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Class II MHC cytoplasmic domain-mediated signaling in B cells: A tail of two signals

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ABSTRACT

In addition to their role in antigen presentation, class II MHC molecules also transmit signals to B lymphocytes. Class II MHC-mediated signals initiate a range of events in B cells, including induction of cell surface proteins, initiation of cell-cycle progression/proliferation, activation of or protection from apoptosis, and antigen-dependent plasma cell differentiation. Although various transmembrane signaling proteins associate with class II MHC molecules, the class II MHC cytoplasmic domains are essential for signals leading to increased intracellular cAMP and activation of protein kinase C (PKC). Although truncation and mutagenesis studies have provided considerable information about the cytoplasmic domain sequences required, how class II MHC molecules elicit cAMP and PKC activation is not known. Further, appropriate T-dependent B cell responses require intact cAMP and PKC signaling, but the extent to which class II MHC signals are involved is also unknown. This review details our current knowledge of class II MHC cytoplasmic domain signaling in B cells with an emphasis on the likely importance of class II MHC signals for T-dependent antibody responses.

1. Introduction

Studies in the 1970's and 80's sought to understand class II MHC-restricted antigen presentation to T helper cells and the corresponding activation of B cells by T cell-dependent antigens. Appreciation that signals transmitted by class II major histocompatibility complex (MHC) molecules were potentially important during class II MHC-restricted B cell activation and differentiation paralleled work implicating T helper cytokines [1]. Over the next few years, several groups established various B cell activation and differentiation outcomes triggered by MHC class II signaling (for a review of the earlier studies see [2]). This was followed rapidly by work to characterize the cellular events elicited by such signals, decipher the molecules involved, and evaluate class II MHC signals in other cell types. However, while MHC class I and II molecules had become exceptionally important, efforts emphasized solving their structure and deciphering the details of antigen processing and presentation. Further, although complementary to the nascent class II MHC signaling field, understanding T- and B-cell receptor antigen recognition and signaling was more pressing. The emergence of these two critical spheres of inquiry, largely overshadowed interest in MHC class II as a signaling receptor.

Most signal receptors are expressed independently of their ligands. However, the ligand for MHC class II, the T cell receptor (TCR)-CD4 complex, is only found on CD4+ T cells which are dependent upon thymic MHC class II for their development. The ability of class II specific antibodies to substitute for T helper cells facilitated studies using purified B cells. Despite overcoming the problem of a receptor-dependent ligand, this approach necessarily focused work away from in vivo models and towards in vitro structure/function studies of MHC class II signals paralleling those seeking to understand antigen-receptor signaling. What intracellular mediators transmit MHC class II signals and how does the MHC class II cytoplasmic tail accomplish this were questions initially explored by several laboratories. This review details our current understanding of the signaling function of the class II MHC cytoplasmic domain in the context of B cell activation and suggests some directions for the questions that remain unaddressed.

2. Class II MHC-mediated B cell functions and biochemical signals

Class II MHC-mediated signals stimulate B cell morphological changes [3], integrin expression [4–7], expression of costimulatory proteins [8], induction or constraint of cell-cycle progression/proliferation [9–12], apoptosis or death [13–17], protection from apoptosis [18], and antigen-dependent plasma cell differentiation [19–21]. In most cases, these events have been observed in both B cell lines and purified primary B cells, primarily of mouse origin, but some studies

Abbreviations: MHC, major histocompatibility complex; cAMP, 3′,5′-cyclic adenosine mono-phosphate; PKC, Protein Kinase C; MAP kinase, mitogen-activated protein kinase; dbcAMP, di-butyryl cAMP; KLH, keyhole limpet hemocyanin; HEL, hen-egg lysozyme; OVA, chicken ovalbumin

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have used human cells. MHC class II-induced expression of B7 and antigen presentation suggest that MHC II signals might be essential for B cell antigen presentation [8,22], but a subsequent in vivo study provided limited support to this hypothesis [23].

