OCA-B regulation of B-cell development and function

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The transcriptional co-activator OCA-B [for Oct co-activator from B cells, also known as OBF-1 (OCT-binding factor-1) and Bob1] is not required for B-cell genesis but does regulate subsequent B-cell development and function. *OCA-B* deficient mice show strain-specific, partial blocks at multiple stages of B-cell maturation and a complete disruption of germinal center formation in all strains, causing humoral immune deficiency and susceptibility to infection. OCA-B probably exerts its effects through the regulation of octamer-motif controlled gene expression. The *OCA-B* gene encodes two proteins of distinct molecular weight, designated p34 and p35. The p34 isoform localizes in the nucleus, whereas the p35 isoform is myristoylated and is bound to the cytoplasmic membrane. p35 can traffic to the nucleus and probably activates octamer-dependent transcription, although this OCA-B isoform might regulate B cells through membrane-related signal transduction.

Enormous effort has been expended to determine the factors controlling B lineage-restricted gene expression and B-cell function. One major focus of this effort has been to define major B-cell-specific regulators of immunoglobulin (Ig) transcription. About fifteen years ago, an essential octamer motif (5′-ATGCAAAT-3′) was discovered in almost all Ig promoters and enhancers [1]. POU (Pit-1, Oct-1, Oct-2 and Unc 86 transcription factors)-domain activator proteins were then described that bind this motif, including Oct-1 and Oct-2 [2,3]. Because Oct-1 is ubiquitously expressed and Oct-2 is B-cell-specific, it was initially expected that Oct-2 would be the major tissue-specific regulator of Ig transcription. However, this notion was subsequently disproved for a variety of reasons, including continued high level Ig expression in *Oct-2* deficient B cells [4–6]. Instead, genetic and biochemical methods identified a B-cell-specific transcriptional co-activator protein termed OCA-B [for Oct co-activator from B cells, also known as OBF-1 (OCT-binding factor-1) and Bob1] [4,7,8]. OCA-B is a proline-rich 34 (or 35) kDa protein that increases the binding affinity of Oct-1 and Oct-2 proteins for DNA by clamping the POU_H and POU_S subdomains, which can further stimulate octamer-dependent gene transcription [9,10]. However, as discussed later, *OCA-B* deficient B cells continue transcribing Ig genes, indicating that, like *Oct-2*, OCA-B is not the major tissue-specific regulator of Ig transcription. A pair of excellent reviews [11,12] and studies on the molecular details of OCA-B protein structure and regulated gene transcription are available and these are thus not explored further [9,10,13–20]. Rather, potential roles for OCA-B in B-cell development, signal transduction and humoral immunity are reviewed here.

Overview of mammalian B-cell development

B cells develop in stages from renewable hematopoietic stem cells in the fetal liver and post-natal bone marrow [21] (Figure 1). Two main subtypes have been determined, termed B-1 and B-2 cells. In mice and humans, B-1 cells are further subdivided into those expressing CD5 (B-1a) and those lacking CD5 expression (B-1b), presumably reflecting distinct developmental origins. Although details of B-1-cell maturation remain unresolved, the endpoint seems established, with the generation of IgM, IgG3 or IgA secreting plasma cells that localize mainly in serosal membranes of the peritoneal and pleural cavities [22,23]. B-2 cells originate in the marrow and become either localized splenic marginal zone B (MZB) cells that secrete IgM on antigenic stimulation or follicular cells that recirculate within and between lymphoid tissues. Both B-1 and MZB cells form a first line, T-independent defense against particulate antigens, such as bacterial coat proteins. This is reflected in their locations in zones of immediate, high antigen concentration [24,25]. By contrast, primary follicular cells might participate in either T-dependent or T-independent antigenic responses. T-dependent antigens induce secondary follicle formation, also termed germinal centers (GCs).

