Inhibitory B cell co-receptors and autoimmune diseases

Takeshi Tsubata

Department of Immunology, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan

ABSTRACT

B cells express various inhibitory co-receptors including CD22 (also known as Siglec-2), Siglec-10 (Siglec-G in mice), CD72, LILRB (PIR-B in mice) and FcγRIIB that contain immunoreceptor tyrosine-based inhibition motifs (ITIMs) in the cytoplasmic region and negatively regulate BCR signaling by recruiting phosphatases to the ITIMs. Some of the inhibitory B cell co-receptors suppress development of SLE. Among these, CD72 most strongly regulates SLE. CD72 recognizes Sm/RNP, a lupus self-antigen and an endogenous TLR7 ligand, as a specific ligand, and suppresses B cell response to this TLR7 ligand. This suppression may inhibit development of SLE because TLR7 is indispensable in multiple mouse SLE models. In contrast, inhibitory B cell co-receptors such as CD22 and CD72 inhibit expansion of regulatory B cells that are known to regulate development of autoimmune diseases including type 1 diabetes (T1D) and multiple sclerosis. CD72 strongly exacerbate development of T1D in NOD mice probably by limiting expansion of regulatory B cells. Thus, inhibitory B cell co-receptors especially CD72 regulates distinct autoimmune diseases either positively or negatively. As B cell depletion therapy clearly reveals crucial roles of B cells in the regulation of various autoimmune diseases, CD72 may be a novel therapeutic target for treatment of autoimmune diseases.

ARTICLE HISTORY

Received 21 May 2019
Accepted 20 August 2019

KEYWORDS

Inhibitory B cell co-receptors; CD72; autoimmune disease; SLE; type 1 diabetes; regulatory B cells

1. Introduction

Studies in the past two decades markedly advanced our understanding of the mechanisms for development of autoimmune diseases. As a consequence, it is well established that B cells play crucial roles in regulation of various autoimmune diseases. First, B cell depletion by anti-CD20 antibody ameliorates various autoimmune diseases including those traditionally viewed as T cell-mediated diseases such as type 1 diabetes (T1D) and multiple sclerosis [1–4]. Second, a large number of disease-associated genes have been identified by genome-wide association studies (GWAS). Analysis of SLE-associated genes are accumulated in genes expressed in B cells [5], suggesting that functional defects in B cells play an important role in development of SLE probably by abrogating tolerance of self-reactive B cells. Third, accumulating evidence suggests pathogenic roles of autoantibodies specifically associated with a disease or a clinical symptom such as anticitrullinated protein antibodies in rheumatoid arthritis and antineutrophil cytoplasmic antibodies in vasculitis [6,7].

B cells appear to contribute to the pathogenesis of autoimmune diseases by multiple mechanisms. First, B cells produce pathogenic autoantibodies. Second, B cells may play a role in development of autoimmune diseases by presenting self-antigens to T cells and secreting cytokines [4,8,9]. In contrast, inhibitory cytokines such as IL-10 produced by B cells are shown to inhibit development of various autoimmune diseases. A fraction of CD1dhi B cells and plasmablasts are responsible for production of inhibitory cytokines, and are therefore called regulatory B (B reg) cells [10–12]. Our recent studies show that inhibitory receptors expressed in B cells especially CD72 inhibit both activation of self-reactive B cells and generation of B reg cells [13,14], thereby regulating autoimmune diseases such as T1D and SLE either positively or negatively depending on the disease [15,16].

2. Inhibitory B cell co-receptors and SLE

B cells express various inhibitory receptors including CD22 (also known as Siglec-2), Siglec-10 (Siglec-G in mice), CD72, LILRB (PIR-B in mice), FcγRIIB (Table 1) [17,18]. These receptors contain immunoreceptor tyrosine-based inhibition motifs (ITIMs) in the cytoplasmic tails. Upon ligation of B cell receptor (BCR), ITIMs are phosphorylated at the tyrosine residue by the BCR-associated kinase Lyn, thereby...
recruiting and activating SH2-containing phosphatases such as SH2-contingin protein tyrosine phosphatase 1 (SHP-1, also known as PTPN6), SHP-2 (also known as PTPN11), and SH2 domain-containing inositol polyphsphate 5-phosphatase 1 (SHIP1, also known as INPP5D). These phosphatases then dephosphorylate signaling molecules activated by BCR ligation, thereby negatively regulate BCR signaling. Because of the functional association with BCR, these inhibitory receptors are called inhibitory B cell co-receptors. Expression of CD22, Siglec-10/2, and CD72 is mostly restricted to B cells, whereas other inhibitory receptors are expressed in various immune cell types as well as B cells (Table 1).