Biochemical signaling events observed in B cells following class II MHC engagement include intracellular calcium mobilization [24], production of intracellular cAMP [25], as well as activation of PKC, Src, and MAP family kinases [25–27]. Work by Cambier et al. first showed that antibodies against class II MHC (I-A) induced both cAMP and nuclear translocation of PKC in splenic B cells from AKR (H-2^k) mice [25]. Treating B cells with cAMP analogs such as di-butyryl-cAMP (dbcAMP) or adenylate cyclase inhibitors, respectively reproduces a variety of anti-MHC II antibody-mediated effects, including nuclear translocation of PKC [2], induction of B7 expression [22], and antigen-dependent B cell differentiation [28]. Although not well-appreciated or fully understood, the cytoplasmic domain signaling functions of class II MHC are essential.

3. The class II MHC cytoplasmic domain

Receptor signaling is predominantly mediated by features within membrane proximal sequences including cytoplasmic tails. The membrane proximal sequences of MHC class II α and β chains, including the connecting peptide, transmembrane domain, and cytoplasmic tails, are essentially invariant among inbred mouse I-A and I-E molecules but exhibit variation between human HLA-D isoforms and among the diverse array of human alleles [29]. Unlike those of most signaling receptors and adapter proteins, the cytoplasmic tails of α and β are relatively short at 12–15 and 18 amino acids respectively in both mice and humans. The cytoplasmic tail amino acid sequences for mouse I-A/I-E and some human HLA-DR, DP, and DQ isoforms along with the residues implicated for specific signaling events are depicted in Fig. 1.

Truncation of the entire Aα and Aβ cytoplasmic tails abolishes class II MHC elicited PKC nuclear translation in the M12.C3 B cell line [30]. In this same study, however, removal of 12 residues from Aβ alone

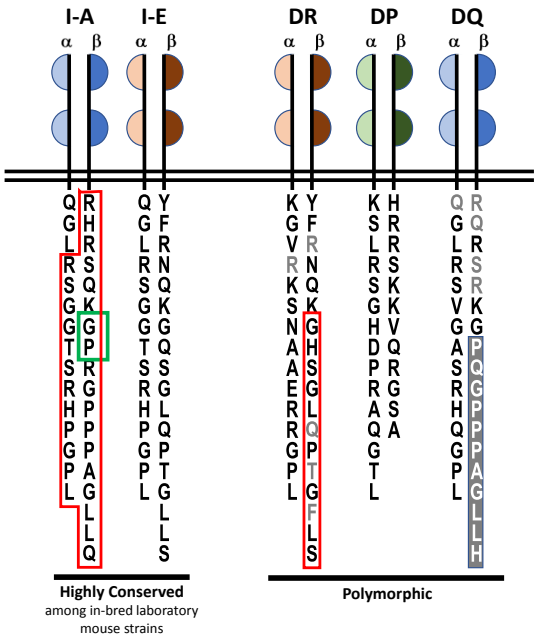

Fig. 1. Cytoplasmic domain sequences from common alleles of class II MHC isoforms. Class II MHC isoforms of inbred mice (I-A and I-E; left) have highly conserved sequences between haplotypes, while the human isoforms (HLA-DR, DP, and DQ; right) exhibit more haplotype polymorphism. Red boxes: sequences implicated in PKC activation. Green box: sequence required for cAMP response. Grey residues: those positions showing allelic variation. Grey boxed sequence: a region deleted in some allelic variants of HLA-DQ.

alters PKC translocation kinetics, while the amount of translocated PKC is dependent upon the Aα cytoplasmic tail. Culturing these cells with dbcAMP evokes PKC translocation with magnitude and kinetics essentially identical to antibody engagement of class II MHC, further suggesting that MHC class II activates an adenylate cyclase [2] via its cytoplasmic tails.

