(JNK), and p38.

Intrinsic and BCR-induced signals are also regulated by B lymphocyte cell-surface molecules that modify and provide a context for BCR signal transduction.[15] These cell-surface molecules are commonly called "co-stimulatory molecules" when they function in conjunction with the BCR to amplify signal transduction. However, another class of cell surface molecules are the "response-regulators" of lymphocyte signaling.[15] Response-regulators carry out broader functions than costimulatory molecules since they establish intrinsic signaling thresholds that provide a context for transmembrane signals including BCR-generated signals. We have recently suggested that CD19 and CD22 are members of the response-regulator class of cell-surface molecules.[16,17] CD19 and CD22 may each reciprocally regulate BCR signaling by associating directly with cell-surface IgM.[18–20] Herein this review, we propose a unique molecular mechanism through which tyrosine phosphorylated CD19 and CD22 function cooperatively to regulate a Src-family PTK activation loop that modulates intrinsic and BCR-induced signals.[21] These findings provide a mechanistic explanation of how CD19 regulates basal signaling thresholds and accelerates BCR signaling *in vivo*. Increased activity of this CD19/Src family kinase amplification loop may explain why patients and mice that overexpress CD19 are predisposed to produce autoantibodies.

CD19 and CD22 Expression Influence Autoimmunity

The production of autoantibodies is regulated by self-antigens signaling through B cell antigen receptors. These responses are further influenced by CD19, CD22 and other signal transduction molecules that function as response regulators to amplify or inhibit BCR signaling.[22] Intracellular regulatory molecules that appear to control BCR signaling intensity also include Lyn, Btk, Vav, and the SHP1 protein tyrosine phosphatase.[9,22,23] Recently, we have demonstrated that CD19, CD21, CD22, Lyn, Vav, and SHP1 are functionally linked in a common signaling pathway.

Remarkably, mice with altered CD19, CD21, CD22, Lyn or SHP1 expression produce autoantibodies and develop autoimmunity to varying degrees. Peripheral tolerance is disrupted in mice that overexpress CD19, which results in the spontaneous production of IgG subclass autoantibodies.[24,25] Self-reactive B cells deficient in CD21 expression are not anergized by soluble self-antigen in mouse models of tolerance.[26] CD22 deficiency is sufficient to predispose to development of high affinity autoantibodies in mice.[27] Lyn-deficient mice exhibit glomerulonephritis due to the presence of immune complexes containing autoantibodies.[28,29] Motheaten viable mice which bear SHP1 mutations demonstrate elevated levels of spontaneous autoantibodies, hypergammaglobulinemia, and tissue deposition of immune complexes.[30] Thus, each of these response-regulators for BCR signaling are suggested to play a critical role in autoantibody production.[22]

Although multiple molecules involved in a common CD19 signal transduction pathway influence autoimmunity in mice, similar examples in humans have only recently become available. Systemic sclerosis (SSc) is a multisystem disorder of connective tissue characterized by sclerotic changes in the skin and internal organs. Autoantibodies are detected in more than 90% of SSc patients and are considered to play a critical role in the pathogenesis of SSc.[31] In a recent study, we found that CD19 and CD21 expression levels were 20% higher on B cells from SSc patients compared with healthy individuals, while CD20, CD22, and CD40 expression were normal (Sato S, Hasegawa M, Tedder TF, Takehara K: Quantitative genetic variation in CD19 expression correlates with autoimmunity, manuscript submitted). Evidence that a 20% increase in CD19 expressed induces the autoantibodies found in SSc was obtained using transgenic mice that overexpress CD19 to a similar extent. Like in SSc patients, CD19 overexpression by 20% induced autoantibody production in a normally non-autoimmune strain of mice. Antinuclear antibodies, especially anti-spindle pole antibodies, as well as anti-single-stranded DNA, anti-double-stranded DNA and anti-histone antibodies, and rheumatoid factor were induced in these mice, but not wild type littermate controls. Thus, modest alterations in CD19 function or expression could contribute to the development of autoantibodies in humans. Moreover, similar subtle alterations in the expression or function of other regulatory molecules involved in the CD19 signal transduction pathway may also predetermine autoimmunity susceptibility in other autoimmune syndromes. Although speculation, it is possible that graded alterations in expression or function in these "response-regulators" may result in the spectra of autoantibody specificities characteristic of the different autoimmune diseases.

CD19

CD19 expression, structure and function

CD19 is a ~95 kDa B lymphocyte-specific cell-surface glycoprotein of the Ig superfamily expressed by early pre-B cells until plasma cell differentiation.[24,32] CD19 density on the cell surface is highly regulated during development with similar expression levels by all mature conventional B cells from different peripheral lymphoid tissues.[32,33] Cellular activation induced by anti-IgM antibodies, lipopolysaccharide (LPS) and IL-4 does not alter CD19 expression in either mice or