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Review

B cell MHC class II signaling: A story of life and death

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ABSTRACT

MHC class II regulates B cell activation, proliferation, and differentiation during cognate B cell-T cell interaction. This is, in part, due to the MHC class II signaling in B cells. Activation of MHC Class II in human B cells or "primed" murine B cells leads to tyrosine phosphorylation, calcium mobilization, AKT, ERK, JNK activation. In addition, crosslinking MHC class II with monoclonal Abs kill malignant human B cells. Several humanized anti-HLA-DR/MHC class II monoclonal Abs entered clinical trials for lymphoma/leukemia and MHC class II-expressing melanomas. Mechanistically, MHC class II is associated with a wealth of transmembrane proteins including the B cell-specific signaling proteins CD79a/b, CD19 and a group of four-transmembrane proteins including tetraspanins and the apoptotic protein MPYS/STING. Furthermore, MHC class II signals are compartmentalized in the tetraspanin-enriched microdomains. In this review, we discuss our current understanding of MHC class II signaling in B cells focusing on its physiological significance and the therapeutic potential.

1. Introduction

B cells include B-1 and B-2 cells. B-1 cells spontaneously secrete natural IgM and reside mainly in pleural and peritoneal cavities. B-2 cells (herein referred to as B cells), on the other hand, mediate the majority of T cell-dependent antibody response. Besides secreting antibodies, B cells express MHC class II and serve as antigen-presenting cells (APCs) for $CD4^+$ T cells. The APCs function of B cells has been demonstrated recently using B cells-specific MHC class II conditional knockout mice ($CD19^{cre}$-MHC $II^{fl/fl}$) [1–3]. These studies found that MHC class II on B cells contributes to the development, differentiation, and effector functions of $CD4^+$ T cells in response to T cell-dependent antigen [3], during the development of autoimmune disease such as $MRL.Fas^{lpr}$ lupus model [1] and the multiple sclerosis model experimental autoimmune encephalomyelitis [2].

During cognate B cell -T cell interaction, MHC Class II is also critical for B cell activation, proliferation, and differentiation [1]. In comparison to MHC II^- B cells, MHC II^+ B cells had a substantial advantage in proliferation, differentiation into plasmablasts, or germinal center B cells, and isotype switching [1]. B cell-activating signals during cognate B-T cell interaction is mainly mediated by CD40. However, T-cell dependent IgM production can proceed in the absence of CD40 signals [4–7]. Several lines of evidence suggested that MHC class II, besides their antigen presentation ability, are signaling molecules that may promote T-cell dependent IgM production during the cognate B-T cell interaction [8–12].

MHC class II delivers a variety of signals to B cells [13]. The cytoplasmic tails of MHC class II are required for the induction of 3′,5′-cyclic adenosine monophosphate (cAMP) [14] and ubiquitination[15]. In this review, we focus on two distinct MHC class II signal pathways that are independent of the cytoplasmic tails or the antigen recognition domains (ARD) of MHC class II. i) the activation, proliferation (life) signals mediated by MHC class II-associated CD79a/b during cognate B-T cells interaction (Fig. 1). ii) The anti-tumor activity (death) of anti-MHC class II/HLA-DR monoclonal antibodies (mAbs) (Fig. 2). During the cognate B cell-T cell interaction, signaling via MHC class II in B cells lead to Src-family kinase activation, $Ca2^+$ mobilization, and B cell proliferation [13] (Fig. 1). These responses are mainly mediated by MHC class II-associated CD79a/b in B cells, which depends on the connecting peptide region of the MHC class II [9,16]. Anti-MHC class II mAbs kill malignant B cells, which is independent of the cytoplasmic tails of MHC class II [16–20] (Fig. 2). Consequently, human HLA-DR is a therapeutic target for lymphoma/leukemia and MHC class II-expressing melanomas [18,21–27]. The four-transmembrane protein MPYS, also

Abbreviations: Alum, aluminum hydroxide; APCs, antigen-presenting cells; ARD, antigen-recognition-domain; BCR, B cell receptor; CDNs, cyclic dinucleotides; cGAS, cyclic GMP-AMP synthase; DCs, dendritic cells; HAQ, R71**H**-G230**A**-R293**Q**; IFN, interferon; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibition motif; mAb, monoclonal antibody; MCD, methyl β-cyclodextrin; MPYS, N-Terminal **M**ethionine-**P**roline-T**y**rosine-**S**erine tetraspanner; PI-3K, phosphoinositide 3-kinase; PLCγ2, phospholipase-Cγ2; SAVI, STING-associated vasculopathy with onset in infancy; SCIMP, SLP65/SLP76, Csk-interacting membrane protein; SHIP, SH2-domain-containing inositol phosphatase; STING, stimulator of interferon genes; Syk, spleen tyrosine kinase; TBK1, TANK-Binding Kinase 1; TCR, T cell receptor