Engagement of class II MHC I-E^k molecules by T cells or antibodies mediates antigen-dependent B cell differentiation of the B cell lymphoma line CH12.LX, while the I-A^k molecule does not [31,32]. Intriguingly, despite having membrane proximal regions identical to $A\beta^k$, co-expressing $A\beta^b$ results in a I-A molecule capable of delivering a differentiative signal equivalent to that of I-E^k. Indeed, only the Aβ chain of certain haplotypes yielded differentiation signal-competent I-A molecules in these cells, while other Aβ chains did not or were less competent [32,33]. Given that the only sequence differences between these proteins lie outside the membrane proximal regions (primarily in the peptide binding α1 and β1 domains), why some Aβ chains facilitate MHC class II signaling in this model while others do not remains unclear [32,33]. One potential explanation is the presence of MHC class II conformers selectively recognized by antibodies or TCR, although this has only been described for signaling via A^k [34,35] a class II MHC protein previously thought to be signal incompetent. Truncation analysis of the signaling competent $A\beta^b$ molecule revealed that glycine and proline at positions 228 and 229 in the cytoplasmic tail are required for induction of cAMP and B cell differentiation [36,37]. Curiously, this glycine and proline are also sufficient for class II MHC induced cAMP responses in CH12.LX, provided they are in the correct position, suggesting a spatial requirement for adenylate cyclase activation. Addition of dbcAMP restores full differentiation of CH12.LX cells bearing truncated $A\beta^b$ molecules incapable of eliciting a cAMP signal. Although these studies suggest that the cAMP signal and PKC translocation are intimately linked, this may not be entirely accurate. Human HLA-DR molecules bearing alanine substitutions in the glycine and histidine residues corresponding to mouse glycine227 and proline228 retain the ability to activate PKCα and PKCβII translocation while truncations removing these residues do not [38]. While some other residues might facilitate adenylate cyclase activation, cAMP levels were, unfortunately, not evaluated in this study. The simpler explanation that PKC activation may be independent of MHC II elicited cAMP is discussed further below.

A functional MHC class II cytoplasmic tail may also be required for antigen presentation. The chemically induced A^k mutant B cell line 2B1 bears a complete (12 amino acid) truncation of the $A\alpha^k$ chain and exhibits a selective defect in activation of some auto-reactive T cell lines [39]. This finding suggested that the Aα cytoplasmic tail contributes in some fashion to T cell recognition. Further, transfectants of the class II MHC negative M12.C3 B cell clone expressing truncated A^k (AαΔ12/AβΔ10) fail to activate a KLH-specific and several auto-reactive T cell hybridomas, although stimulation of another KLH-specific and HEL-specific hybridomas by these A^k mutant-expressing cells is similar to cells expressing wildtype A^k [40]. This truncated molecule also fails to fully activate PKC translocation, suggesting that structural and/or signaling defects owing to the truncated cytoplasmic tail are responsible. This same truncation also exhibits a concentration-dependent defect in HEL presentation which is restored by dbcAMP, further implicating cytoplasmic tail-dependent cAMP and PKC signals in regulating antigen presentation [5]. A further study by the same group demonstrated that class II A^k interaction with T cells and cAMP are required for B cell expression of B7 and successful antigen presentation [22].

In vitro cellular data supporting defective antigen presentation prompted an in vivo approach. Mice bearing an AβΔ13 truncation lacking the GP motif and downstream COOH-terminal residues were generated by Smiley et al. [24]. While live or fixed antigen-presenting cells from these mice are impaired in their ability to stimulate T cell hybridomas or primed T cells in vitro, this is overcome by providing a more physiologic low pH (pH 5.5) environment [23]. No evidence of

defective antigen presentation to isolated LN T cells is observed ex vivo following infection with *L. major* or challenge with OVA or bovine insulin. Further, B cell expression of B7-1 (CD80) induced with anti-A^b antibodies is unaffected by the truncation. This study concluded that signaling-independent mechanisms likely account for the cytoplasmic-domain dependent aspects of antigen presentation. However, there is an important caveat. In the cell line studies, impaired antigen-specific antigen presentation and complete loss of PKC translocation was only seen with truncation of both Aα and Aβ. In addition, although Aβ truncations (Aβ10) fail to activate autoreactive T cell lines, they retain the residues required for the cAMP response and PKC translocation. Thus, class II MHC signal-dependent aspects of antigen presentation requiring the cytoplasmic domains have not been ruled out. Ubiquitination of K225 in Aβ may be involved as ubiquitinated class II MHC is maintained at the B cell surface [41], but whether ubiquitination impacts the cAMP signal or vice versa has not been explored. The AβΔ13 construct however lacks K225, suggesting the antigen presentation effects of ubiquitination at this residue may either be subtle or possibly inhibitory [64]. Although AβΔ13 mice lack the Aβ residues critical for the essential cAMP differentiation signal needed in CH12.LX cells, antibody responses to whole organisms (*L. major* and *B. burgdoferi*) are not altered [23]. As only polyclonal antibody responses were measured, whether these mice are deficient in critical aspects of T-dependent B cell activation/differentiation remains unclear. However, as recently described in the MRL.Faslpr mouse model of SLE, B cell expressed MHC II is important for CD4+ T cell activation, the production of certain autoantibodies, and development of glomerular nephritis [42]. While MHC class II signaling might be important for antigen presentation in this specific context, signaling defective MHC II molecules have not been examined in this model.

