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Review Article

B cell signaling and autoimmune diseases: CD19/CD22 loop as a B cell signaling device to regulate the balance of autoimmunity

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Summary

Autoimmune diseases including connective tissue diseases and bullous diseases are life-threatening diseases. Recent clinical and experimental approaches have demonstrated that B cells play critical roles in autoimmune disease manifestation by well-established autoantibody-mediated mechanisms but also by a variety of other functions. These B cell functions are under regulation of B cell antigen receptor (BCR)-induced signals and by specialized cell surface coreceptors, or "response regulators," which inform B cells of their microenvironment. These response regulators include CD19 and CD22. CD19 and CD22 do not merely regulate BCR signals independently, but they have their own regulatory network. CD19 regulates CD22 phoshorylation by augmenting Lyn kinase activity, while CD22 inhibits CD19 phosphorylation via SHP-1. Importantly, these molecules consisting of this "CD19/CD22 loop" are significantly related with autoimmune phenotype in mice. Thus, CD19/CD22 loop may be a potential therapeutic target in autoimmune disease by modulating B cell signaling.

1. Introduction

Recent studies have revealed that B lymphocytes have more diverse functions in the immune system than were appreciated (1). Disruption of these functions leads to autoimmunity, in which B cells do not merely serve as passive producers of autoantibodies but also play a pivotal role via nonconventional mechanisms, including antigen presentation, cytokine production, and modulation of other immune cells. These functions of B cells depend on the activity of intrinsic and B cell antigen receptor (BCR)-induced signals. BCR signals are amplified, perpetuated, or suppressed through the regulation by specialized cell surface coreceptors, or "response regulators," which inform B cells of their microenvironment (2, 3). These response regulators include CD19, CD22, CD72, and Fcγ receptor IIb (FcγRIIb), and can be categorized into positive regulators or negative regulators. CD19 acts as a positive response regulator by establishing a Src-family protein tyrosine kinase (PTK) activation amplification loop that regulates basal signaling thresholds and intensifies Src-family PTK activity following BCR ligation as well as maintaining phosphatidylinositol (PI) 3-kinase and Vav activation (4). By contrast, CD22, CD72, and FcγRIIb provide negative feedback pathways to downregulate BCR signaling through the recruitment of tyrosine phosphatases including SHP-1 and/or SHIP (5, 6). Altering expression/function of these signaling components in mice can lead to autoimmune phenotypes. For example, a deficiency of Lyn, a Src-family PTK, leads to a severe lupus-like autoimmunity. This is likely to result from a failure of inhibitory feedback loops in which Lyn phosphorylates CD22 and CD72, triggering recruitment of SHP-1 to the plasma membrane, which then dampens BCR and/or CD19 signaling (5). Lyn deficiency also compromises an inhibitory pathway involving FcγRIIb and SHIP. In human, genetic and/or functional abnormalities have been found in these B cell signaling molecules as well. Herein we will discuss our current understanding of the molecular mechanisms of how B cell signaling components, especially CD19 and CD22, govern the emergence and intensity of BCR-mediated

signals, and of how alterations in these tightly controlled regulatory activities contribute to autoimmunity in mice and humans. Precise understanding of these mechanisms will enable us to develop new therapeutic approaches of targeting specific components in B cell signaling pathways that govern the autoimmunity. This review focuses on recent advances in B cell signaling and autoimmune diseases, especially in terms with CD19 and CD22.

2. Roles of B cells in autoimmune diseases

It is widely accepted that antibodies (Abs) produced by autoreactive B cells can directly contribute to the pathogenesis in various autoimmune diseases. This is especially obvious in organ-specific autoimmune diseases such as pemphigus in dermatology field. For example, production of anti-desmoglein Ab in pemphigus directly causes interference of keratinocyte adhesion, resulting in blister formation. In systemic autoimmune diseases, autoantibodies can also play a pathogenic role (1). In systemic lupus erythematosus (SLE), immune complex deposition containing anti-double-stranded DNA Ab cause nephritis. In addition, anti-SS-A Ab is considered to play a pathogenic role in neonatal lupus. Animal models of systemic autoimmune diseases have also provided new insights into possible roles of autoantibodies. K/BxN mice, a spontaneous model of rheumatoid arthritis (RA), have hyperactive B cells that cause an increase in B cell numbers, hyper-γ-globulinemia, and autoantibody production (7). Injection of serum from sick K/BxN mice into healthy animals induces arthritis within days and the target of this arthritogenic Abs is shown to be glucose-6-phosphate isomerase, a ubiquitously expressed glycolytic enzyme (8). Furthermore, a potion of patients with RA, especially active patients, possess pathogenic autoantibodies reactive with glucose-6-phosphate isomerase that is expressed on the surface of the synovial lining as well as on the endothelial cells (9, 10). Thus, K/BxN mice model demonstrates that arthritis can be provoked by pathogenic autoantibodies.