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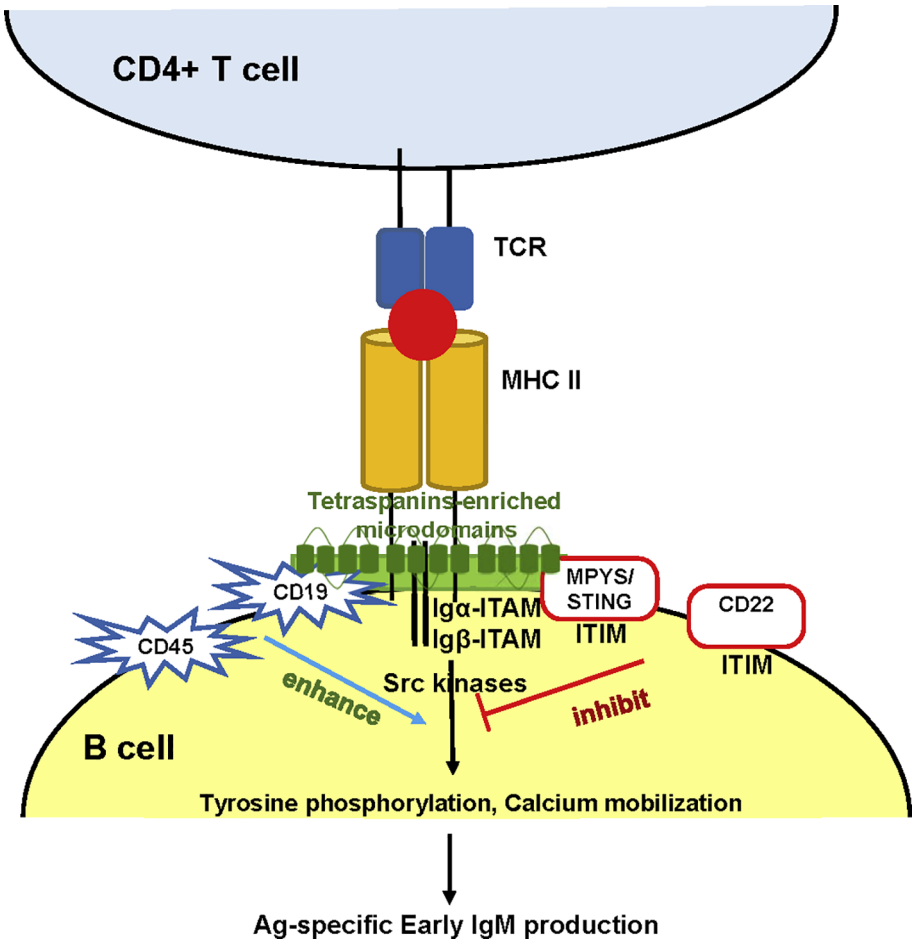

Fig. 1. Cognate B cell–T cell interaction activates CD79a/b mediated MHC class II signaling in B cells. In primed B cells, MHC class II is associated with CD79a/b. The activation of CD79a/b leads to phosphorylation of their ITAM that leads to downstream tyrosine phosphorylation and calcium mobilization. CD19 and CD45 can enhance MHC class II signaling while the ITIM-containing molecules CD22 and MPY/ STING inhibit MHC class II Igα/β signaling. CD19, MPYS/STING and MHC class II are in the tetraspanins-enriched microdomains. The MHC Class II signaling during the cognate B–T cells interaction contributes to the early antigen-specific IgM production.