Most of the inhibitory co-receptors activate SHP-1 but not SHIP1, whereas FcγRIIB activates SHIP1 but not SHP-1 [17,18]. B cell-specific SHP-1 deletion causes defects in B cell development, marked expansion of B-1 cells and development of severe lupus-like disease in mice [19]. Mice deficient in SHIP1 in B cells show similar phenotypes [20]. Thus, both of these phosphatases regulate multiple phenotypes in B cells probably by globally regulating BCR signaling. In contrast, inhibitory co-receptors regulate distinct phenotypes depending on the receptors. CD22⁻⁻ mice show defects in B cell development [21–23] similar to those in B cell specific SHP-1⁻⁻ mice whereas Siglec-G⁻⁻ mice show marked B-1 cell expansion [24] as is the case for B cell specific SHP-1⁻⁻ mice. CD22⁻⁻ mice and PIR-B⁻⁻ mice do not develop lupus-like disease [25,26]. However, mice that are deficient in PIR-B and carry Fas⁽pr⁾, a loss-of-function mutant of Fas, develop renal disease [26], and PECAM1⁻⁻ mice and Siglec-G⁻⁻ mice develop mild lupus-like nephritis in a fraction of mice over 12 months of age [25,27]. Interestingly, CD72⁻⁻ mice develop severe lupus-like disease similar to B cell-specific SHP-1-deficient mice [16,28]. CD72⁻⁻ mice produce autoantibodies such as anti-DNA antibodies, and develop nephritis in almost all the mice already at 6-month of age. CD72⁻⁻/Faslpr/lpr mice develop more severe lupus-like disease comparable to MRL-Faslpr/lpr mice [16] (Figure 1). Thus, many of the inhibitory B cell co-receptors regulate development of SLE though weakly, but CD72 strongly inhibits development of this autoimmune disease. A crucial role of CD72 in development of SLE is supported by the finding that CD72 is associated with lupus nephritis in patients with SLE by candidate gene approach [29], although association of CD72 with SLE has not yet been shown by GWAS probably because of the absence of CD72 alleles with significant functional difference. Because the severity of the lupus-like disease in CD72⁻⁻ mice is comparable to that in B cell-specific SHP-1-deficient mice [16,19], CD72 appears to be the major activator of SHP-1 in self-reactive B cells. Likewise, CD22 and Siglec-G are the major activators of SHP-1 in the regulation of B cell development and B-1 cell homeostasis, respectively. Thus, different inhibitory B cell co-receptors regulate distinct phenotypes of B cells probably by regulating BCR signaling under specific conditions [18].

---

**Table 1. Inhibitory B cell co-receptors.**

| Inhibitory receptor | Expression | Ligand | Phosphatase | B cell development in knock-out mice | Spontaneous autoimmune disease in knock-out mice |
|---------------------|------------|--------|-------------|-------------------------------------|-----------------------------------------------|
| CD22 (Siglec-2)     | B, (DC)*   | α2,6 sialic acid (mouse CD22 prefers Neu5Gc) | SHP-1 | Reduction of marginal zone B cells, reduction of surface IgM level in follicular B cells, expansion of B reg cells |
| Siglec-10 (Siglec-G in mouse) | Mouse: B, DC, human: B (Mø, Eo) | α2,6 sialic acid, α2,3 sialic acid | SHP-1 | Expansion of B-1 cells |
| CD72                | B          | 5m/RNP (agonist), CD100 (antagonist) | SHP-1 | Expansion of B reg cells |
| LILRB (PIR-B in mouse) | B, Mø, N, DC, Mast, osteoclast | MHCI | SHP-1, SHP-2 | Mild expansion of B-1 cells |
| PECAM-1             | B, T, Mø, N, NK, P, endothel | PECAM-1, sialic acid | SHP-1, SHP-2 | Mild expansion of B-1 cells |
| FcγRIIB             | human: B, Mø, DC, NK, (Mo, N), mouse: B, Mast Baso | IgG (Fc region) | SHIP1 | Combination with Fas⁽pr⁾ causes severe lupus-like disease |

N: neutrophils; Mø: monocytes; Møc: macrophage; P: platelet; Eo: eosinophil. *Parenthesis indicates weak expression.
FcγRIIB is the only one inhibitory B cell coreceptor known to activate SHIP1 [30]. Although B cell-specific SHIP1 deletion causes phenotypes similar to B cell-specific SHP-1−/− mice including development of severe lupus-like disease [20], FcγRIIB−/− mice do not develop lupus-like disease at least on C57BL/6 background, the same genetic background as the B cell-specific SHIP1−/− mice. Initially, FcγRIIB−/− mice were reported to develop lupus-like disease [32]. Later, development of the disease turned out to require the 129 mouse strain-derived autoimmune-prone SLAM haplotype, which is closely located to the FcγRIIB locus on the chromatin, and FcγRIIB−/− mice on the C57BL/6 background do not develop autoimmune disease [33]. Thus, SHIP1 appears to be activated by a mechanism independent of inhibitory receptors to regulate autoimmune disease. Indeed, SHIP1 is recruited and activated by Igα/Igβ in the BCR complex upon phosphorylation [34]. SHIP1 may be activated by Igα/Igβ in B cells including self-reactive B cells, leading to protection from autoimmunity.