Control over both B-1- and B-2-cell development and function is exerted by epigenetic, genetic and environmental factors that regulate key transcription factors [26,27]. For B-2 cells, developmental milestones are determined by Ig locus gene rearrangements and stage-specific gene and protein expression [21,23,28,29]. B-2-cell progenitors become surface IgM^+, IgD^+ B cells (variously termed immature, naïve or transitional B cells) in the marrow, independent of selecting antigens. Transitional B cells then enter the circulation and home to peripheral lymphoid tissues where antigen-dependent selection and final maturation occurs. Peripheral transitional B cells enter either the MZ or form primary follicles, largely based on Ig heavy and light chain V-region gene usage [24]. Both pathways result in the production of plasma cells that

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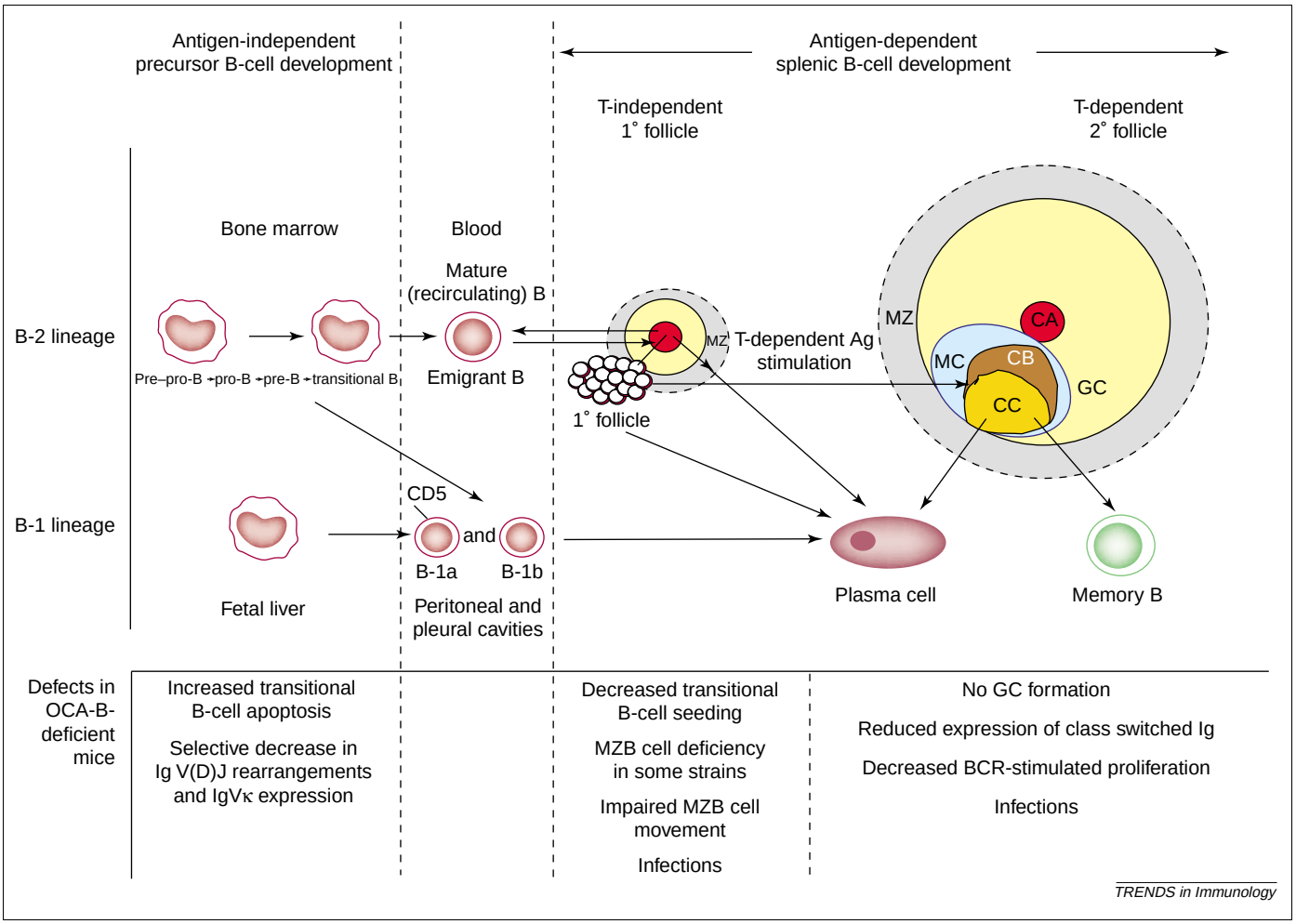