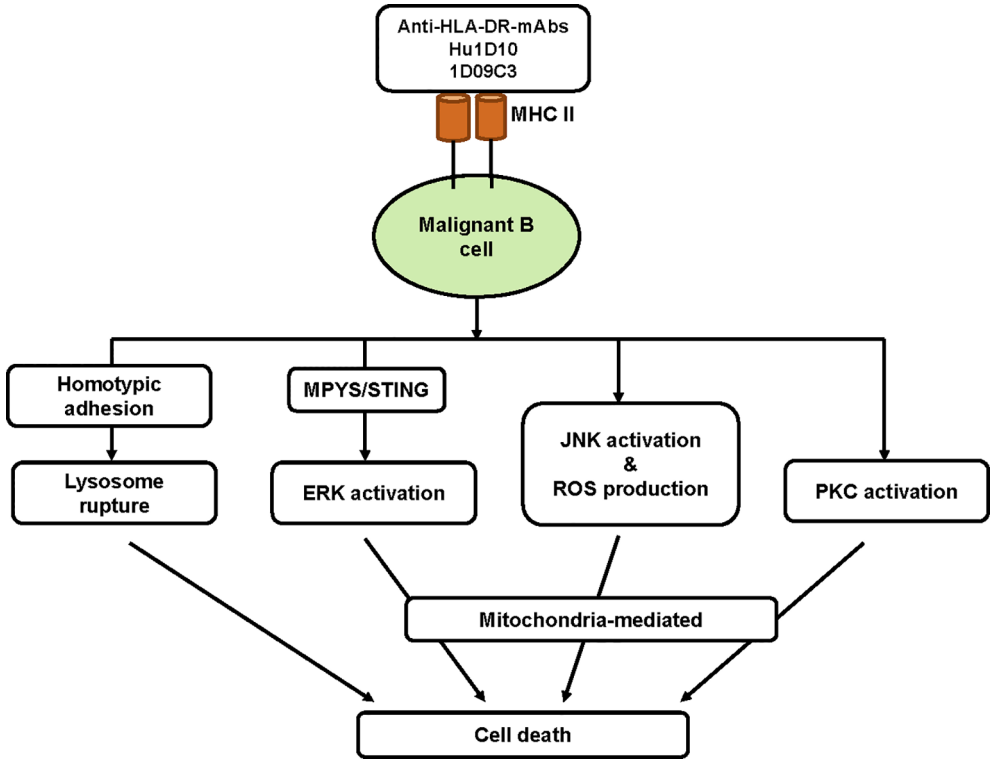

Fig. 2. Anti-MHC class II mAbs induce cell death in malignant B cells. Humanized anti-MHC class II mAbs kill malignant B cells via multiple mechanisms.

known as STING (stimulator of the interferon genes), seemed to play an important role in mediating MHC class II mAbs induced murine B lymphoma cell death [28].

2. Discussion

2.1. In vivo "priming" induces CD79a/b-MHC class II association in spleen B cells and contributes to the early Ag-specific IgM response

Lang P. et al. first found that MHC class II molecules can associate with CD79a/b heterodimers, which was previously found only in the B cell receptor (BCR) complex [9]. Notably, BCR and MHC class II are associated with different pools of CD79a/b [9]. Signal through MHC class II only activates MHC class II-associated CD79a/b, not CD79a/b in the BCR complex [9]. Importantly, the MHC class II/ CD79a/b association requires prior treatment of IL-4 or antigen engagement via BCR, referred to here as "priming" [9]. The authors further suggest that MHC class II-associated CD79a/b were from recycling BCR [9]. This notion could be significant. Very small amounts of MHC class II on cell surface bind to antigen-specific-peptide capable of stimulating antigen-specific $CD4^+$ T cells. It is tempting to suggest that the CD79a/b is transferred from IgM to MHC class II while the antigen is passed on from IgM to MHC class II. Thus, the CD79a/b associated MHC class II may define these small numbers of antigen-specific MHC class II complex that stimulates TCR.

Jordan M.B. et al. later found that vaccine adjuvant aluminum hydroxide (alum) induced MHC class II/ CD79a/b complex in B cells in vivo [8]. They further identified a spleen IL-4-producing $Gr1^+$ $CD11B^+$ myeloid population that is responsible for the inducible MHC class II/ CD79a/b association in alum-treated B cells [8]. Depleting this $Gr\text{-}1^+$ cells or deleting the IL-4 gene caused decreased thymus-dependent, early antigen-specific IgM Ab responses while the antigen-specific IgG1 response was not affected [8].

Wang H. et al. later identified the spleen $Gr\text{-}1^+$ $IL\text{-}4^+$ cells as eosinophils [29]. They found that alum failed to prime B cell to elicit MHC class II signaling in the ΔdblGATA BALB/c mice [29]. The ΔdblGATA BALB/c mice lack mature eosinophils as a result of a mutation in the promoter region of the *gata-1* gene. Adoptive transfer of WT eosinophils to the ΔdblGATA BALB/c mice fully restored the alum-elicited MHC class II signaling in splenic B cells and the early antigen-specific IgM response in vivo [29].