The class II MHC cytoplasmic domains are essential for cAMP and downstream PKCα and β signals important for B cell activation, have some regulatory impact on the magnitude as well as the kinetics of PKC activation, and are potentially involved in B cell antigen presentation. However, while specific regions and residues within the MHC II cytoplasmic tails contributing to these functions have been detailed, the network of proteins responsible are not well-understood.

4. Signaling proteins associated with MHC class II

A variety of transmembrane proteins with signaling functions appear to be physically associated with MHC class II, including CD79, a variety of tetraspanins (e.g. CD81, CD82, CD53, MPYS/STING), CD40, CD19, CD20 and CD21 [26,43–51]. Most of these proteins have some association with MHC class II protein tyrosine kinase (PTK) signaling. PTK activation by class II MHC is mediated by structural elements distinct from the cytoplasmic tail [37,52]. Whether any of these co-receptors interact with the MHC class II cytoplasmic tail or participate in mediating cytoplasmic tail-dependent class II MHC signal events is unknown. A few studies suggest some further possibilities.

The pyruvate kinase PKM2, Annexin A11, a sodium/potassium transporter subunit ATP1B1, 14-3-3e, as well as the heat shock proteins HSP90AA1, HSP90AB1, and HSPA8 are associated with class II MHC isolated from B cell exosomes [53]. All of these, except for ATP1B1 are cytosolic proteins that may interact with class II MHC cytoplasmic tails. In the human B cell line RAJI, engagement of HLA-DP or HLA-DQ, but not HLA-DR, increases MEK1/2 and ERK1/2 phosphorylation leading to increased c-fos expression and AP-1 DNA binding activity [54]. Whether these signals rely on the class II MHC cytoplasmic tail is unknown. However, in human monocytes, class II MHC is required for the MyD88-dependent inflammatory cytokine response to Staphylococcal enterotoxins, superantigens that bind MHC class II molecules [55]. MyD88 is also a cytosolic protein and could, potentially, directly interact with the class II MHC cytoplasmic domain in B cells, a possibility consistent with reports that class II MHC constrains the LPS responsiveness of B cells [56,57]

5. How is the cyclic AMP signal generated?

Despite the necessity of the β chain GP (or GH) motif for propagation of the cAMP signal, the requisite adenylate cyclase is unknown. However, the lymphocyte specific adenylate cyclase 7 (Adcy7) is a very likely candidate. The cAMP response of B cells to G_s-coupled β-adrenergic receptor agonists terbutaline and isoproterenol, as well as synergistic cAMP production following lysophosphatidic acid stimulation, is largely absent in Adcy7-deficient B cells [58]. Moreover, in vivo T-independent and T-dependent antibody responses are reduced in mice with Adcy7-deficient B and T cells, an observation likely resulting from defects in T cell help, the B cell response, or both. Adcy7 knockout mice are commercially available, although mice with a floxed Adcy7 locus would be helpful for conditional studies of B cell function.

6. What is the relationship between cAMP and PKC?

Elevated cAMP is presumed to activate PKA which was initially suggested as a potential link to PKC activation in B cells [2]. However, Epac-1, a guanine-nucleotide exchange factor for Ras-like small GTPase (e.g. Rap1), is expressed in B cells and directly activated by cAMP [59]. Epac-1 is therefore likely to be involved in cAMP-dependent B cell activation events. But, whether Epac-1 provides the link to PKCα/β in B cells is unknown. In contrast, the role of tyrosine kinases, IP_3-gated calcium mobilization, and PLCγ elaborated DAG in PKCα/β activation is well-known. A schematic model of cytoplasmic domain-dependent class II MHC signals is shown in Fig. 2. A perplexing dichotomy emerges from the data connecting cAMP generation with the activation of PKC. While cAMP analogs like dbcAMP are sufficient to provoke PKC translocation of the same magnitude and kinetics as class II MHC engagement, this activation is largely lost in the absence of the α chain even when the β chain retains the residues critical for the cAMP response [30]. Two possible interpretations are clear. First, that complete truncation of the Aα chain reduces the cAMP response despite an otherwise functional β chain, thus diminishing and delaying the PKC response. Second, that while cAMP analogs are sufficient for PKC activation, MHC class II cAMP signals are not. In this case, a potentially unknown α chain-dependent signaling event might be required. However, experiments with the CH12.LX B cell line suggest a third possibility. In addition to cAMP, antigen-dependent, class II MHC-mediated B cell differentiation of CH12.LX also requires a tyrosine kinase signal [37], presumably Lyn [43], which might provide the required

