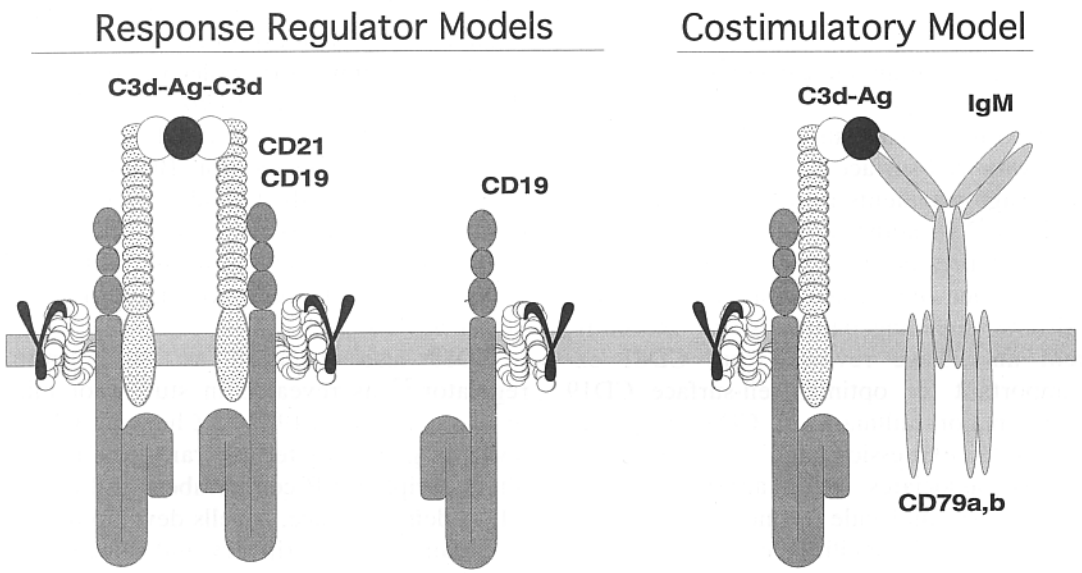


**Fig. 2** Models for CD19 function *in vivo*. CD21 associated with CD19 binds antigen complexes covalently modified with the C3d fragment of complement (C3d-Ag-C3d). In the costimulatory model, Ag-C3d complexes crosslink Ag-specific BCRs and CD19 by engaging both CD21 and the BCR.

ing molecules at normal levels, BCR ligation induces only modest phosphorylation and activation of downstream signaling molecules.[21] Thereby, CD19-deficient mice generate modest humoral immune responses.[24,32,46,48–50]

B cells from transgenic mice that overexpress CD19 mature normally within the periphery.[46,47] However, these B cells are hyper-responsive to transmembrane signals, proliferate at elevated levels, and generate elevated humoral immune responses.[24,32,49,50] Although these transgenic mice overexpress human CD19, human and mouse CD19 proteins appear functionally equivalent *in vivo*.[32] The effects of CD19 overexpression and resultant hyperactivity are diverse and dramatic. For example, there is a >95% reduction in the number of B cells exiting the bone marrow and entering the circulating B cell pool, presumably the result of enhanced negative selection during development. Similarly, B cells from mice that overexpress CD19 are hyperproliferative following mitogen stimulation *ex vivo*. Thus, CD19 functions as a general response-regulator or rheostat that functions independent of BCR ligation, which defines signaling thresholds critical for expansion of the peripheral B cell pool.[15,17]

While both the costimulatory molecule and response-regulator models of CD19 function are synergistic, they imply different regulatory roles for CD19 (Fig. 2). That the majority of mature B cells are affected by loss or overexpression of CD19 suggests that CD19 regulates B cell function independent of BCR engagement, but antigen-induced complement activation may activate CD19 signaling. In addition, it remains likely that a substantial component of CD19 function is independent of CD21 expression. Thereby, intrinsic expression levels of CD19 could regulate autonomous CD19 activity. Although CD19 may itself possess ligand-binding activity, this remains to be demonstrated. Nonetheless, it is clear that CD19 functions as both a costimulatory molecule and response-regulator to modulate both basal and BCR-induced signaling in B cells.

### *CD19 regulates Src-family PTK activation*

The ~240 amino acid cytoplasmic region of CD19 contains nine conserved tyrosine residues (Fig. 1),[51] some of which become rapidly phosphorylated following BCR and/or CD19 ligation.[22,44] Lyn is the primary PTK responsible for CD19 phosphorylation, since constitutive CD19/Lyn complexes are found in resting B cells,[21] and CD19 phosphorylation is not detected in Lyn-deficient B cells. After phosphorylation, CD19 provides functionally active SH2 recognition motifs that mediate the recruitment of regulatory molecules to the cell surface (Fig. 1) including Lyn, Fyn and Lck.[52–54] CD19 ligation alone can also induce Lyn activation independent of BCR expression.[53] Lyn and Fyn can be precipitated from cell lysates by CD19 phosphopeptides containing phosphorylated $Y^{391}$, $Y^{421}$, $Y^{482}$, or $Y^{513}$, and weakly using $Y^{403}$ and $Y^{443}$ phosphopeptides (Fig. 1). By contrast, Syk and Btk do not interact with CD19