Nonetheless, recent studies have clarified that B cells have more functions other than producing autoantibodies. Abnormalities of these B cell functions are likely to contribute to the induction or development of systemic autoimmune diseases. These functions include antigen-presentation, production of various cytokines, lymphoid organogenesis, differentiation of T effector cells, and influence of antigen-presenting dendritic cell function (11) (Fig. 1). For example, in lupus-prone MRL/lpr mice, elimination of B cells results in a complete abrogation of nephritis, vasculitis, and skin disease (12). Furthermore, MRL/lpr mice with B cells that cannot secrete Abs still develop nephritis and vasculitis (13). Therefore, these results suggest that, independent of autoantibodies, B cells are essential for disease expression by serving as antigen-presenting cells or by contributing to local inflammation through secreting cytokines (14). Thus, B cells play a critical role in systemic autoimmunity and manifestation of autoimmune diseases via a variety of functions.

Recent clinical observations that B cell depletion is therapeutically beneficial in autoimmune disease patients have directly proved significant pathogenic roles for B cells in the initiation and progression of human autoimmune diseases. Treatment with monoclonal Ab against CD20, which is expressed by mature B cells, depletes B cells in vivo and ameliorates the manifestations of RA, SLE, idiopathic thrombocytopenic purpura and hemolytic anemia, as well as other immune-mediated diseases (15).

3. B cell signaling and response regulators

To facilitate protective immunity to pathogens while avoiding self-reactivity and autoimmunity, B cell responses to antigens are tightly regulated through intracellular signaling pathways. Importantly, this balanced regulation is achieved by signals generated through BCR and other cell-surface molecules that provide a context in the specific circumstances. Such response regulators can either positively or negatively regulate the context of BCR signaling, and thus establish signaling thresholds that control

the magnitude and duration of B cell activation. Positive response regulators that augment signals through BCR include CD19, while CD22, CD72, and FcγRIIb are among negative response regulators that dampen BCR signals (2, 16) (Fig. 2).

4. CD19: a positive response regulator

CD19 serves as a major positive response regulator in B cells. CD19 expression is restricted to the B cell lineage and follicular dendritic cells which function as antigen-presenting cells located in the murine spleen. CD19 is a 95-kDa immunoglobulin (Ig) superfamily member which has an extracellular region consisted of two C2-type Ig-like domains and a cytoplasmic region of ~240 amino acids including 9 conserved tyrosine residues. On B cell surface, CD19 forms a complex with CD21, CD81, and Leu-13 (CD225). CD21 is a receptor for complement C3 cleavage fragments and Epstain-Bar virus. Upon CD21 ligation, CD19 serves as a signal-transducing element of the complex. CD81 expression is critical for optimal CD19 expression and localization within lipid rafts (17). Accordingly, CD81-deificent mice exhibit a phenotype which resembles but is milder than that of CD19-deficient (CD19$^{-/-}$) mice (18).