Figure 1. Dependence of B-cell development on OCA-B expression. B-1 and B-2 cell maturation pathways in mice are shown along with the effect of targeted removal of *OCA-B*. MZ and 1° follicle B-2 cells arise from precursors in the adult bone marrow whereas the origin and development of B-1 cell subsets is unresolved. Plasma cells are produced from both B-1 and B-2 cells by T-independent antigenic stimulation. 1° follicle and possibly MZB cells can further participate in T-dependent antigenic responses and form GC in wild type mice. Mice deficient in *OCA-B* have reduced transitional B cells during antigen-independent development and might lack MZB and possibly B-1b cells, depending on strain. T-dependent GC formation is completely blocked. These partial and complete developmental blocks inhibit plasma-cell differentiation from at least two (MZ and GC) of four (MZ, 1° follicle, B-1 and GC) B-cell reservoirs. Periarteriolar lymphoid sheaths are depicted in yellow; the 1° to 2° follicle transition in the spleen results from stimulation with a T-dependent antigen. Abbreviations: BCR, B-cell receptor; B-1a, CD5 expressing B cells; B-1b, CD5 non-expressing B cells; CA, central arteriole; CB, centroblast; CC, centrocyte; GC, germinal center; MC, mantle cell zone; MZ, marginal zone.

secrete antigen-specific Ig at levels sufficient to neutralize foreign pathogens [21]. Follicular B cells responding to T-dependent antigens obtain $CD4^+$ T-cell help during passage through a GC phase of antibody refinement that can include Ig isotype switching and somatic hypermutation (Figure 1). Both GC-educated and GC-independent plasma cells derived from B-1 and B-2 cell maturation are essential for protective humoral immunity in the host.

OCA-B expression in B cells

The *OCA-B* gene encodes a single mRNA transcript that yields two proteins of 34 and 35 kDa. Through the use of distinct translational initiation codons, the 35 kDa isoform is generated from post-translational processing of a transient, precursor 40 kDa intermediate [30] (Figure 2). The 35 kDa isoform becomes further modified by myristoylation of its N-terminus and locates to the cell membrane where its function is currently undefined. However, both p34 and p35 isoforms can also be isolated from the nucleus and can stimulate octamer-dependent transcription, suggesting that the p35 isoform could function at the membrane and/or be a component of a B-cell-specific signaling pathway that causes it to relocate to the nucleus, activating transcription.

Both p34 and p35 are expressed at almost equivalent levels in B-1 cells isolated from the peritoneum and in B-2 cells from early marrow pre-pro B-cell precursors through late stages of development in mice [31,32]. Mouse plasma cell lines express abundant OCA-B but primary mouse plasma cells have yet to be investigated for OCA-B expression [33,34]. Protein expression peaks in cycling, low-density splenic B cells (including GC centroblasts) and can also be induced to high levels by stimulation that mimics T-cell help [B-cell receptor (BCR), CD40 ligand (CD40L) and interleukin-4 (IL-4)] or bacterial Toll-like receptor 4 (TLR4) responses to lipopolysaccharide (LPS) [31,33–35]. By contrast, OCA-B protein is almost undetectable in resting, high-density splenic B cells (naïve B cells, memory B cells and GC centrocytes). Interestingly, *OCA-B* mRNA levels are elevated and equivalent in cycling, low-density and resting, high-density B cells [36]. This suggests two mechanisms