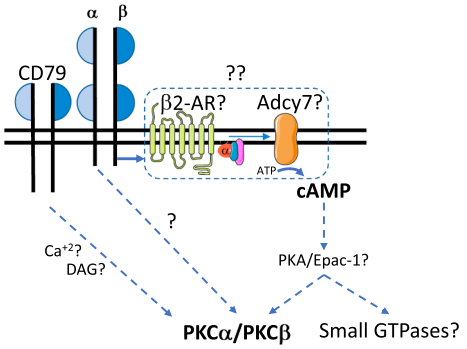

Fig. 2. Schematic of early MHC class II cytoplasmic domain signals. G227 and P228 in the class II MHC β chain lead to cAMP generation via an unknown G-protein activated adenylate cyclase. The β2-adrenergic receptor coupled Gs protein and adenylate cyclase 7 are likely candidates. How cAMP signals translate to PKC activation is also unclear. PKA and/or Epac-1 may be involved, but Epac-1 is known to activate small Ras-like GTPases which also participate in B cell activation/T-dependent B cell responses. PKCa and b are typically activated by classical protein tyrosine kinase-dependent intracellular calcium ions and diacylglycerol (DAG). CD79 signals are known to elicit these intermediates. But how the class II MHC α chain is involved is not clear.

intermediate signals for PKC activation. As addition of dbcAMP restored differentiation to CH12.LX transfectants lacking the cytoplasmic tail of Aβ, but retaining an intact Aα chain [37], it may be that the α cytoplasmic tail is important for class II MHC-mediated tyrosine kinase activation through CD79 or another associated co-receptor.

7. What is the immunologic role of PKC?

Aside from its potential role in antigen presentation discussed above and the likely importance of PKC for other MHC II signal-dependent B cell activation/differentiation events, little is known about the contribution of PKC to B cell immunobiology. Mice deficient in PKCβI/II or expressing an inactive form of PKC-associated kinase (PKK) provide some insight. PKCβI/II deficient mice have normal numbers of mature bone marrow B cells as well as CD4+ and CD8+ T cells, but the number of splenic B cells is reduced and B1a (CD5+) B cells are markedly reduced [60]. Antibody responses to a T-independent and a T-dependent antigen are reduced, but apart from IgM and IgG3 which are significantly lower, serum immunoglobulin levels are unaffected. PKK is necessary for PKC activation of NF-κB [61] and mice expressing a lymphoid targeted inactive PKK mutant have reduced peripheral B cell numbers along with absent B1a and B1b cells without any noticeable defect in follicular or marginal zone B cell development [62]. However, antibody responses were not examined in this model.