3. CD72 recognizes the lupus self-antigen Sm/RNP as a specific ligand

It is already established that development of SLE involves nucleic acid (NA) sensors [35–38]. NA sensors activate various immune cells including B cells by recognizing microbial nucleic acids as pathogen-associated molecular patterns (PAMPs) thereby contributing host defense against pathogens. However, aberrant responses of NA sensors to self-NAs appear to play a central role in the pathogenic processes of SLE. GWAS have shown that SLE is associated with various genes encoding NA sensors and signaling molecules involved in signaling through NA sensors [39,40]. Moreover, mice deficient in various genes involved in NA metabolism develop lupus-like disease [41]. These findings strongly suggest that excessive responses to NAs are involved in development of lupus. Responses of B cells to self-NAs induce autoantibody production to various NAs and NA-related nuclear self-antigens that characterizes SLE. Responses of plasmacytoid dendritic cells (pDCs) to self-NAs cause type 1 interferon (IFN I) production, resulting in expression of various IFN-responsive genes known as interferon signature, which is the most significant changes in gene expression in SLE patients.

Among various NA sensors TLR7 plays a central role in development of SLE at least in mice because mice deficient in the RNA sensor TLR7 no longer develop the autoimmune disease in multiple mouse SLE models such as MRL-Faslpr/lpr mice and pristine-induced lupus [42,43]. In contrast, the DNA sensor TLR9 suppresses development of lupus by competing transport of TLR7 to endosome [42,44] where NA-sensing TLRs are converted to functional receptors by proteolytic processing [45], indicating that immune responses to RNA-related self-antigens but not DNA play a central role in development of SLE. Sm/RNP is an RNA-containing nuclear self-antigen, whose major component is U1-snRNP.

Figure 1. Lupus-like nephritis in CD72−/− and CD72−/− Faslpr/lpr C57BL/6 mice at 6 months of age. Representative PAS staining and immunohistochemistry for IgG and C3 of kidney sections (A), and scores of the severity of glomerulonephritis (B) in female wild-type (WT), CD72−/−, Faslpr/lpr and CD72−/− Faslpr/lpr C57BL/6 mice at 6 months of age are shown. Severity of glomerular damage was scored as described previously [31]. Grade 0, no involvement; grade 1, 2, and 3, changes in 0–25%, 25–50%, 50–75% of total glomeruli, respectively; grade 4, sclerosis or crescent formation in greater than 90% of glomeruli. *p < .05; **p < .001. Note that both CD72−/− and CD72−/− Faslpr/lpr mice develop nephritis in all the mice at 6 months of age. Originally published in The Journal of Immunology, Xu et al. 2013 [16]. Copyright © [2013] The American Association of Immunologists, Inc.
involved in RNA splicing. Anti-Sm/RNP antibody is known as a disease-specific autoantibody in SLE [46]. Sm/RNP was shown to be an endogenous TLR7 ligand [47]. Although most of the endogenous ligands of innate receptors including TLRs induce inflammation as damage-associated molecular patterns (DAMPs) [48], endogenous ligands of TLR7 such as Sm/RNP appear to be involved in development of SLE by activating self-reactive B cells to produce autoantibodies to NA-related self-antigens and activating pDCs to produce IFN-I.

CD72 contains a C-type lectin-like domain (CTLD) in the extracellular region. Previously, we demonstrated that CD72 CTLD specifically recognizes Sm/RNP [13]. By recognizing Sm/RNP as a ligand, CD72 negatively regulates BCR signaling induced by Sm/RNP. As is the case for other inhibitory B cell co-receptors, CD72 is phosphorylated at
an ITIM by the BCR-associated kinase Lyn, thereby recruiting and activating SHP-1. Thus, CD72 needs to be located in the proximity of BCR to negatively regulate BCR signaling. When BCR is ligated by Sm/RNP, CD72 is recruited to BCR by recognizing BCR-bound Sm/RNP, and is phosphorylated by Lyn associated with BCR. In contrast, CD72 is kept away from BCR when BCR is ligated by other antigens (Figure 2). By this mechanism, CD72 appears to negatively regulate BCR signaling when BCR is ligated by Sm/RNP but not other antigens. We further demonstrated that CD72 inhibits proliferation of Sm/RNP-reactive B cells upon stimulation with Sm/RNP [13]. Proliferation of B cells stimulated by Sm/RNP was shown to depend on TLR7 [47]. It is not yet known whether CD72 inhibits TLR signaling. However, CD72-mediated inhibition of BCR signaling generated by Sm/RNP may inhibit B cell proliferation induced by Sm/RNP as dual signaling through BCR and TLR7 may be required for proliferation of these B cells. Thus, CD72 antagonizes TLR7 in autoantibody production by suppressing BCR signaling induced by the endogenous TLR7 ligand Sm/RNP (Figure 3).