The cytoplasmic region of CD19 contains 9 tyrosines, which are critical for CD19 function as a signaling molecule. While CD19 does not have enzymatic activity, CD19 acts as a cell-surface adapter protein that recruits signaling molecules through the interaction with phosphoryated tyrosines. CD19 tyrosines are phosphorylated by Lyn, a dominant Src-family PTK member in B cells (19, 20). CD19 regulates a variety of extracellular stimuli since CD19 is phosphorylated not only upon CD19/CD21 ligation but also BCR, CD38, CD40, or CD72 ligation as well as lipopolysaccharide stimulation (4, 21). Furthermore, simultaneous stimulation of CD19 with BCR, CD72, or CD40 induces synergistic transmembrane signals. Tyrosine-phosphorylated CD19 provides SH2 recognition motifs that serve as docking sites for Src-family PTKs, Vav, and PI 3-kinase (22). Furthermore, through the interaction with Src-family PTKs, CD19

upregulates and maintains Src-family PTK activity, and also facilitates and prolongs phosphorylation of other binding proteins, Vav and PI 3-kinase. Phosphorylated Vav can also recruit other SH2-domain-containing signaling molecules to this CD19 complex, which leads to downstream activation of mitogen-activated protein kinase family cascades. PI 3-kinase is another important effector molecule that interacts with CD19 (23). PI 3-kinase is necessary for Bruton's tyrosine kinase (Btk) activation. CD19 deficiency results in decreased and transient Btk activation induced by BCR ligation, suggesting an important role of CD19 in maintaining activation of PI 3-kinase/Btk pathway (24, 25).

CD19 expression is intrinsically and tightly regulated through B cell differentiation. CD19 is expressed by early pre-B cells from the time of Ig heavy chain rearrangement until plasma cell differentiation. CD19 expression gradually increase during the development, and B-1 cells express higher levels of CD19 than B-2 cells. By contrast, CD19 expression is not affected by B cell activation. Moreover, intrinsic CD19 expression levels may determine a genetic predisposition to autoimmunity. CD19 functions in vivo have been clarified using CD19$^{-/-}$ mice and CD19-transgenic (CD19-TG) mice that overexpress CD19 by ~3-fold (26-28). In general, CD19$^{-/-}$ mice are immunodeficient, while CD19-TG mice are autoimmune-prone (16). B cells from CD19$^{-/-}$ mice exhibit reduced proliferation to a variety of transmembrane signals, while B cells from CD19-TG mice show augmented proliferation to them. Serum Ig levels are decreased in CD19$^{-/-}$ mice and are increased in CD19-TG mice. CD19 expression on B cells also closely correlates with autoantibody production. Serum autoantibodies, such as anti-DNA Ab and rheumatoid factor, are decreased in CD19$^{-/-}$ mice, while they are increased in CD19-TG mice. Analysis using transgenic mouse model of autoreactive B cells and peripheral tolerance has revealed that CD19 overexpression disrupts peripheral tolerance in B cells and thereby induces autoantibody production (29).

5. CD19/CD22 signaling loop

CD22 is another B cell-specific transmembrane molecule critical for B cell survival and activation (30). CD22 is a 130-140-kDa protein that belong to "SIgLec" subclass of Ig superfamily. Extracellular domain of CD22 contain 5 (CD22α) or 7 (CD22β) Ig domains, while the cytoplasmic domain has 141 amino acids including 6 tyrosine residues, which are phosphorylated by Lyn (31). Amino acid sequences surrounding some of CD22 tyrosines are considered as immunoreceptor tyrosine-based inhibitory motifs (ITIMs), which recruit potent tyrosine phosphatase SHP-1. CD22 phosphorylation also induces formation of a CD22/Shc/Grb-2 ternary complex (32). Therefore, CD22 plays an inhibitory role in cellular tyrosine and phospholipid phosphorylation via SHP-1 and SHIP activation.

By contrast to the role of CD19 as a positive regulator, CD22 is generally categorized as a negative response regulator. Importantly, these two response regulators do not merely regulate BCR signals independently, but they have their own regulatory network (33) (Fig. 3). B cells from CD19$^{-/-}$ mice exhibit modest CD22 phosphorylation following BCR ligation, while CD19 tyrosine phosphorylation is increased in B cells from CD22$^{-/-}$ mice following BCR ligation (33). These evidences suggest that CD19 expression facilitates CD22 phosphorylation and that CD22 expression inhibits CD19 phosphorylation (4). CD19 positively regulates CD22 phsophorylation by augmenting Lyn kinase activity. Phosphorylated CD22 recruits SHP-1, which dephosphorylates CD19 in turn. Thus, CD19 and CD22 establish a loop that reciprocally regulates each other's functions to modulate cellular tyrosine and phospholipid phosphorylation.