McKee A. et al., around the same time, found that similar to alum, schistosome eggs also induced the generation of $IL\text{-}4^+$ $Gr\text{-}1^+$ innate cells in spleen and primed B cells for MHC class II/ CD79a/b signaling [30]. Interestingly, unlike alum, schistosome eggs did not induce $CD4^+$ T cells priming to a co-administered antigen, which suggested that the MHC class II/ CD79a/b signaling was not sufficient for promoting T helper cells activation [30]. Furthermore, they demonstrated that the $IL\text{-}4^+Gr\text{-}1^+$ innate cells were predominantly responsible for the suppression of Th1 response, i.e. the production of IgG2a/2c while the Th2 response in terms of IgG1 remained intact after the depletion of the $Gr\text{-}1^+$ $IL\text{-}4^+$ innate cells [30]. Notably, Alum, schistosome egg and IL-4 promote mainly Th2 response. It is unknown if MHC class II/CD79a/b association occurs during a Th1 response. Do IFNγ, IL-12p70, like IL-4, promote MHC class II/CD79a/b association in ex vivo B cells? If so, which cell population is responsible for the priming of B cells during the Th1 response in vivo? If not, can B cell MHC class II transmit signaling during a Th1 response in vivo?

HLA-DR, not HLA-DP or HLA-DQ, engagements induce calcium mobilization and tyrosine phosphorylation in human B cell lines and primary human B cells [10,31,32]. Different from murine splenic B cells, human B cells do not require "priming" for HLA-DR-induced calcium mobilization [10,31,32]. Vaccinations are common in the modern society. Alum is included in many human vaccines. Thus, human B cells are likely already "primed" due to the repeated vaccinations. Consistently, a significant portion of human PBMC B cells is antigen-experienced IgM^+ or IgG^+ memory B cells [33]. The molecular mechanism by which HLA-DR-induces calcium mobilization and tyrosine phosphorylation is not clear. Whether human CD79a/b mediate HLA-DR signaling, as they do in murine B cells, remains to be determined.

In summary, alum induces IL-4-producing eosinophils in the spleen that primes murine B cells to elicit MHC class II- CD79a/b association and signaling. The MHC class II/ CD79a/b signaling then may play an important role in optimizing thymus-dependent, early antigen-specific IgM Ab responses.

2.2. MHC class II/CD79a/b signaling in primed B cells

CD79a/b is a heterodimer with disulfide bonds, which in association with IgM form BCR. BCR has two main functions. First is antigen recognition. The IgM-bound antigen is internalized, processed, loaded onto MHC class II and expressed on the cell surface as MHC class II-peptide complex to stimulate antigen-specific $CD4^+$ T cells [34]. The second function of BCR is signal transduction, which is mediated by CD79a/b [34]. The MHC class II/CD79a/b signaling largely mimics the BCR signaling.

MHC class II/CD79a/b complex is activated by TCR on the T cell surface [9]. Though B cells are capable of recognizing and responding to soluble antigen, the predominant form of antigen that mediates B cell activation in vivo is on the membrane surface of APCs, such as dendritic cells (DCs), follicular DCs, and macrophages [35–38]. Thus, both MHC class II and IgM use CD79a/b to transduce signals from membrane-bound molecules.

CD79a/b are a transmembrane protein with cytoplasmic tails bearing an immunoreceptor tyrosine-based activation motif (ITAM) of consensus YxxL/Ix(6–8)YxxL/I) [39]. The ITAM is also found in CD3, ζ-chains of the T cell receptor (TCR) and is a common mechanism used by many molecules to transduce activating signals. Upon MHC class II aggregation, the dual tyrosine residues in CD79a (ENL$\underline{Y}_{182}$EGLNLDD-CSM$\underline{Y}_{193}$EDI) and CD79b (DHT$\underline{Y}$EGLDIDQTAT$\underline{Y}$EDI) are phosphorylated by Src family protein tyrosine kinases spleen tyrosine kinase (Syk), Fyn and Lyn [39]. The dual-phosphorylated ITAMs of CD79a/b serve as docking sites for the tandem SH2 domains containing signaling molecules including Syk, phospholipase-Cγ2 (PLCγ2), Bruton's tyrosine kinase, phosphoinositide 3-kinase (PI-3 K) [39]. The CD79a/b signaling can lead to many distinct outcomes, including survival, differentiation, proliferation or apoptosis [39].

2.3. Positive and negative regulator of the MHC class II/CD79a/b signaling in B cells

Similar to the BCR signaling, the MHC class II signaling is tightly regulated (Fig. 1). MHC class II is associated with BCR co-receptors CD19, CD22, and CD45 that modulates BCR signaling [40,41]. Using the K46 mouse B lymphoma cells, which exhibit a primed MHC class II signaling phenotype, Greer S., et al., showed that CD45 was critical for MHC class II signaling [41]. MHC class II-mediated Src family kinase Lyn activation was abrogated, and the Ca^{2+} mobilization was drastically reduced in the absence of CD45 expression [41].