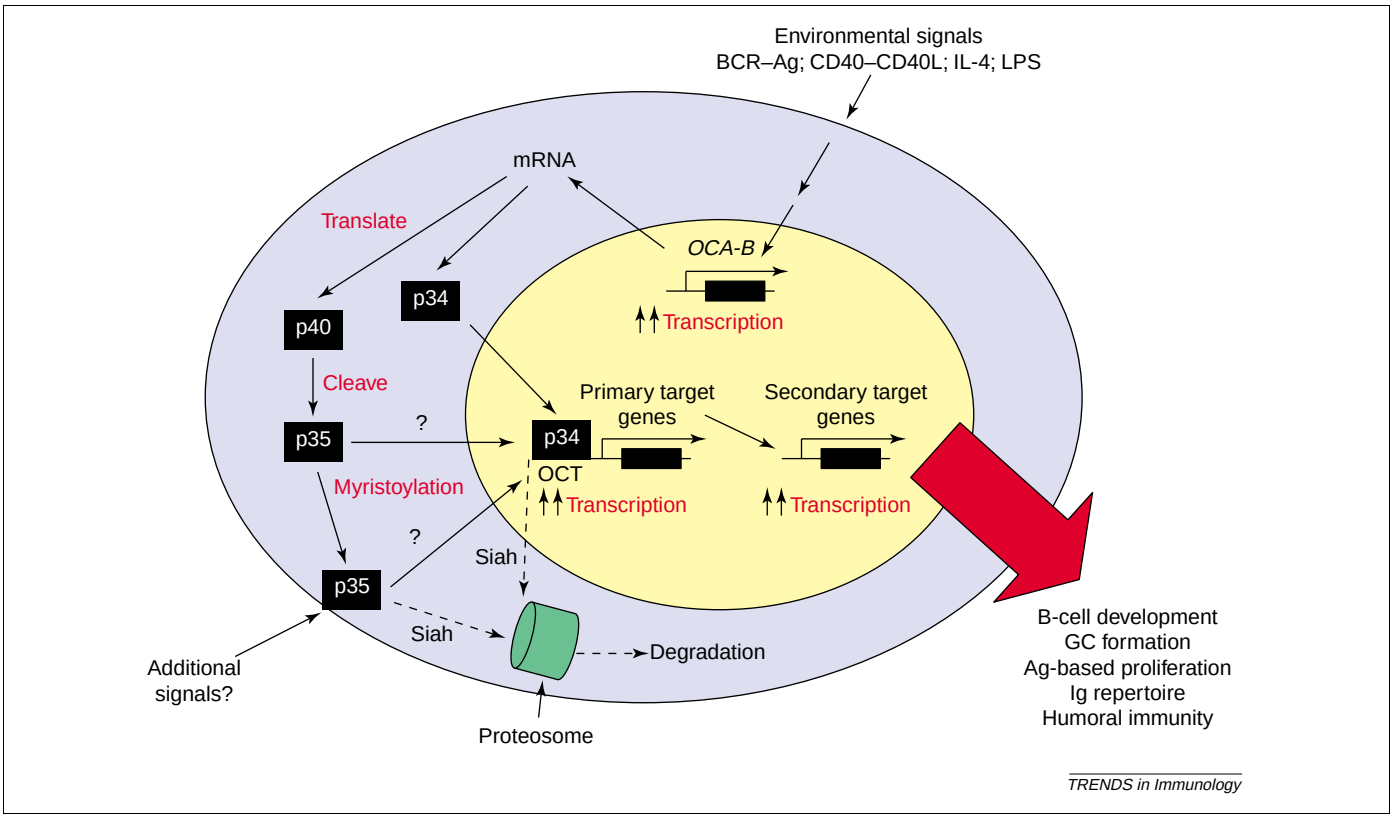

Figure 2. Regulation of OCA-B expression in B cells. T-independent, T-dependent and Toll-like receptor 4 (TLR4) signals stimulate *OCA-B* transcription resulting in a common *OCA-B* mRNA that is translated into transient p40 and functional p34 isoforms. The p34 isoform localizes in the nucleus and can bind Oct-1 or Oct-2 POU domain-containing transcription factors to selectively activate certain octamer-motif dependent primary target genes. These genes probably have secondary, indirect targets that they affect, yielding a complicated mixture of direct and indirect target genes regulated through OCA-B expression levels. By contrast, the p40 isoform is processed to a smaller 35 kDa size and myristoylated, facilitating its localization at the inner leaflet of the plasma membrane. Here, it might participate in undefined signal transduction processes. Alternatively, p35 could leave the membrane and enter the nucleus where it could augment p34-mediated, octamer-dependent target gene transcription. Both p34 and p35 are subject to further regulation, through binding to the RING finger protein Siah leading to ubiquitin-mediated proteosome degradation and decreased OCA-B expression (hatched arrows). The sum of OCA-B mediated activity results in normal B-cell development and function, with the production of functional GC and sufficient levels of pathogen-protective Ig. Abbreviations: Ag, antigen; BCR, B-cell receptor; GC, germinal center; IL-4, interleukin-4; LPS, lipopolysaccharide.

regulating OCA-B protein expression, one transcriptional and one post-transcriptional. Regulation of OCA-B through p34 and/or p35 stabilization has recently been established by showing an interaction between OCA-B isoforms and the Siah RING (really interesting new gene) finger proteins that mediate ubiquitin-proteosome induced OCA-B degradation [36,37] (Figure 2).