Although recognition of microbial NAs especially viral NAs is crucial in immune responses to microbes, recognition of self NAs causes inflammation and autoimmunity [38]. Recognition of self NAs is suppressed by multiple mechanisms in normal immune system. First, many of NA sensors recognize structure of NAs specific to microbial NAs such as double-stranded RNA and 5’-triphosphate RNA [50], although some NA sensors such as TLR7, TLR9 [47,51,52], and the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) recognize endogenous NAs [53,54] as well as microbial NAs. Second, NA sensors are located in either cytosol or endosome but not on the cell surface. Self-NAs derived from dead cells are mostly free NAs, which are rapidly degraded by nucleases in the body fluid. In contrast, microbial NAs located inside of microbes are released from microbes either in endosome or cytosol only after they are taken up by host cells. Thus, NA sensors in cytosol and endosome efficiently sense microbial NAs but not self NAs. A role of NA sensor localization in discrimination of microbial vs. host NAs is underlined by the finding that aberrant expression of TLR9 on the cell surface causes autoimmune disease [55]. However, complexes composed of NAs and nuclear proteins such as Sm/RNP are relatively resistant to nucleases. When Sm/RNP is released from dead cells, Sm/RNP may be able to access endosomal NA sensors after it is taken up by self-reactive B cells, and activate B cells to produce autoantibodies. CD72 inhibits responses of B cells to Sm/RNP, thereby constituting a mechanism that discriminates self NAs complexed with proteins from microbial NAs (Figure 3). CD72 appears to recognize the protein part of Sm/RNP but not RNA. This recognition may avoid impairment of immune responses to microbes.

4. Regulation of B reg cells and autoimmune diseases by inhibitory co-receptors

It is already established that a subset of B cells called B reg cells regulate development of autoimmune diseases such as MS and T1D by secreting inhibitory cytokines such as IL-10 and IL-35 [10–12]. B reg cells were initially shown to be accumulated in CD1dhi B cells [56]. Later studies demonstrated that the majority of B reg cells are present in plasmablasts especially LAG3+ plasmablasts [11,14]. More recently, IgA+ plasma cells are also shown to function as B reg cells [57]. Defect in IL-10 production from B cells was reported in patients with various autoimmune diseases such as MS, T1D, and SLE [58–61], suggesting a role of B reg cells in the regulation of autoimmune diseases. However, effect of B cell-specific IL-10 deficiency depends on the diseases. B cell specific IL-10 deficiency exacerbates experimental allergic encephalomyelitis (EAE) [62], a mouse model of MS. In contrast, global IL-10 deficiency but not B cell-specific IL-10 deficiency exacerbates lupus-like disease in MRL-Fas<sup>hp/hp</sup> mice [63,64], suggesting that SLE is regulated by IL-10 from cell types other than B cells. Thus, B reg cells suppress development of some but not all autoimmune diseases. These findings do not contradict with the findings that autoimmune diseases including T1D and MS are ameliorated by B cell depletion therapy using anti-CD20 antibody [1–4]. Because plasmablasts are CD20−, majority of B reg cells may not be depleted by rituximab.

Inhibitory B cell co-receptors such as CD22 and CD72 have been shown to regulate expansion of B reg cells. CD22<sup>−/−</sup> mice show expansion of CD1d<sup>hi</sup> B cells and B cells that produce IL-10 upon stimulation with LPS, PMA, and ionomycin [65]. CD22<sup>−/−</sup> mice show expansion of LAG-3<sup>+</sup> plasmablasts, and B cells that produce IL-10 upon Salmonella infection [14]. These findings clearly demonstrate that both CD22 and CD72 inhibit B reg expansion. TLR signaling has been shown to induce IL-10 production and expansion of B reg cells [65,66]. Because CD22 negatively regulates B cell activation induced by TLR ligands such as LPS, CpG and imiquimod [67], CD22 may inhibit expansion of B reg cells by negatively regulating B cell responses to TLR ligands. It is not yet known whether CD72 regulates B cell activation induced by TLR ligands. However, CD72 recognizes the endogenous TLR7 ligand Sm/RNP as
a specific ligand, and inhibits B cell responses to Sm/RNP [13]. Suppression of responses to Sm/RNP might be involved in inhibition of B reg expansion by CD72.