CD19 and CD22 are positive and negative regulators of BCR signaling respectively. Bobbitt E.R. et al. showed that aggregation of MHC class II in activated B cells rapidly induced tyrosine phosphorylation on CD19 and CD22 [40]. Phosphorylated CD19 recruited Vav and PI-3 K, that enhanced MHC class II signaling [40]. In contrast, phosphorylated CD22 recruited SHP-1 and inhibited MHC class II signaling [40]. Co-ligation of CD19 with MHC class II in primed splenic B cells resulted in a significant increase in calcium mobilization while co-ligation of CD22 with MHC class II decreased calcium mobilization [40]. Thus, similar to BCR signaling, MHC class II signaling in B cells is modulated by CD19 and CD22.

SCIMP (SLP65/SLP76, Csk-interacting membrane protein) is a

transmembrane adaptor protein regulating MHC class II induced sustained ERK activation [42]. SCIMP does not appear to directly bind MHC class II [42]. Instead, it binds tetraspanin CD37, CD53 and CD81 and likely associates with MHC class II via the tetraspanin-enriched microdomains [42]. SCIMP is tyrosine phosphorylated by Src family kinases and recruits the adaptor protein SLP65 and Grb2 [42]. However, SCIMP deficiency did not affect MHC class II-induced calcium mobilization [42]. Unlike CD19, CD22 or CD45, only MHC class II, not BCR, activation led to SCIMP tyrosine phosphorylation [42]. Interestingly, Luo L. et al., recently found that SCIMP directly binds TLR4 in macrophage and is required for TLR4-induced IL-6 and IL-12p40 but not TNF production [43].

MPYS/STING is a four-transmembrane protein that associates with MHC class II in B cells [28]. MPYS has an antiproliferative and proapoptotic function, which will be discussed in Section 4. Meanwhile, MPYS contains an immunoreceptor tyrosine-based inhibition motif (ITIM) (SI$\underline{Y}_{245}$ELL) and negatively regulates MHC class II signaling in B cells [28]. The ITIM consensus sequence is S/I/V/Lx$\underline{Y}$xxI/V/L [44]. Tyrosine phosphorylation on ITIM by Src kinase results in the recruitment of phosphotyrosine phosphatases, such as SHP-1 and SHP-2, or the SH2-domain-containing inositol phosphatase, SHIP, which inhibits tyrosine phosphorylation and calcium flux [44]. Indeed, anti-MHC class II mAbs induce MPYS tyrosine phosphorylation and SHP-1, SHIP recruitment [28]. Furthermore, overexpressing MPYS inhibited MHC class II induced Ca^+ flux [28]. Thus, MPYS negatively regulates MHC class II signaling.

Li X. et al., recently found that the P_8xxP_{11} of MPYS/STING can bind the Src tyrosine kinases [45]. Dong G. et al., further demonstrated that MPYS/STING inhibited JAK1-STAT1 signaling in B cells by the recruitment of SHP-1 and SHP-2 [46]. The authors proposed that the inhibitory function of MPYS/STING in B cells may prevent the development of B cell-dominant autoimmune disease [46].

2.4. Compartmentalization of the MHC class II signaling

Different from BCR, MHC class II is associated with a large group of four-transmembrane proteins called tetraspanins, which include CD9, CD20, CD37, CD38, CD53, CD63, CD81 and CD82 [47–51]. Tetraspanins are small hydrophobic proteins with four transmembrane domains, a small and a large extracellular loop and two short cytoplasmic tails [52,53]. Tetraspanins laterally organize membrane proteins to form tetraspanin-enriched microdomains [52,54]. A recent study using super-resolution microscopy found that tetraspanins form individual nanoclusters smaller than 120 nm and were distributed on the plasma membrane at densities of 1–5 domains per μm [53].

MHC class II was also reported in the “lipid rafts” microdomains [55]. Both lipid rafts microdomains and tetraspanin-enriched microdomains are resistant to non-ionic detergents, such as Triton X-100 [47,48]. Furthermore, depleting cholesterol with methyl β-cyclodextrin (MCD) disrupt both lipid rafts microdomains and tetraspanin-enriched microdomains [56,57]. Thus tetraspanin-enriched microdomains and lipid raft microdomains are likely inter-related [58]. It is possible that tetraspanin-enriched microdomains are one of many forms of lipid rafts.

MHC class II molecules loaded with specific antigenic peptides appear to be enriched in the tetraspanin-enriched microdomains [56]. CD19, SCIMP, and MPYS, which modulate MHC class II signaling are associated with tetraspanins [59]. CD19 forms a complex with tetraspanin CD81 [59]. SCIMP binds to tetraspanin CD37, CD53 and CD81 [42]. MPYS is a four-transmembrane protein itself and binds to CD37 in B cells [28]. Thus, MHC class II signaling occurs in tetraspanin-enriched microdomains.