Analysis of CD19/CD22 double-deficient (CD19$^{-/-}$CD22$^{-/-}$) mice has demonstrated that CD19 is upstream of CD22 function during B cell activation in most cases; CD22 deficiency does not influence the reduced serum Ig levels or the impaired Ab responses to T cell-dependent antigens that occurs in CD19$^{-/-}$ mice (33). Furthermore, numbers of splenic B cells and peritoneal B1 cells in CD19$^{-/-}$CD22$^{-/-}$ mice are similarly

reduced as in CD19$^{-/-}$ mice (34, 35). Therefore, CD19 regulation on Src-family PTK activation is critical for the initiation of inhibitory regulation by CD22, and in turn CD19 itself is a primary target of CD22/SHP-1.

6. Switching off CD22 negative pathway by CD19

While CD19 can function independent of the ligation of CD19 itself, co-engagement of CD19/CD21 complex with BCR results in synergistically enhanced signaling in response to complement-tagged antigens. Recent studies have shown that antigen binding leads to the translocation of BCR into plasma membrane lipid rafts that serve as platforms for efficient signal transduction. The binding of complement-tagged antigens stimulates the translocation of both the BCR and the CD19/CD21 complex into lipid rafts, resulting in prolonged residency in and signaling from the rafts, as compared to BCR cross-linking alone. When coligated to the BCR, the CD19/CD21 complex retards the internalization and degradation of the BCR (36).

A mechanism for augmented signaling by simultaneous BCR and CD19 ligation is explained by a finding that simultaneous BCR and CD19 ligation inhibits tyrosine phosphorylation of CD22, as well as SHP-1 recruitment to phosphorylated CD22 (37, 38). Thus, activation occurs without engagement of CD22 inhibitory pathway. Simultaneous CD19 and BCR engagement may sequester the functionally available pool of Lyn away from CD22. Especially, the spatial relationship between the BCR, CD19 and CD22 is likely to be important to this process since CD22 locates outside of lipid rafts. Consistent with this, B cells from CD22-deficient and Lyn-deficient mice exhibit augmented BCR-induced $[Ca^{2+}]_i$ responses, although simultaneous CD19 engagement does not further enhance the BCR-induced $[Ca^{2+}]_i$ responses in Lyn- or CD22-deficient B cells (37). Thus, CD19 recruitment of Lyn and their preferential localization within detergent-insoluble lipid raft domains may preferentially activate selected signaling pathways regulated by the CD19/Lyn complex to the exclusion of other downstream

regulatory and effector pathways.

7. CD19/CD22 autoimmune loop

CD19/CD22 is not only important for normal B cell function, but increasing evidences have suggested that this unit serves as a critical signaling device to regulate the balance of autoimmunity in B cells. The components of the CD19/CD22 signaling loop, CD19/CD21, Lyn, CD22, and SHP-1, appear closely linked to autoimmune disorders (39, 40) (Fig. 4). Altering their expression/function in mice leads to the manifestation of autoimmune phenotype. For example, Lyn-deficient mice and transgenic mice with hyperactivated form of Lyn both result in lupus-like disease (41). Transgenic mice that overexpress CD19 by ~3-fold lose tolerance and generate high titer of autoantibodies spontaneously including anti-double-stranded DNA Ab (40). Mice lacking CD22 have chronically activated B cells with various spontaneous autoantibody production including anti-cardiolipin Ab and anti-myeloperoxidase Ab (42). Motheaten viable (me^v/me^v) mice that have SHP-1 mutations produce elevated levels of spontaneous autoantibodies including anti-topoisomerase I (topo I) Ab, hyper-γ-globulinemia, and tissue deposition of immune complexes (43). Therefore, this "CD19/CD22 autoimmune loop" may be a potential therapeutic target in autoimmune disorders.

8. Tight-skin mouse and CD19/CD22 autoimmune loop

The Tight-skin (TSK) mouse, originally identified as a spontaneous mutation, is an animal model for human systemic sclerosis (SSc) (44). A tandem duplication within the fibrillin 1 gene is considered to responsible for the TSK phenotype (45). Fibrillin 1 is a major structural protein of a widely distributed class of connective tissue microfibrils. Homozygous mutation (TSK/TSK) results in embryo lethality, while heterozygous (TSK/+) mice survive, but develop cutaneous hyperplasia, pulmonary emphysema and cardiac hypertrophy.