5. CD72 augments T1D in NOD mice

There are three allelic forms of CD72, i.e., CD72a, CD72b, and CD72c [68]. CD72a and CD72b are highly homologous each other. In contrast, CD72c contains a number of amino acid substitutions and a 7 amino-acid deletion compared to the other allelic forms. MRL-Faslpr/lpr mice carries CD72c, and CD72c plays a role in development of lupus-like disease in these mice [16,69,70]. Although Faslpr, a loss-of-function mutant of Fas, is required for development of severe lupus-like disease in MRL-Faslpr/lpr mice, the MRL background is also required because mice carrying Faslpr on other background such as C57BL/6 and C3H do not develop lupus-like disease [71]. First, genetic analysis demonstrated that CD72c is associated with the disease in MRL-Faslpr/lpr mice [69]. Later, introduction of CD72b was shown to ameliorate the disease in MRL-Faslpr/lpr mice [16,70]. These results clearly indicate that CD72c in the MRL background is involved in development of lupus-like disease in MRL-Faslpr/lpr mice. Recently, we demonstrated that binding of CD72c to Sm/RNP is weaker than that of CD72a [13], indicating that CD72c is a hypomorphic allele. CD72c is involved in development of lupus-like disease probably because CD72c may inhibit B cell responses to Sm/RNP only weakly.

NOD mice that spontaneously develop T1D also carry CD72c [72]. To address whether CD72 regulates T1D, we generated NOD mice carrying CD72b by backcrossing C57BL/6 mice to NOD mice. Although introduction of CD72b into MRL-Faslpr/lpr mice ameliorates lupus-like disease [16], CD72b markedly exacerbates T1D in NOD mice [15]. Our study showed that NOD.CD72b mice become diabetic in significantly higher frequency and at younger age than NOD mice that carry CD72c (Figure 4). Incidence and severity of insulitis in NOD.CD72b mice are much higher than those in NOD mice. Because CD72c is a hypomorphic allele, these results strongly suggest that CD72 accelerates development of T1D. It is not yet elucidated how CD72 regulates T1D. However, CD72-mediated inhibition of B reg expansion may augment T1D because development of T1D is suppressed by B reg cells [59].

Figure 4. Accelerated T1D development in NOD.CD72b mice. (A and B) Representative HE staining of pancreas sections (A), and scores of the severity of insulinis (B) in 10-12 week-old female NOD (CD72c) (n = 9) and NOD.CD72b mice (n = 12). Severity scale: 0, normal islet; 1, peri-insulitis or infiltration of less than 25% of the islet surface area; 2, infiltration of 25–50% of the islet surface area; 3, infiltration of more than 50% of the islet surface area. (C and D) Blood glucose levels (C) and incidence of diabetes (D) at indicated age. Each symbol represents data of each mouse (C). Diabetes was diagnosed when the blood glucose level was greater than 250 mg/ml. Reprinted from Hou et al. [15]. Copyright 2009, with permission from Elsevier.
6. Conclusions

B cells play a role in development of autoimmune diseases by producing autoantibodies, and also contribute to T cell-mediated autoimmunity probably by activating self-reactive T cells as APCs and secreting cytokines [4,8,9]. In contrast, B reg cells inhibit development of autoimmune diseases by producing inhibitory cytokines such as IL-10 [10–12]. Thus, B cells regulate autoimmunity either positively or negatively. Inhibitory B cell co-receptors regulate autoimmunity by suppressing B cell activation. Among these inhibitory B cell co-receptors, CD72 regulates development of autoimmune diseases SLE and T1D most strongly probably because of its recognition of Sm/RNP [13], a lupus self-antigen and an endogenous TLR7 ligand, as a specific ligand. As TLR7 is essential for development of SLE at least in mouse models, CD72 appears to inhibit development of SLE by suppressing B cell responses to endogenous TLR7 ligands such as Sm/RNP. B cell responses to endogenous TLR ligands are also crucial in expansion of B reg cells [65,66]. CD72 accelerates T1D probably by suppressing B cell responses to endogenous TLR7 ligands required for B reg expansion. Because CD72 efficiently regulates development of various autoimmune diseases, CD72 appears to be a good therapeutic target for autoimmune diseases.

Disclosure statement

No potential conflict of interest was reported by the author.

Funding

The author’s work was supported by JSPS Grant-in-Aid for Scientific Research 26293062, 17H05790, and 18H02610.