OCA-B control of bone marrow B-cell precursors

B-cell maturation in the marrow was initially considered independent of OCA-B because precursor development appeared normal in *OCA-B* deficient mice [38–40]. Yet, several reports have noted a two- to four-fold reduction of total $B220^+$ splenic B cells in *OCA-B* null mice [38,39]. A detailed re-examination subsequently showed that one part of this deficiency is a reduction of splenic transitional B cells owing to increased apoptosis of marrow transitional B cells and reduced splenic seeding [41,42] (Figure 1). Interestingly, this partial block occurred at the first negative selection checkpoint for self-reactive B cells [43]. In further studies, Bcl2 was sharply reduced in pre-B cells, but not in mature $B220^+$ splenic B cells, from *OCA-B* null mice [44] (Table 1). Crossing *OCA-B* null with *Bcl2* overexpressing transgenic mice decreased marrow transitional B-cell apoptosis and resulted in splenic B-cell counts resembling *Bcl2* transgenic mice, which were about two-to three-fold higher than wild-type splenic B-cell numbers. Because OCA-B regulation of Bcl2 mRNA and protein expression appears stage-specific, it remains possible that *Bcl2* regulation is not part of the mechanism by which OCA-B maintains marrow transitional B cells. This stage was not evaluated for endogenous Bcl2 levels, leaving open the possibility that supraphysiologic Bcl2 could overwhelm OCA-B-dependent functions in *OCA-B* knockout mice.

In separate studies, the level of surface CD22 expression is increased predominantly in pre-B and immature or transitional B cells in *OCA-B* deficient mice [45] (Table 1). CD22 is a B-lineage-restricted adhesion molecule whose expression begins at the pre-B-cell stage in the marrow, where it has an unknown role. It is also a negative regulator of BCR-initiated signaling in mature B cells, shown by increased Ca^+ mobilization on BCR stimulation in *CD22* deficient mice [46]. Interestingly, mice doubly deficient in *OCA-B* and *CD22* exhibit a partial rescue of transitional marrow B cells compared to *OCA-B* null mice. *OCA-B* deficient B cells fail to induce BCR-activated Ca^+ mobilization and this response is restored in doubly deficient mice. The concurrent lack of both *OCA-B* and *CD22* also increases mature splenic B-cell numbers to a level intermediate between wild type and OCA-B null mice. Despite this, neither T-dependent

Table 1. Non-Ig gene and/or protein expression affected in *OCA-B* deficient mice[a]

Affected gene[b]	Function	Cell source	Method(s) of assessment	Refs
B4galt1	Glycosylation	C57BL/6 X 129Sv splenic B cells	RNA (microarray, NB)	[58]
BAFFR	Surface receptor	C57BL/6 peripheral B-1 and B-2 cells	RNA (RT-PCR)	[47]
Bcl2	Cell survival	C57BL/6 pre-B cells	RNA (RPA); protein (WB, Impox)	[44]
BCMA	Surface receptor	C57BL/6 peripheral B-1 and B-2 cells	RNA (RT-PCR)	[47]
Blr1	Chemokine receptor	C57BL/6 lymph node B cells	Protein (flow cytometry)	[50]
Blr1	Chemokine receptor	C57BL/6 splenic B cells (no effect)	RNA (NB)	[35]
CD22	BCR antagonist, cell adhesion	C57BL/6 pre-B and immature B cells	Protein (WB, Impox)	[45]
CD36	Scavenger receptor	C57BL/6 splenic B cells	RNA (NB)	[35]
CDC37	Cell cycle	C57BL/6 X 129Sv splenic B cells	RNA (microarray, NB, QPCR)	[58]
Cyclin D3	Cell cycle	C57BL/6 X 129Sv splenic B cells	RNA (microarray, QPCR)	[58]
Kcnn4	Ion transport	C57BL/6 X 129Sv splenic B cells	RNA (microarray, NB, QPCR); protein (ChIP onA20 B cells)	[58]
Lck	Signal transduction	C57BL/6 X 129Sv splenic B cells	RNA (microarray, NB, QPCR); protein (ChIP onA20 B cells)	[58]
Ms4a11	Transmembrane protein	C57BL/6 X 129Sv splenic B cells	RNA (microarray, NB)	[58]
Osteopontin	Cell migration and adhesion	C57BL/6 splenocytes	RNA (NB)	[20]
S100a10	Calcium binding protein	C57BL/6 X 129Sv splenic B cells	RNA (microarray, NB, QPCR)	[58]

[a]Abbreviations: BAFF, B-cell activating factor; BCMA, B-cell maturation factor; BCR, B-cell receptor; Blr1, Burkitt lymphoma receptor 1; ChIP, chromatin immunoprecipitation; Impox, immunoperoxidase tissue staining; NB, northern blot; QPCR, semi-quantitative reall-time RT–PCR; RPA, RNA protection assay; WB, western blot.
[b]All analyses resulted in a decrease in expression of the listed RNA and/or protein except for *CD22*, which was elevated compared to wild type controls. A discordant result for *Blr1* is noted by a double listing and is potentially explained by post-transcriptional processing, as for OCA-B in resting versus proliferating splenic B cells [36].

immune responses nor GC formation are restored in doubly deficient B cells. These findings support a potential, probably indirect role for negative regulation of CD22 expression by OCA-B on marrow transitional B cells.