The compartmentalization of the MHC class II signaling likely reflects the need for MHC class II to recognize physically constrained membrane molecule, i.e., TCR, which exist as clusters on $CD4^+$ T cell surface [60]. This is evident in BCR signaling, where BCR can recognize both soluble and membrane-bound antigens [61]. While CD19/CD81 tetraspanin complex is required for BCR recognition of membrane-bound antigens, they are dispensable for soluble antigens induced BCR activation [61].

In summary, CD79a/b mediates MHC class II-induced tyrosine phosphorylation and calcium mobilization in primed B cells. These signals are modulated by both positive co-receptors such as CD45, CD19 and negative co-receptors CD22 and MPYS. Last, MHC class II signaling is confined in the tetraspanin-enriched microdomains (Fig. 1).

2.5. Anti-MHC class II mAbs kill malignant B cells

Bridges S.H. et al., first found, in 1987, that anti-MHC class II mAbs killed B cell lymphoma in mice [62]. They found that ~50% of mice could be cured of lymphoma by multiple doses of anti-MHC class II mAb treatments [62]. They further suggested that anti-MHC class II inhibited tumor growth via a complement-independent mechanism [62]. Subsequent studies by many other labs found that anti-human HLA-DR mAbs could induce cell death in various malignant human B cells including the Burkitt lymphoma cells Raji and BJAB, B-lymphoblastoid cells ARH-77, LG-2, Hodgkin lymphoma cells HDML-2, L-428, L1236 cells, non-Hodgkin B cell lymphoma GRANTA-519 and primary B cell chronic lymphocytic leukemia samples [17–20]. Several studies reported anti-tumor activity of anti-HLA-DR mAbs [18,22,25,27]. Shi J. D. et al. found that the humanized mAb Hu1D10 (Apolizumab) rapidly and effectively depleted circulating B cells in rhesus monkeys for up to 10 days following the last dose [22]. Nagy Z.A. et al. found that another humanized anti-HLA-DR mAb 1D09C3 efficiently depleted B cells in cynomologus monkeys [18]. 1D09C3 significantly prolonged the median survival times in SCID or NOD/SCID mice xenografted with human CLL line JVM-2 or MCL line GRANTA-519 [18,25].

Unlike other mAb-based therapies such as CD20 for lymphoid malignancies, anti-MHC class II therapy did not depend on complement-mediated lysis and/or antibody-dependent cell-mediated cytotoxicity [49]. Consequently, the anti-MHC class II mAb therapy depends less on the intact of the immune responses of patients and may also have fewer side-effects. Based on these promising characteristics, clinical trials were subsequently initiated [21,22,27].

2.6. Clinical trials of humanized anti-HLA-DR mAbs

Three Phase II clinical trials were conducted with Apolizumab (Hu1D10) on patients with progressive or recurrent Hodgkin's lymphoma (ClinicalTrials.gov: NCT00055783), patients with relapsed or refractory non-Hodgkin's lymphoma (ClinicalTrials.gov Identifier: NCT00014664) and patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (ClinicalTrials.gov Identifier: NCT00089154). The overall clinical benefit was limited [21]. Some patients exhibited treatment-related dose-limiting toxicity (aseptic meningitis, hemolytic uremia). Apolizumab was subsequently discontinued by the manufacturer [21].

1D09C3 clinical trials were conducted on patients with relapsed/refractory B cell type leukemia/lymphoma [27]. The treatment was well tolerated with mostly mild side effects [27]. However, 1D09C3 demonstrated limited activity clinically [27]. Furthermore, 1D09C3 was engineered with the Fc region of the IgG4 isotype [25]. It was later found that IgG4-type antibodies underwent Fab exchange with endogenous immunoglobulins in vivo [63]. In fact, 1D09C3 did undergo Fab arm exchange with other IgG4 molecules in a distinct redox environment in vitro [64]. Due to these concerns, the manufacturer halted further clinical development on 1D09C3.

IMMU-114, a new humanized IgG4 anti HLA-DR mAb, has recently undergone clinical trial (ClinicalTrials.gov Identifier: NCT01728207) on patients with Non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL). The initial results were promising including one NHL patient with a complete response [65]. Unlike Hu1D10 or 1D09c3, IMMU-114 was administered subcutaneously. The

clinical trial was expected to be completed by the end of 2017.