The phenotype of TSK/+ mice appears regulated not only by fibrillin 1 mutation alone, since transgenic mice expressing a mutated fibrillin 1 gene develop subcutaneous hyperplasia, but not pulmonary emphysema and myocardial hypertrophy (46). Especially, an immunological component appears to influence the phenotype significantly. In addition to the fact that TSK/+ mice produce autoantibodies against SSc-specific target autoantigens including topo I, fibrillin 1, and RNA polymerase I, the lack of CD4 expression in TSK/+ mice decreases subcutaneous hyperplasia but does not influence lung emphysema (47). Additionally, disruption of one or both IL-4 alleles allows survival of 29 and 47%, respectively, of homozygous TSK/TSK mice (48). These mice do not exhibit subcutaneous hyperplasia but develop pulmonary emphysema. Collectively, these suggest that abnormal immune functions contribute to the complex phenotype of TSK mice. Consistent with this, polymorphisms of the transforming growth factor-β1 promoter in TSK mice have been also described (49).

Analyses of B cells from TSK/+ mice have also demonstrated their skewed phenotype (50, 51). As in human SSc, TSK/+ B cells are persistently activated, characterized by reduced cell surface IgM level as well as upregulated MHC class II and CD23 density. B cells from human SSc patients show increased surface CD19 expression (52-54), while CD19 expression is not altered in B cells from TSK/+ mice. Nonetheless, remarkably, CD19 tyrosine phosphorylation is constitutively augmented (50), suggesting that the CD19 signaling pathway is intrinsically activated in TSK/+ B cells.

Furthermore, TSK/+ B cells are hyperresponsive to BCR signaling. They exhibit exaggerated calcium responses and augmented activation of extracellular signal-regulated kinase (ERK) upon BCR crosslinking (51). BCR-induced CD19 phosphorylation is also augmented compared with wild type B cells. Among many signaling molecules assessed, CD22 phosphorylation was specifically impaired in TSK/+ B cells. Decreased tyrosine phsphorylation of CD22 is consistent with CD19 hyperphosphorylation in TSK/+ B cells, since CD19 is considered as a major target of

CD22 negative regulation via dephosphorylation by SHP-1 (33). Furthermore, CD22-deficient TSK/+ mice and CD22-deficient mice without TSK mutation showed identical $[Ca^{2+}]_i$ response and ERK activation (51), suggesting that disruption of inhibitory signal provided by CD22 is the dominant mechanism of hyperactivated TSK/+ B cells.

Remarkably, CD19 deficiency in TSK/+ mice results in ~40% reduction of subcutaneous fibrosis (50). Therefore, B cells contribute to skin fibrosis in TSK/+ mice through a CD19-dependent pathway. TSK/+ mice exhibit hyper-γ-globulinemia and elevated autoantibody levels including anti-topo I Ab, both of which are also eliminated by CD19 deficiency. Reciprocally, anti-topo I Ab levels are significantly augmented in TSK/+ mice carrying CD19 transgene (51). Nonetheless, subcutaneous fibrosis does not increase in TSK/+ mice overexpressing CD19 or TSK/+ mice with CD22 deficiency (51). Therefore, while silencing B cell hyperactivation can reduce skin fibrosis, exaggerating B cell hyperactivation does not lead to further fibrosis. While the precise mechanism of how silencing B cell hyperactivation by CD19 pathway can influence skin fibrosis is yet to be solved, CD19 loss inhibits IL-6 production by TSK/+ B cells, which produce higher amount of IL-6 compared with wild type B cells when stimulated with anti-IgM Ab plus anti-CD40 Ab (50). Since recent reports have suggested that CD19 is a key regulator of cytokine production from B cells (55), CD19 expression may influence fibrosing process by controlling cytokine production such as IL-6.

9. Conclusion

Therapy using anti-CD20 Ab in human autoimmune diseases have elucidated pathogenic roles of B cells in various aspects and have provided a new paradigm how to treat them. Future therapeutic directions include modifying B cell signaling functions such as CD19/CD22 loop.