OCA-B regulation of T-independent B-1- and MZB-cell development

A role for OCA-B in B-1-cell development and function is emerging. Normal B-1-cell numbers were reported in one study of *OCA-B* null mice; another study confirmed this result and also showed normal BCR signaling and B-1-cell migration in distinct chemokine environments [38,47]. By contrast, others noted a small decrease in total B-1-cell numbers [32] and still others detected increased total B-1 cells, with elevated B-1a- and slightly reduced B-1b-cell subtypes [48]. Strain-specific modifiers in C57BL/6 versus C57BL/6 X 129Sv *OCA-B* null mice are probably responsible for these distinct B-1-cell results. Interestingly, *Nf-κb1* null mice, *OCA-B* null mice, have specific (but distinct) defects in peripheral B-cell development and immunologic function [49]. A cross between *Nf-κb1* and *OCA-B* null mice results in a severe deficit in both B-1a and B-1b populations, suggesting that *Nf-κb1* and *OCA-B* have non-overlapping and complementary roles in controlling B-1-cell development [48]. A similar dependence on *OCA-B* and *Oct-2* for B-1-cell generation has also been observed in doubly deficient mice [35].

MZB cells were originally considered independent of *OCA-B* until a detailed re-examination of C57BL/6 strain *OCA-B* null mice showed that they were reduced 20-fold [31,38–40,47]. As with B-1 cells, this decrease is probably strain dependent because BALB/C and C57BL/6 X NMR1 *OCA-B* null mice also have strongly reduced MZB cells whereas C57BL/6 X 129Sv *OCA-B* null mice show only a slight MZB-cell deficit (Figure 1). Bone marrow adoptive transfer studies further showed that this deficit is MZB-cell autonomous. MZB functions are also impaired in knockout mice because the MZB cell-specific antigen TNP-ficoll (tri-nitro-phenol-ficoll) is not efficiently captured and basal motility, along with chemotactic cell migration, is perturbed. A reduction in the receptor for B-lymphocyte chemoattractant (BLC), termed Burkitt lymphoma receptor 1 (BLR1), could account for these movement defects [35,47,50] (Table 1). MZB cells also depend on B-cell activating factor (BAFF) of the tumor necrosis factor (TNF) family [51]. Targeted deletion of either BAFF or one of its receptors leads to impairment in MZB-cell development. mRNA levels of two BAFF receptors, BAFFR and BCMA (B-cell maturation factor), are reduced in MZB and B-1 cells of *OCA-B* null mice [47] (Table 1). Furthermore, *OCA-B* null B cells have impaired BCR signaling with IgM stimulation as shown by reduced Ca^{2+} influx and weak phosphorylation patterns in total protein lysates. These results contradict the prevailing model that weak BCR signaling favors MZB-cell development and function over B-1 and follicular B cells [52–54]. It also suggests that weak BCR signaling originates from impaired follicular B cells because MZB cells and GC are sharply reduced or lacking in these *OCA-B* null mice. Combined, the results indicate a strong, strain-specific dependence of MZB-cell development and function on *OCA-B* expression, perhaps through antigen–BCR, BLC–BLR1 and/or BAFF–BAFFR or BCMA signaling cascades and perturbations in cell trafficking and sub-compartmentalization [55]. In contrast to transitional B cells, crossing C57BL/6 strain *OCA-B* null with *Bcl2* transgenic mice does not correct the MZB cell deficit [44].

