glycoprotein of the Ig superfamily expressed only on B cells. CD22 is expressed in the cytoplasm of pro-B and pre-B cells, and on the cell surface as B cells mature to become IgD positive.[70] CD22 is an adhesion receptor for sialic acid bearing ligands expressed in serum, and on disparate hematopoietic and non-hematopoietic cells.[82,83] The dominant form of CD22 has seven Ig domains, of which the two amino-terminal Ig domains mediate ligand binding. Although the biological significance of CD22 as a mediator of intercellular interactions remains unclear, CD22 has critical roles in intracellular signal transduction. The ~140 amino acid cytoplasmic domain of CD22 contains six tyrosines that are targets for rapid phosphorylation following surface Ig or CD22 ligation.[84,85] These tyrosines are localized within ITAM-like sequences and ITIMs, suggesting positive and negative signaling functions for CD22.[19,20]

Development of CD22-deficient mice has clarified the functions of CD22 *in vivo*.[16,86–89] B cells from CD22-deficient mice develop normally, but their numbers are reduced in the periphery. Shorter lifespans and enhanced apoptosis are observed in CD22-deficient mice.[87] B cells from CD22-deficient mice demonstrate decreased surface IgM expression with increased major histocompatibility complex class II antigen expression. This phenotype resembles that of B cells that have been chronically exposed to self-antigens or B cells from mice that overexpress CD19. However, the prominent feature of CD22-deficient B cells is that they generate augmented $[Ca^{++}]_i$ responses following BCR cross-linking. Therefore, CD22 is also likely to act as a cell-surface response-regulator in B cells that modulates signaling thresholds.

A negative regulatory role for CD22 has been proposed since phosphorylated CD22 recruits SHP1, a potent phosphotyrosine phosphatase that is proposed to limit BCR signaling.[90–94] However, CD22 functions are complex since CD22-deficient B cells exhibit impaired proliferative responses to anti-IgM stimulation. Consistent with a positive role for CD22, overall protein tyrosine phosphorylation is reduced in B cells from CD22-deficient mice after BCR cross-linking. Tyrosine phosphorylation of CD79a/CD79b, PLC-γ2, and SHIP (for SH2 domain-containing inositol polyphosphate 5′-phosphatase) is decreased in CD22-deficient B cells following BCR crosslinking, while Src-family PTKs and Syk are phosphorylated at wild type levels.[65] Supporting this notion, phosphorylated CD22 is reported to physically interact with positive effector molecules including Syk, PI 3-kinase, PLC-γ2, Grb2, and SOS.[19,20,93–97] Thus, interactions between CD22 and multiple other effector molecules contribute to both positive and negative signaling pathways.

Molecular interactions between CD19 and CD22

CD19 and CD22 appear to have positive and nega-