8. Barriers to progress

While the published data is intriguing and provides an outline of the pathways involved and the relevant cellular processes, the absence of an in vivo model with a defined MHC class II signaling defect is the most significant barrier to further progress in this field. Even though C57BL/6 mice have a single intact MHC class II locus (I-A), and standard knockin or CRISPR/Cas9 technologies allow relatively straightforward engineering of mice, models capable of revealing the essential immunological functions which rely upon class II MHC signaling are not trivial to produce. To evaluate the role of MHC class II signaling in T-dependent B cell activation, several significant technical hurdles need to be overcome. First, to help establish that any observed differences in B cell activation are not the result of diminished CD4+ T cell numbers, the CD4+ T cell compartment needs to be maintained by ensuring appropriate class II MHC antigen-presentation in the thymus. For example, mice with MHC II-deficient B cells have been produced by crossing mice with a loxP-targeted Aβ locus with those bearing CD19-Cre and T cell development appears to be normal [42,63]. However, mice with < 2% of residual class II MHC expressing B cells, have undetectable T-dependent primary antibody responses even after 8 weeks following immunization [63]. Even in mice where > 2% of B cells express MHC class II, T-dependent antibody responses were delayed, establishment of long-lived plasma cells was impaired, and antigen stimulation alone was insufficient to activate plasma cell differentiation of class II MHC deficient memory B cells. Similar deletion of class II MHC in the MRL.Faslpr model of SLE substantially reduced plasmablast differentiation, isotype switched IgG antibody forming cells, the attendant levels of certain autoantibodies, and ameliorated glomerular nephritis [42]. These experiments suggest that signals delivered via MHC class II might be important for T-dependent B cell antibody production, autoantibody responses, the establishment of long-lived plasma cells, and maintenance of B cell memory. However, the absence of MHC class II on these B cells prevented cognate interaction with CD4+ T cells, making it impossible to distinguish defective/altered functions potentially resulting from absent class II-mediated signals from those that needed T cell help. This difficulty points to the second hurdle, sufficient knowledge of class II MHC structure and function to design a class II MHC molecule that is largely defective in signal transduction yet retains antigen presentation function. Fortunately, the mutations needed to disrupt class II MHC-mediated cAMP generation [37], PKC activation [30], tyrosine kinase activation [24,37], and cell death [47] in B cells are known. Mice with a CD19-Cre-dependent B cell-specific deletion of the endogenous class II MHC gene coupled with expression of a signaling-deficient class II MHC molecule would be ideal in principle. As illustrated above, residual B cells expressing wildtype class II MHC would be a concern, but selecting mice with < 2% of wildtype class II MHC molecules might be possible with inclusion of an appropriate reporter. Another potential avenue may be to produce class II MHC mutant knockin mice to use in bone marrow chimera experiments with μMT mice which lack mature B cells. From the work reviewed above, such mice are expected to exhibit altered or absent T-dependent B cell responses owing to defects in class II MHC signaling. Loss of clonal expansion, dysregulated B cell homeostasis, impaired T:B interaction, selective antibody immunodeficiencies, and autoimmune disease are among some of the potential outcomes. The complete absence of any impact to the B cell compartment and antibody responses would be quite remarkable and surprising.

Some studies suggest haplotype and isotype specific differences in class II MHC signaling [27,32,33,56], although our understanding of class II MHC signaling provides little mechanistic insight for molecules with essentially identical membrane proximal sequences. Of perhaps more immediate significance are known human HLA-DP alleles lacking the GP/GH residues important for the cAMP signal and HLA-DQ alleles that are truncated [29]. These truncated HLA-DQ alleles resemble the βΔ12 mutant defective in both cAMP signaling as well as PKCα and βII activation [37,38] (Fig. 1). With the vast number of unique HLA-D alleles in the human population, relatively few have been completely sequenced. The extent to which human class II MHC molecules vary in their CY sequences variation is unknown. This lack of knowledge is another barrier to progress for understanding the immunological significance of class II MHC signaling, but also has implications for HLA-D disease associations in general. Signaling differences between HLA alleles resulting from such variation could account for HLA-D disease associations that are independent of differences in peptide binding and T cell recognition. Mouse models such as those proposed above, in combination with a fuller appreciation for those alleles that harbor signal-defective or -deficient class II MHC alleles have the potential to be transformative for our understanding of fundamental B cell biology and its relation to human disease.

9. Conclusion

A significant body of research points to the almost certain importance of class II MHC cytoplasmic domain-mediated signals for T-dependent B cell responses. Further, recent mouse models suggest that deficiencies in the likely downstream effectors of class II MHC signals lead to pronounced defects in, or even the complete absence of, T-dependent B cell and antibody responses, including B cell memory. Further, incomplete human sequence data may be obscuring a plethora of class II MHC variants that are predicted to influence T-dependent B cell function. Either overwhelming interest in other aspects of B cell immunology, at best, or disregard for intriguing and consistent data pointing to the importance of class II MHC signals, at worst, has unfortunately hindered progress that promises to open a potentially transformative chapter in B cell biology.

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