ORCID

Takeshi Tsubata http://orcid.org/0000-0003-0760-1258

References

[1] Gurcan HM, Keskin DB, Stern JN, et al. A review of the current use of rituximab in autoimmune diseases. Int Immunopharmacol. 2009;9(1):10–25.
[2] Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med. 2009;361(22):2143–2152.
[3] Granqvist M, Borealm M, Poorghobad A, et al. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. J Am Med Assoc Neurol. 2018;75(3):320–327.
[4] Hofmann K, Claudia AK, Manz RA. Targeting B cells and plasma cells in autoimmune diseases. Front Immunol. 2018;9:835.
[5] Hu X, Kim H, Stahl E, et al. Integrating autoimmune risk loci with gene-expression data identifies specific pathogenic immune cell subsets. Am J Hum Genet. 2011;89(5):682.
[6] Xiao H, Hu P, Falk RJ, et al. Overview of the pathogenesis of ANCA-associated vasculitis. Kidney Dis (Basel). 2016;1(4):205–215.
[7] Coutant F. Pathogenic effects of anti-citrullinated protein antibodies in rheumatoid arthritis – role for glycosylation. Joint Bone Spine. 2019. DOI:10.1016/j.jbspin.2019.01.005
[8] Wong FS, Wen L, Tang M, et al. Investigation of the role of B-cells in type 1 diabetes in the NOD mouse. Diabetes. 2004;53(10):2581–2587.
[9] Marino E, Tan B, Binge L, et al. B-cell cross-presentation of autologous antigen precipitates diabetes. Diabetes. 2012;61(11):2893–2905.
[10] Tedder TF. B10 cells: a functionally defined regulatory B cell subset. J Immunol. 2015;194(4):1395–1401.
[11] Fillatreau S. Regulatory plasma cells. Curr Opin Pharmacol. 2015;23:1–5.
[12] Mauri C, Menon M. Human regulatory B cells in health and disease: therapeutic potential. J Clin Invest. 2017;127(3):772–779.
[13] Akatsu C, Shinagawa K, Numoto N, et al. CD72 negatively regulates B lymphocyte responses to the lupus-related endogenous toll-like receptor 7 ligand Sm/RNP. J Exp Med. 2016;213(12):2691–2706.
[14] Lino AC, Dang VD, Lampropoulou V, et al. LAG-3 inhibitory receptor expression identifies immunosuppressive natural regulatory plasma cells. Immunity. 2018;49(1):120–133 e9.
[15] Hou R, Ohtsuji M, Ohtsuji N, et al. Centromeric interval of chromosome 4 derived from C57BL/6 mice accelerates type 1 diabetes in NOD.CD72b congenic mice. Biochem Biophys Res Commun. 2009;380(1):193–197.
[16] Xu M, Hou R, Sato-Hayashizaki A, et al. Cd72(c) is a modifier gene that regulates Fas(lpr)-induced autoimmune disease. J Immunol. 2013;190(11):5436–5445.
[17] Tsubata T. Role of inhibitory BCR co-receptors in immunity. Infect Disord Drug Targets. 2012;12(3):181–190.
[18] Tsubata T. Ligand recognition determines the role of inhibitory B cell co-receptors in the regulation of B cell homeostasis and autoimmunity. Front Immunol. 2018;9:2276.
[19] Pao LI, Lam KP, Henderson JM, et al. B cell-specific deletion of protein-tyrosine phosphatase Shp1 promotes B-1a cell development and causes systemic autoimmunity. Immunity. 2007;27(1):35–48.
[20] Maxwell MJ, Duan M, Armes JE, et al. Genetic segregation of inflammatory lung disease and autoimmune disease severity in SHIP-1/- mice. J Immunol. 2011;186(12):7164–7175.
[21] Nitschke L, Carsetti R, Ocker B, et al. CD22 is a negative regulator of B-cell receptor signalling. Curr Biol. 1997;7(2):133–143.
[22] Otipoby KL, Andersson KB, Draves KE, et al. CD22 regulates thymus-independent responses and the lifespan of B cells. Nature. 1996;384(6610):634–637.
[23] Sato S, Miller AS, Inaoki M, et al. CD22 is both a positive and negative regulator of B lymphocyte antigen receptor signal transduction: altered
signaling in CD22-deficient mice. Immunity. 1996; 5(6):551–562.

[24] Hoffmann A, Kerr S, Jellusova J, et al. Siglec-G is a B1 cell-inhibitory receptor that controls expansion and calcium signaling of the B1 cell population. Nat Immunol. 2007;8(7):695–704.

[25] Jellusova J, Wellmann U, Amann K, et al. CD22 x Siglec-G double-deficient mice have massively increased B1 cell numbers and develop systemic autoimmune. J Immunol. 2010;184(7):3618–3627.