OCA-B impacts T-dependent GC formation

The most severe defects in mice lacking *OCA-B* expression are strain-independent reductions in the number of mature splenic and recirculating B cells, along with the inability of primary follicular B cells to form GC or produce isotype-switched secondary Ig [38–40] (Figure 1). Although expression of isotype switched Ig is impaired, the mechanism of Ig class switching remains intact in *OCA-B* null B cells [40]. This impairment seems at least partially owing to the dependence of the 3′ Ig heavy chain enhancer on OCA-B expression in class

switched Ig [56,57]. In addition, mature splenic B-cell proliferative responses to BCR stimulation in *OCA-B* null B cells are reduced [40]. The combined consequences of a blunted proliferative response, impaired transitional B-cell seeding, sharply decreased MZB cells and an absence of GC formation could account for the two to four-fold decrease in $B220^{+}$ splenic B cells originally reported in *OCA-B* knockout mice [38,39]. These results also indicate that regulation of additional non-Ig target genes is probably responsible for OCA-B-dependent GC formation with antigenic stimulation. Several of these candidates have already been mentioned, such as *Bcl2* in pre-B cells and *Blr1* and *BAFFR* and/or *BCMA* in transitional immature B cells. However, it has already been shown that *Blr1* null mice form GC and mount T-dependent immune responses, suggesting the need for a more systematic approach to finding OCA-B regulated candidates that control GC formation [55].

A recent search for direct and indirect OCA-B target genes used a 9800 gene cDNA microarray [58]. These studies showed that with BCR stimulation alone, Cdc37, Kcnn4, Lck, Cyclin D3 and S100a10 gene expression levels are OCA-B dependent, whereas B4galt1 and Ms4a11 expression levels with BCR and T-helper stimulation (CD40L plus IL-4) required OCA-B (Table 1). Chromatin immunoprecipitation of OCA-B from Kcnn4 and Lck octamer-containing promoter regions supports a direct role for OCA-B regulation of at least these two genes in expressing B-cell lines. Although involved in B-cell proliferation and differentiation, none of these genes are known to be singly required for GC formation, in contrast to CD40, CD40L, Bcl-3, Bcl-6 or OCA-B itself, all of which are required to develop GCs. In fact, *Bcl-3* and *Bcl-6* genes appear unaffected in OCA-B null mice [31]. Bcl2, which is activated by OCA-B in pre-B cells is an unlikely key target because it undergoes a physiologic down-regulation in the GC. Overall, it seems that major candidate genes have not emerged from this microarray analysis of OCA-B-dependent B-cell stimulation, at least so far [58].

A key molecule that has not been mentioned yet is activation-induced cytidine deaminase (AID), which is the central effector of Ig class switching and somatic hypermutation reactions in the GC [59]. AID inactivation causes one form of hyper-IgM syndrome (HIGM2) that is characterized by a lack of class switching and somatic hypermutation with the formation of a giant GC [60]. Although the AID promoter has not been studied in detail, and a region suspected to harbor promoter activity contains two octamer motifs that are also OCA-B consensus sites, reduced OCA-B-dependent AID expression is unlikely to be the sole source of disrupted GC formation in mice. The current data therefore suggest that OCA-B regulates GC formation through its effect on numerous additive or synergistic direct and indirect target gene expression levels. Alternatively, additional GC-dependent OCA-B target genes might not have been included in this single array survey and/or p35 signal transduction effects outside of the nucleus might also be involved in GC formation.

Ig recombination, regulation and humoral deficiency in *OCA-B* null mice

In addition to reduced isotype switched Ig production, further skewing of the Ig repertoire occurs through alterations of specific Igκ light chain germline transcription linked to a selective reduction of Igκ V(D)J recombination and distinct levels of rearranged *Igκ* gene transcription [61]. Interestingly, Ig transcription and gene rearrangements at the heavy chain loci are not affected by OCA-B [41]. These results indicate that OCA-B-influenced Ig expression relies on co-stimulatory sequences flanking the octamer motif and more directly on alterations in the conserved octamer core in specific Vκ promoter regions, in agreement with structural studies [9,10,14,16,18,20].

The mild to marked disruption in all stages of B-cell development, coupled with a dramatic reduction in secondary switched Ig isotypes and skewed Ig repertoire predicts that *OCA-B* null mice will be susceptible to environmental and possibly opportunistic infections. Surprisingly, only one study has reported an effect on humoral immunity owing to deficient OCA-B expression. Vesicular stomatitis virus (VSV) induces a potent T-independent neutralizing IgM response in mice. *OCA-B* null mice are sensitive to immunization with live VSV, producing markedly reduced IgM and IgG titers and succumbing to viral infection at high frequency [62]. Similarly, T-dependent lymphocytic choriomeningitis virus (LCMV) elicits severely abrogated or absent humoral immunity in *OCA-B* deficient mice [62]. An increased sensitivity to additional pathogens that are controlled by either T-independent or T-dependent humoral immunity is predicted in *OCA-B* deficient mice.

