naling may therefore be responsible for the establishment of baseline signaling thresholds in B cells prior to antigen receptor ligation, in addition to accelerating signaling following BCR engagement or other transmembrane signals. Augmented formation of CD19/Lyn/Vav complexes may also predispose to autoimmunity.

These studies unite the previous concept that CD19, CD21, CD22, Lyn, Vav and SHP1 are involved in the regulation of B lymphocyte signal transduction thresholds and show that each of these molecules contributes to a CD19-regulated pathway. Undoubtedly each molecule also contributes to other pathways. For example, although synergistic interactions between Lyn and CD19 amplify basal and BCR-induced signal transduction, the phenotype of CD19-deficient mice contrasts with that of Lyn-deficient mice, which are autoimmune.[28,29,46,48,100] This may result in part from CD19 expression being B cell-restricted, while Lyn is expressed broadly within hematopoietic tissues. Lyn-deficiency also leads to exaggerated inflammatory stimuli that may contribute to autoimmunity since Lyn negatively regulates cytokine signaling in macrophages through its ability to phosphorylate inhibitory receptors.[5] Nonetheless, Lyn and CD19 have both positive and negative roles in BCR-mediated signal transduction.[5,15] For example, signal termination following activation of the CD22 inhibitory pathway is a critical function for Lyn.[28,29,100]. Lyn is responsible for CD22 phosphorylation,[7] while CD22 phosphorylation and function is upregulated by CD19 expression as well.[65,81] Therefore, we propose that CD19-mediated amplification of the Src-family PTK pathway is required for initiating the down-regulatory functions of CD22. Remarkably, CD19 is a major target for the down-regulatory functions of CD22.[81] Thereby, CD19 expression synergistically modulates the positive and negative roles of Lyn, although Lyn regulates other pathways as well. Furthermore, CD19 may only modulate the activation of a specialized pool of intracellular Lyn kinase since the majority of intracellular Lyn did not associated with CD19. Whether CD19 and the BCR complex share the same small pool of cellular Lyn is unknown. CD19 may also regulate the activation of other Src-family PTK members since Fyn and Blk tyrosine phosphorylation are diminished in CD19-deficient B cells.[21] Thus, the collective phenotypes of Lyn-deficient and CD19-deficient mice are likely to reflect multiple qualitative and quantitative factors which account for their differences.

The identification of a subset of patients that overexpress CD19 and the demonstration that similar CD19 overexpression in mice leads to the production of autoantibodies suggests that the CD19 signaling pathway contributes to human disease. This also establishes a new paradigm by which very subtle changes in expression or function of tightly regulated signal transduction molecules may predispose to autoimmunity. Since multiple signaling molecules (CD19, CD21, CD22, Lyn, Vav and SHP1) appear to contribute to a common signaling pathway it is possible that subtle alterations in the expression or function of any of these molecules could induce pathology. In a broader sense, any alteration that disrupts the normal balance of signal transduction in resting or activated B cells may also predispose to autoimmunity.[9] A further understanding of how B lymphocyte signaling thresholds are regulated at the molecular level will undoubtedly reveal additional autoimmunity susceptibility genes that function at the cell surface and within the cytoplasm. The further challenge will be to understand how these molecules interact and how combinations of subtle alterations interact to cause the different manifestations of autoimmune disease.

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