[26] Kubo T, Uchida Y, Watanabe Y, et al. Augmented TLR9-induced Btk activation in PIR-B-deficient B-1 cells provokes excessive autoantibody production and autoimmunity. J Exp Med. 2009;206(9):1971–1982.

[27] Wilkinson R, Lyons AB, Roberts D, et al. Platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31) acts as a regulator of B-cell development, B-cell antigen receptor (BCR)-mediated activation, and autoimmune disease. Blood. 2002;100(1):184–193.

[28] Li DH, Winslow MM, Cao TM, et al. Modulation of peripheral B cell tolerance by CD72 in a murine model. Arthritis Rheum. 2008;58(10):3192–3204.

[29] Hitomi Y, Tsuchiya N, Kawasaki A, et al. CD72 polymorphisms associated with alternative splicing modify susceptibility to human systemic lupus erythematosus through epistatic interaction with FCGR2B. Hum Mol Genet. 2004;13(23):2907–2917.

[30] Ono M, Bolland S, Tempst P, et al. Role of the inositol phosphatase SHIP in negative regulation of the immune system by the receptor Fc( gamma)RIIB. Nature. 1996;383(6597):263–266.

[31] Napierei M, Karsunko H, Zevnik B, et al. Features of systemic lupus erythematosus in Dnasel-deficient mice. Nat Genet. 2000;25(2):177–181.

[32] Bolland S, Ravetch JV. Spontaneous autoimmune disease in Fc(gamma)RIIB-deficient mice results from strain-specific epistasis. Immunity. 2000;13(2):277–285.

[33] Kanari Y, Sugahara-Tobinai A, Takahashi H, et al. Dichotomy in Fc/RIIB deficiency and autoimmune-prone SLAM haplotype clarifies the roles of the Fc receptor in development of autoantibodies and glomerulonephritis. BMC Immunol. 2014;15:47.

[34] O'Neill SK, Getahun A, Gauld SB, et al. Monophosphorylation of CD79a and CD79b ITAM motifs initiates a SHIP-1 phosphatase-mediated inhibitory signaling cascade required for B cell anergy. Immunity. 2011;35(5):746–756.

[35] Shlomchik MJ. Sites and stages of autoreactive B cell activation and regulation. Immunity. 2008;28(1):18–28.

[36] Crow MK. Type I interferon in the pathogenesis of lupus. J Immunol. 2014;192(12):5439–5468.

[37] Tsutabata T. B cell tolerance and autoimmunity. Version 1. F1000Res. 2017;6:391.

[38] Crow JT, Gray EE, Pestal K, et al. Intracellular nucleic acid detection in autoimmunity. Annu Rev Immunol. 2017;35:313–336.

[39] Mohan C, Puttermann C. Genetics and pathogenesis of systemic lupus erythematosus and lupus nephritis. Nat Rev Nephrol. 2015;11(6):329–341.

[40] Goulieinos GN, Zervou ML, Vazgiourakis VM, et al. The genetics and molecular pathogenesis of systemic lupus erythematosus (SLE) in populations of different ancestry. Gene. 2018;668:59–72.

[41] Guo Y, Orme J, Mohan C. A genopedia of lupus genes – lessons from gene knockouts. Curr Rheumatol Rev. 2013;9(2):90–99.

[42] Christensen SR, Shupe J, Nickerson K, et al. Toll-like receptor 7 and TLR9 dictate autoantibody specificity and have opposing inflammatory and regulatory roles in a murine model of lupus. Immunity. 2006;25(3):417–428.

[43] Savarese E, Steinberg C, Pawar RD, et al. Requirement of Toll-like receptor 7 for pristane-induced production of autoantibodies and development of murine lupus nephritis. Arthritis Rheum. 2008;58(4):1107–1115.

[44] Nickerson KM, Christensen SR, Shupe J, et al. TLR9 regulates TLR7- and MyD88-dependent autoantibody production and disease in a murine model of lupus. J Immunol. 2010;184(4):1840–1848.

[45] Majer O, Liu B, Barton GM. Nucleic acid-sensing TLRs: trafficking and regulation. Curr Opin Immunol. 2017;44:26–33.

[46] Rosen A, Casciola-Rosen L. Autoantigens as partners in initiation and propagation of autoimmune rheumatic diseases. Annu Rev Immunol. 2016;34:395–420.

[47] Lau CM, Broughton C, Tabor AS, et al. RNA-associated autoantigens activate B cells by combined B cell antigen receptor/Toll-like receptor 7 engagement. J Exp Med. 2005;202(9):1171–1177.

[48] Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol. 2010;11(5):373–384.

[49] Tsutabata T. Negative regulation of B cell responses and self-tolerance to RNA-related lupus self-antigens. Proc Jpn Acad, Ser B: Phys Biol Sci. 2018;94(1):35–44.