Mice lacking *Aiolos*, a nuclear factor of the *Ikaros* gene family that participates in chromatin remodeling and histone deacetylation complexes, exhibit B-cell hyperproliferation and spontaneous GC formation in the absence of inciting antigens [63]. These mice develop an autoimmune disease resembling human systemic lupus erythematosus (SLE), with anti-nuclear antibodies and immune complex-mediated glomerulonephritis. Deletion of *OCA-B* causes a reduction in marrow transitional B cells, a decrease in proliferation in response to B-cell mitogens, failure of spontaneous or induced GC formation and inhibition of SLE-like immune complex and autoantibody production in *Aiolos* deficient mice [64]. The reversal of SLE-like disease is probably due to changes in B-cell function, specifically in the generation of the Ig repertoire, with a loss of autoreactive Ig induced by *OCA-B* deficiency.

Potential roles for OCA-B in B-cell malignancy

OCA-B in human tonsillar B cells shows a similar pattern of expression to that seen in mouse splenic B cells, with the possible exception that human plasma cells have low or undetectable OCA-B expression [34]. Surveys of human non-Hodgkin B-cell lymphomas (B-NHLs) show strong OCA-B protein expression in GC-derived malignancies and no expression in pre- and post-GC derived cases [34,65]. This pattern is almost identical with the expression pattern for BCL-6 (B-cell lymphoma-6), which is an excellent marker for tumors of GC origin. Retention

of the normal OCA-B expression pattern in tumors derived from distinct B-cell developmental stages does not preclude a mechanistic role for OCA-B in most B-NHL but that role is probably independent of OCA-B expression levels.

Classical Hodgkin disease (cHD) is a B-cell tumor that has multiple histologic subtypes, with the signature malignant Reed-Sternberg (RS) cells lacking expression of most, if not all, B-cell-specific genes and proteins. RS cells can show Ig gene rearrangements, isotype class switching and somatic hypermutation of Ig loci, placing them mainly in the GC at the time of transformation [66,67]. In contrast to B-NHL, OCA-B is aberrantly silenced in RS cells, providing a potential mechanism for decreased or absent Ig and target non-Ig transcription in almost all cHD cases [68–73]. Silencing of OCA-B as an inciting event for cHD is possible but unlikely because this would block GC formation and interfere with the signature alterations detected in Ig loci of cHD tumor cells. As an alternate, the vast majority of cHD demonstrate inappropriately activated NF-κB pathway activation by a variety of mechanisms [74]. One hypothesis for developing cHD is that B cells failing GC selection with inappropriately activated NF-κB have a survival advantage, with additional complementing mutations resulting in malignant transformation. In this model, loss of OCA-B and additional B-cell-specific gene expression could be part of a normal B-cell shutdown before induced cell death from selective failure. Alternatively, it is possible that following GC formation, OCA-B is inappropriately silenced and, combined with additional mutations, such as constitutive NF-κB activation, has a causative role in cHD. Interestingly, primary effusion lymphoma, a GC or post-GC derived B-NHL, also fails to express the B-cell-specific transcription program and lacks OCA-B expression through inappropriate gene silencing mechanisms [75,76].

Conclusions

Roles for OCA-B in all stages of B-cell development have been described, although the major effect remains an absolute block in GC formation. Skewing of the Ig repertoire through reduced expression of class switched Ig, coupled with selective rearrangement and expression of Igκ light chains, predict humoral immune deficits and OCA-B control over these aspects of resistance to infection. Aberrant silencing in GC-derived cHD and primary effusion lymphoma indicates a potential role in opposing B-cell transformation. Probably, these OCA-B controlled B-cell functions depend on regulation of combinations of thus far undefined direct and indirect target genes and perhaps effects from OCA-B signaling at the membrane. The effect on cell motility and chemotactic gradient migration could block GC formation because it seems likely to inhibit MZB-cell compartmentalization and development. As mentioned, not all octamer-dependent genes are targets for OCA-B regulation, as exemplified by the lack of an OCA-B effect on octamer-dependent Ig heavy chain transcription and a probable indirect effect on octamer-dependent CD36 transcription [35,61,77] (Table 1). Therefore, simple sequence inspection for probable direct targets is inadequate and a systematic approach for finding such targets is required. Priorities for the field to link OCA-B function with biologic outcome are the identification of OCA-B-dependent target genes and determination of the function(s) of the membrane-associated p35 isoform.

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