2.7. The mechanisms of anti-MHC class II mAbs induced cell death

Anti-MHC class II mAbs induced cell death is mediated by MHC-II signaling [18] (Fig. 2). However, knocking down CD79b expression did not affect MHC class II induced cell death [16]. Moreover, DCs, which express MHC class II but not CD79a/b, were also killed by anti-MHC class II mAbs [66]. Thus, MHC class II-associated CD79a/b signaling is dispensable for cell death. MHC class II-mediated cell death did not require Src family kinase or caspase activation although mitochondrial cell death pathway was activated by anti-MHC class II mAbs [16,20,25,32]. Nevertheless, the exact molecular mechanism for anti-MHC class II mAbs induced cell death is controversial and likely depends on the mAbs and type of cells being targeted [67].

Protein kinase C activation was reportedly required for MHC-II-mediated death in Raji human B-cell lymphoma, mature DCs, and activated THP-1 monocytes but not in primary human plasmacytoid DCs [32,66,68]. Reactive oxygen species production and JNK kinase activation have been implicated in MHC class II-mediated death in lymphomas line JVM-2 and GRANTA-519 [25]. In 2009, Ivanov a. et al., reported that the anti-HLA-DR mAb L-243 induced cell death in Raji and primary chronic lymphocytic leukemia cells via the induction of homotypic adhesion and lysosome-mediated cell death pathway [69]. They observed that L-243 induced actin-dependent homotypic adhesion was sensitive to MCD depletion of membrane cholesterol [69]. They further found that homotypic adhesion led to lysosome swelling, which dispersed their contents into the cytoplasm [69]. Concanamycin A or bafilomycin A1, which inhibits vacuolar ATPases and prevents the acidification of organelles, reduced the cell death induced by L-243[69].

In 2008, we identified a new MHC class II-associated four-transmembrane protein named MPYS [28]. We found that overexpressing MPYS inhibited B lymphoma cell growth and knocking down MPYS impaired anti-MHC class II mAbs induced cell death in the K46 mouse B lymphoma cells [28]. We further found that anti-MHC class II mAbs induced ERK activation in K46 cells and inhibited ERK activation by PD98059 reduced MHC class II induced cell death [28]. Last, we found that MPYS was required for anti-MHC class II mAbs induced ERK activation on the K46 cells [28].

In 2010, Stein R. et al. found that the humanized anti-HLA-DR mAb IMMU-114 induced cell death in leukemia, lymphoma, multiple myeloma cell lines and chronic lymphocytic leukemia patient specimens [23]. Furthermore, IMMU-114 induced disease-free survival in SCID mice xenografted with three non-Hodgkin lymphoma models [23]. Mechanistically, they found that the IMMU-114 cytotoxicity required the activation of ERK and JNK [23]. Blocking ERK activation by U0126 or knocking down ERK reduced IMMU-114 induced death in chronic lymphocytic leukemia patient samples [23].

2.8. The antiproliferative function of MPYS/STING

MPYS/STING is a four-transmembrane endoplasmic reticulum resident protein that plays a central role in DNA induced type I IFN production and proinflammatory responses [70]. STING exists as a homodimer [28] and undergoes a conformational change when binding to its physiological ligand 2′5′-cyclic GMP-AMP generated by cyclic GMP-AMP synthase (cGAS) upon sensing DNA [71]. Activated STING homodimer then traffics through Golgi to the perinuclear region where it activates TANK-Binding Kinase 1 (TBK1) leading to type I IFN production [71].

We first showed that overexpressing MPYS inhibited mouse B lymphoma cell growth [28]. Recently, the growth inhibition/antiproliferative ability of MPYS/STING was observed in T cells [72]. Cerboni S. et al. found that the gain-of-function human STING mutant V155M inhibits T cell growth [72]. Surprisingly, they found that this antiproliferative function of MPYS/STING was independent of TBK1 and type I IFN [72]. They generated a STING mutant that can't bind TBK1 (deletion of aa 354–379) and found that it was still able to inhibit T cell growth. Neutralizing type I IFN did not abolish the antiproliferative function of V155M of STING in T cells [72]. They identified that aa 343–354 of human STING is required for the growth inhibitory function of V155M of STING [72]. The same region is also required for NF-κB activation [72]. The authors proposed that STING-mediated NF-κB activation, not TBK1 activation, is responsible for the antiproliferative effect [72]. The activation of NF-κB in T cells is associated with cell proliferation and differentiation [73]. How STING-mediated NF-κB activation inhibits T cell growth remains to be determined. Interestingly, the antiproliferative function of the V155M was lost in the common human STING variant HAQ [72]. HAQ contains three non-synonymous SNPs, R71H-G230A-R293Q. HAQ is the second most common human *STING* allele [74]. It will be interesting to see if the HAQ individuals are prone to the development of B or T cell tumors due to their decreased antiproliferative function.

