tive regulatory effects on BCR signaling, respectively. For example, Vav tyrosine phosphorylation is modest and transient after BCR cross-linking in CD19-deficient B cells, yet uniquely augmented after BCR or CD19 ligation in CD22-deficient B cells.[65] Furthermore, CD19 and CD22 have counter-regulatory effects on MAPK activation.[71] However, recent studies have shown that CD19 and CD22 reciprocally regulate each other's functions and may thereby regulate BCR signal transduction indirectly. In support of this hypothesis, CD19 expression is required for CD22 phosphorylation after BCR ligation.[65] Decreased phosphorylation of CD22 in CD19-deficient B cells reduces the amount of CD22 associated with SHP1, thereby reducing the negative regulatory effects of CD22. By contrast, CD19 tyrosine phosphorylation is constitutively higher in CD22-deficient B cells and is increased significantly after BCR ligation relative to wild type B cells.[81] Augmented CD19 tyrosine phosphorylation in CD22-deficient B cells contrasts markedly with BCR phosphorylation, which is reduced in CD22-deficient B cells following BCR ligation.[65] Thus, CD19 is necessary to initiate negative regulation provided by CD22 expression, while CD19 is also likely to be a major target of the CD22 inhibitory pathway (Fig. 3F).

The generation of CD19/CD22-double deficient mice has provided additional insight into the cross-regulation between CD19 and CD22 on B cell signaling.[81] Functional studies of CD19/CD22-deficient B cells have revealed that CD19-deficiency is dominant in CD19/CD22-deficient mice, rather than CD19- and CD22-deficiencies having additive effects. BCR-induced tyrosine phosphorylation of total cellular proteins is equally impaired in CD19/CD22-deficient and CD19-deficient B cells, regardless of CD22 expression. Of significance, Lyn kinase activity is only modestly increased in CD19-deficient and CD19/CD22-deficient B cells after BCR ligation. Furthermore, Vav tyrosine phosphorylation following BCR ligation is decreased to a similar extent in CD19/CD22-deficient B cells and CD19-deficient B cells. Mitogen-induced proliferation of CD19/CD22-deficient B cells is reduced to levels identical with CD19-deficient B cells. Despite reduced proliferation by CD22-deficient B cells in response to IgM ligation, the combined loss of CD19 and CD22 does not affect proliferation beyond the effect of CD19 loss alone. Serum Ig levels in CD19/CD22-deficient and CD19-deficient mice are identical, as are antibody responses to T-dependent antigen immunization. Spleen B cell numbers in CD19/CD22-deficient mice are reduced as in CD19-deficient mice. As occurs in CD19-deficient mice, B1 cells within the peritoneum of CD19/CD22-deficient mice are rare, despite increased B1 cell numbers in CD22-deficient mice.[86,88] These studies demonstrate further that CD19 expression is necessary for CD22 function in most cases.

There are instances where CD19 and CD22 appear to have additive effects. In particular, CD19 and CD22 have overlapping influences on unactivated B cells, principally where a role for CD19 is absent or less pronounced. CD22 expression influences circulating B cell numbers with or without CD19 expression. While CD19 loss results in higher IgM expression by immature B cells and CD22 loss results in lower IgM expression by more mature B cells, CD19/CD22-deficient B cells have high IgM expression early and low IgM expression later during maturation. In addition, $[Ca^{++}]_i$ responses in CD19/CD22-deficient B cells are increased after BCR ligation as occurs in CD22-deficient B cells, although the magnitude and kinetics of the response mimic what is seen in CD19-deficient B cells. Thus, CD19 and CD22 are likely to interact through unknown pathways in addition to those highlighted in this review. For example, it remains unknown how either molecule influences $[Ca^{++}]_i$ responses following CD19 or BCR engagement. Nonetheless, the majority of the data suggest that CD19 expression is necessary for most functions of CD22 following BCR ligation.

Conclusions

Studies of CD19 have provided novel insights into normal and autoimmune B cell function. These studies suggest that intrinsic signal transduction thresholds regulated by CD19 are a pivotal element in autoantibody production. The generation of a Src-family PTK amplification loop by CD19 represents a novel mechanism for regulating intracellular signal transduction thresholds in addition to its previously hypothesized role as a specialized adapter protein for recruiting signaling effector molecules to the cell surface.[22,44] CD19 amplification of Src-family PTK function also provides additional insight into why CD19 supplies potent costimulatory function when co-ligated with the BCR complex. That CD19 is associated with both Lyn and Vav in splenic B cells prior to BCR ligation suggests that CD19/Lyn/Vav complexes are constitutively assembled. Similar to the CD19/Lyn/Vav complex, the B cell antigen receptor is constitutively organized into a preformed transducer complex in the absence of antigen ligation,[98] as is the T cell antigen receptor complex.[99] The absence of a constitutive CD19/Lyn/Vav signaling complex potentially explains why B cells from CD19-deficient mice are hypo-responsive to transmembrane signals. Similarly, the augmented formation of CD19/Lyn/Vav complexes in transgenic mice that overexpress CD19 may explain why B cells from these mice are hyper-responsive to transmembrane signals and are phenotypically similar to chronically stimulated B cells.[24,32] Constitutive CD19/Lyn/Vav complex sig-