[50] Schlee M, Hartmann G. Discriminating self from non-self in nucleic acid sensing. Nat Rev Immunol. 2016;16(9):566–580.

[51] Leadbetter EA, Rifkin IR, Hohlbaum AM, et al. Marshall-Rothstein A. Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. Nature. 2002;416(6881):603–607.

[52] Tian J, Avalos AM, Mao SY, et al. Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGBl and RAGE. Nat Immunol. 2007;8(5):487–496.

[53] Li T, Chen ZJ. The cGAS-cGAMP-STING pathway connects DNA damage to inflammation, senescence, and cancer. J Exp Med. 2018;215(5):1287–1299.

[54] Kato Y, Park J, Takamatsu H, et al. Apoptosis-RAGE. Nat Immunol. 2007;8(5):487–496.

[55] Mouchess ML, Arpaia N, Souza G, et al. Transmembrane mutations in Toll-like receptor 9 bypass the requirement for ectodomain proteolysis and induce fatal inflammation. Immunity. 2011;35(5):721–732.
phenotype controls T cell-dependent inflammatory responses. Immunity. 2008;28(5):639–650.

[57] Rojas OL, Probstel AK, Porfilio EA, et al. Recirculating intestinal IgA-producing cells regulate neuroinflammation via IL-10. Cell. 2019; 176(3):610–624 e18.

[58] Knippenberg S, Peelen E, Smolders J, et al. Reduction in IL-10 producing B cells (Breg) in multiple sclerosis is accompanied by a reduced naïve/memory Breg ratio during a relapse but not in remission. J Neuroimmunol. 2011;239(1–2): 80–86.

[59] Kleffel S, Vergani A, Tezza S, et al. Interleukin-10+ regulatory B cells arise within antigen-experienced CD40+ B cells to maintain tolerance to islet autoantigens. Diabetes. 2015;64(1):158–171.

[60] Blair PA, Norena LY, Flores-Borja F, et al. CD19(+)CD24(hi)CD38(hi) B cells exhibit regulatory capacity in healthy individuals but are functionally impaired in systemic lupus erythematosus patients. Immunity. 2010;32(1):129–140.

[61] Gao N, Dresel J, Eckstein V, et al. Impaired suppressive capacity of activation-induced regulatory B cells in systemic lupus erythematosus. Arthritis Rheumatol. 2014;66(10):2849–2861.

[62] Fillatreau S, Sweenie CH, McGeachy MJ, et al. B cells regulate autoimmunity by provision of IL-10. Nat Immunol. 2002;3(10):944–950.

[63] Yin Z, Bahtiyar G, Zhang N, et al. IL-10 regulates murine lupus. J Immunol. 2002;169(4):2148–2155.

[64] Teichmann LL, Kashgarian M, Weaver CT, et al. B cell-derived IL-10 does not regulate spontaneous systemic autoimmunity in MRL.Fas(lpr) mice. J Immunol. 2012;188(2):678–685.

[65] Yanaba K, Bouaziz JD, Matsushita T, et al. The development and function of regulatory B cells expressing IL-10 (B10 cells) requires antigen receptor diversity and TLR signals. J Immunol. 2009; 182(12):7459–7472.

[66] Lampropoulou V, Hoehlig K, Roch T, et al. TLR-activated B cells suppress T cell-mediated autoimmunity. J Immunol. 2008;180(7):4763–4773.

[67] Kawasaki N, Rademacher C, Paulson JC. CD22 regulates adaptive and innate immune responses of B cells. J Innate Immun. 2011;3(4):411–419.

[68] Robinson WH, Ying H, Miceli MC, et al. Extensive polymorphism in the extracellular domain of the mouse B cell differentiation antigen Lyb-2/CD72. J Immunol. 1992;149(3):880–886.

[69] Qu WM, Miyazaki T, Terada M, et al. Genetic dissection of vasculitis in MRL/lpr lupus mice: a novel susceptibility locus involving the CD72 allele. Eur J Immunol. 2000;30(7):2027–2037.

[70] Oishi H, Tsubaki T, Miyazaki T, et al. A bacterial artificial chromosome transgene with polymorphic Cd72 inhibits the development of glomerulonephritis and vasculitis in MRL-Fas lpr lupus mice. J Immunol. 2013;190(5):2129–2137.

[71] Izui S, Kelley VE, Masuda K, et al. Induction of various autoantibodies by mutant gene lpr in several strains of mice. J Immunol. 1984;133(1): 227–233.

[72] Wu J, Marler J, Lenchik NI, et al. Strain differences in allele and expression levels of CD72 on B-lymphocytes from NOD, AKR, NON and C57BL/6 mice. Immunol Lett. 2006;103(2):115–120.