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Figure Legends

Figure 1. B cell functions that may contribute to autoimmunity.

Figure 2. Positive and negative "response regulators" of B cells. Positive regulators include CD19, while negative regulators includes CD22, Cd72, and FCγRIIb. Each mnolecule has tyrosine residues that recruit signaling molecules upon phosphorylation. Particularly, specific tyrosine sequences in negative regulators are designated as ITIMs, which recruit phosphatase such as SHP-1 and SHIP.

Figure 3. Regulation of CD19 and CD22 on BCR signaling.
BCR ligation induces initial activation of Lyn, which phosphorylates CD19. Phosphorylated CD19 enhances and maintains Lyn activation, resulting in CD22 phosphorylation. Phosphorylated CD22 recruits SHP-1, which then dephosphorylates CD19.

Figure 4. CD19/CD22 autoimmune loop.
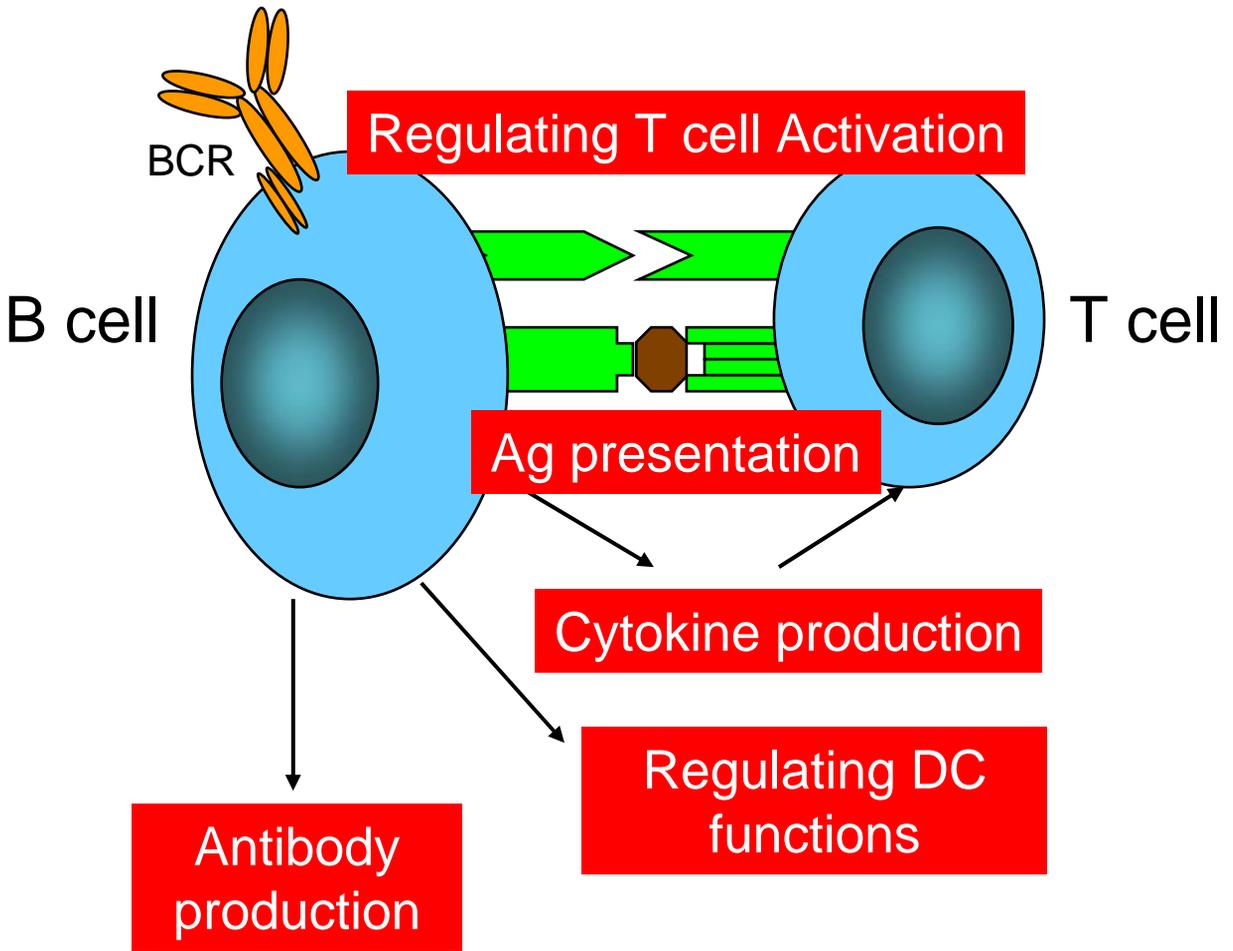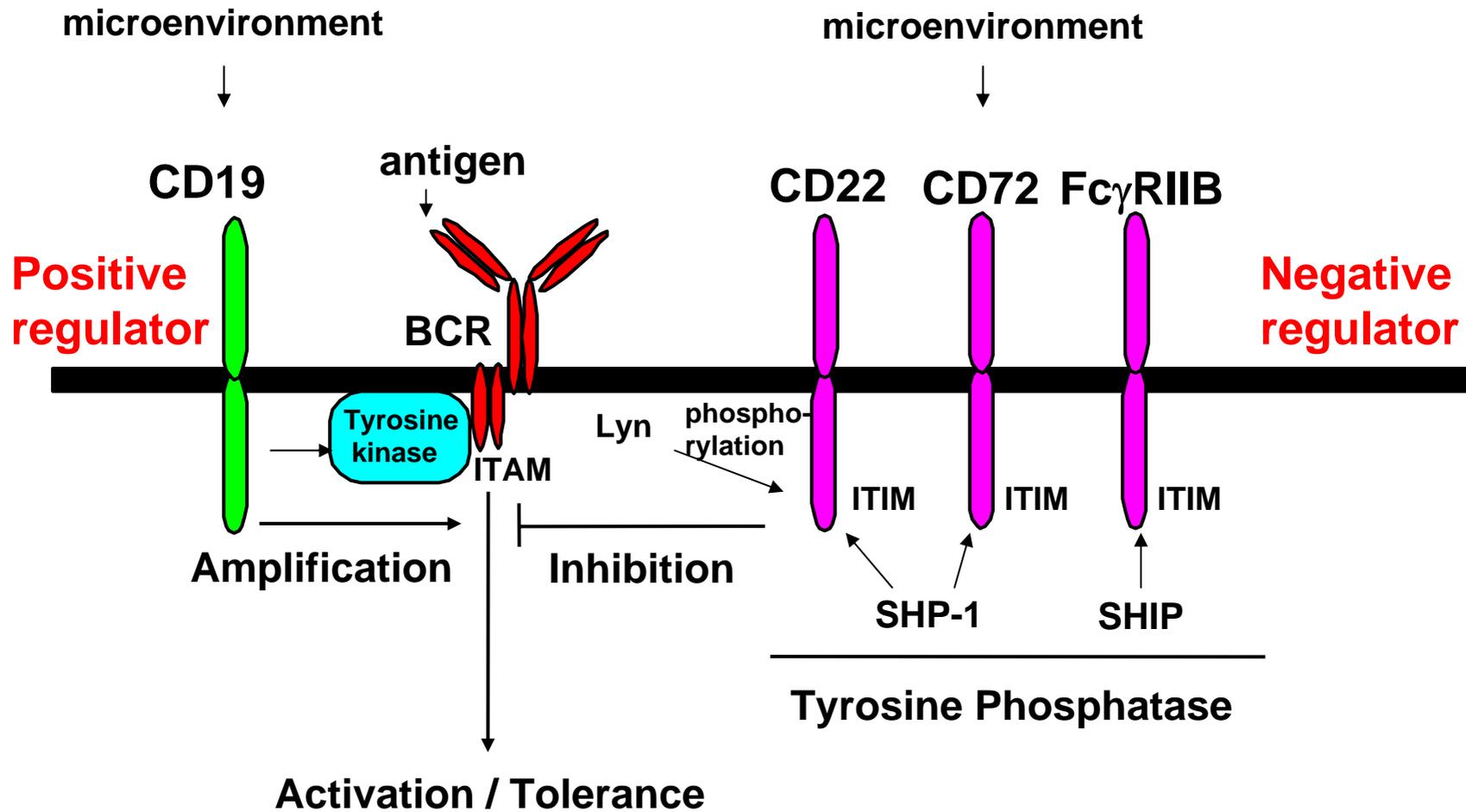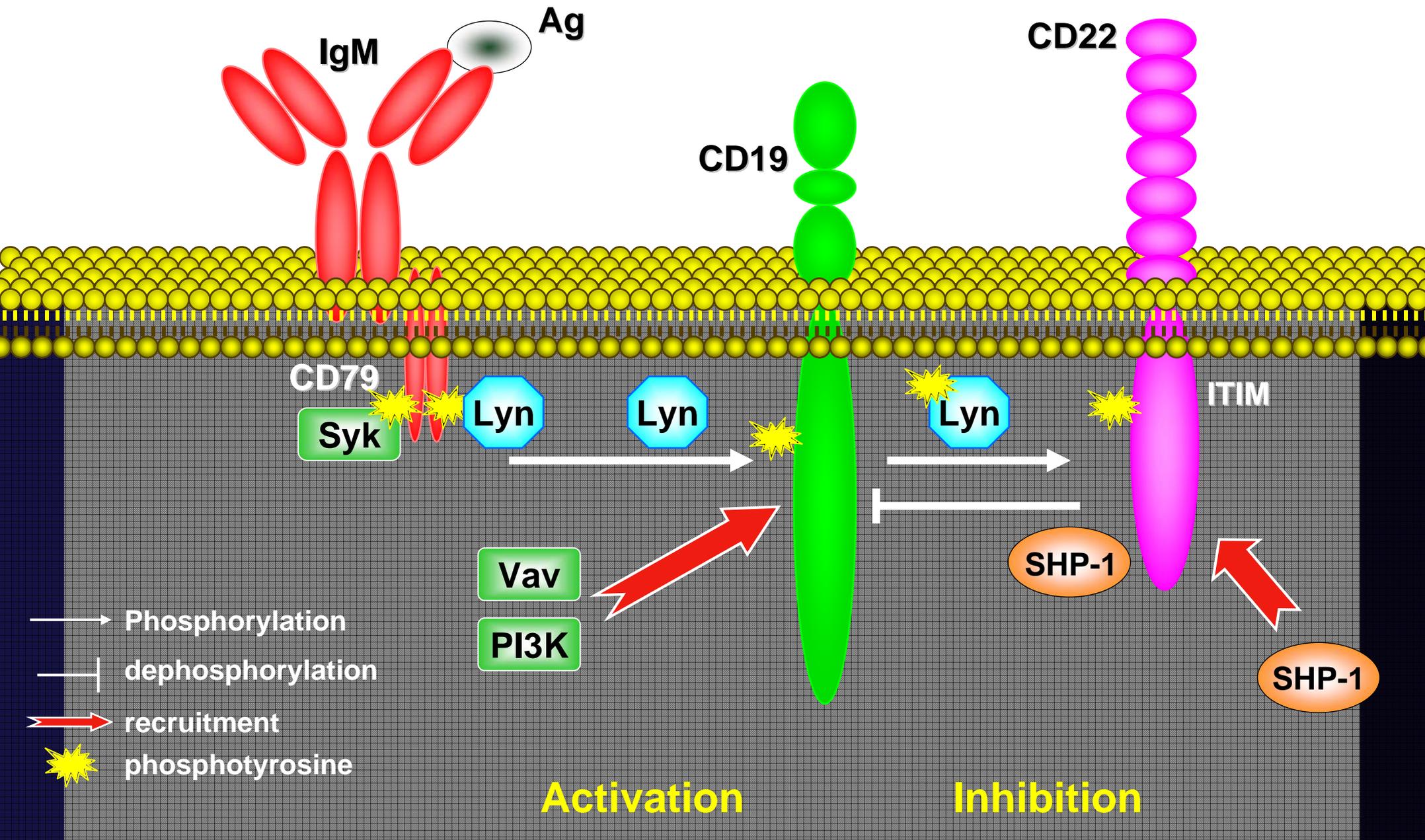Mice and human abnormalities of each molecule that are related to autoimmunity are shown in the square.

Figure 1
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