2.9. The apoptotic function of MPYS/STING

MPYS mediates anti-MHC class II mAbs induced cell death in mouse B lymphoma cells [28]. Recent studies found that directly activating MPYS/STING by its ligands can kill primary and malignant mouse B and T cells [75,76]. Interestingly, activation of STING in mouse embryonic fibroblasts, bone marrow-derived macrophage and bone marrow-derived dendritic cells did not lead to cell death [75,76]. Notably, blocking type I IFN or type I IFN treatment did not alter STING-induced B or T cell death suggesting that the apoptotic function of STING/MPYS is independent of its ability to induce type I IFN [75,76]. The exact mechanism by which MPYS/STING induces cell death in B or T cells is unclear. However, it is worth noting that STING signaling in B and T cells is unique in the sense that the activation of STING does not lead to STING degradation [75,76].

2.10. STING expression in human B cells

In 2014, Liu Y. et al. reported no STING expression in human PBMC B cells [77]. This contradicted our discovery of MPYS/STING expression in mouse B cells [28]. Recently, we detected STING expression in dozens of Epstein–Barr virus (EBV) transformed human B cell lines derived from 1000Genome Project [74]. Dong G. et al., also confirmed STING expression in human B cells and showed that B cells from SLE patients had lower STING expression than the healthy controls [46]. Gram A. et al., reported STING expression in EBV positive human B cells and proposed a correlation between STING expression in human B cells and the status of EBV infection [78]. Considering that EBV is found in a vast majority of adults, most of human B cell samples should be STING positive.

Nevertheless, Liu Y. et al. did find that SAVI (STING-associated vasculopathy with onset in infancy) patients, which had the gain-of-function STING mutations, had elevated p-STAT1 in B cells [77]. Cerboni S. et al. found that PBMC from several SAVI patients had low percentages of $CD27^+/CD19^+$ memory B cells [72]. It remains to be determined if these B cells abnormalities in SAVI patients are B cell intrinsic.

3. Conclusion and future direction

In summary, MHC class II signaling in B cells, mediated predominantly by its associated CD79a/b, contribute to the thymus-dependent, early antigen-specific IgM Ab responses during cognate B-T cell interaction (Fig. 1). Also, MHC class II signaling activated by anti-MHC class II mAbs can kill malignant B cells via multiple mechanisms including MPYS/STING mediated antiproliferative/apoptotic signal (Fig. 2).

The life or death signaling of MHC class II probably takes place under different circumstances. As speculated above, the MHC class II/CD79a/b complex may represent the small population of cell surface MHC class II bound to the antigen-specific relevant peptide. Thus, the activation of MHC class II/CD79a/b occurs during the cognate B-T cells interaction. On the other hand, cross-linking MHC class II/HLA-DR with mAbs may engage a heterogeneous population of MHC class II complex on B cell surface including MHC class II bound to self-peptides and MHC class II with no peptide.

A major unanswered question is the physiological role of HLA-DR signaling in human B cells. Does HLA-DR signaling, like in the murine B cells, contribute to the optimal antigen-specific IgM production? Is HLA-DR signaling a unique feature of antigen-experienced human memory B cells? If so, does HLA-DR signaling in memory B cells influence the vaccine responses? Mechanistically, does human HLA-DR employ CD79a/b for signaling? In this case, does the association depend on the connecting peptide region of HLA-DR?

Improving the efficacy of anti-HLA-DR mAbs for human cancers is another area worth further investigating. While promising in animal experiments, the efficacy of humanized anti-HLA-DR mAbs in human clinical trials was rather disappointing. We showed that MPYS/STING mediated MHC class II mAb-induced cell death in murine B lymphoma cells. It remains to be determined if the therapeutic effect of HLA-DR mAbs also require MPYS/STING especially for the IMMU-114, whose efficacy also depends on ERK activation. Notably, DMXAA [5,6-dimethylXAA (xanthenone-4-acetic acid), Vadimezan, ASA404] a vascular-disrupting activity, which showed promising effects in Phase II clinical trials in non-small-cell lung cancer [79,80], failed in Phase III clinical trials [81,82]. Later, it was found that DMXAA activates murine MPYS/STING, but not human MPYS/STING [83]. Moreover, human *STING* gene is highly heterogeneous. Half of Americans have one copy of non-WT STING allele (the R232 of STING) [74,84]. If the anti-tumor activity of human HLA-DR mAbs depends on human STING, proper population stratification is needed in future human trials. In summary, understanding the molecular mechanism of the anti-tumor activity of HLA-DR mAbs is needed to advance their application in humans.

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.

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