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T cell–B cell interactions in primary immunodeficiencies

Stuart G. Tangye,[1,2] Elissa K. Deenick,[1,2] Umaimainthan Palendira,[1,2] and Cindy S. Ma[1,2]

[1]Immunology Research Program, Garvan Institute of Medical Research, Darlinghurst, NSW, Australia. [2]St. Vincent's Clinical School, University of NSW, Sydney, NSW, Australia

Address for correspondence: Dr. Stuart Tangye, Garvan Institute of Medical Research, 384 Victoria St., Darlinghurst, 2010, NSW, Australia. s.tangye@garvan.org.au

Regulated interactions between cells of the immune system facilitate the generation of successful immune responses, thereby enabling efficient neutralization and clearance of pathogens and the establishment of both cell- and humoral-mediated immunological memory. The corollary of this is that impediments to efficient cell–cell interactions, normally necessary for differentiation and effector functions of immune cells, underly the clinical features and disease pathogenesis of primary immunodeficiencies. In affected individuals, these defects manifest as impaired long-term humoral immunity and susceptibility to infection by specific pathogens. In this review, we discuss the importance of, and requirements for, effective interactions between B cells and T cells during the formation of $CD4^+$ T follicular helper cells and the elicitation of cytotoxic function of virus-specific $CD8^+$ T cells, as well as how these processes are abrogated in primary immunodeficiencies due to loss-of-function mutations in defined genes.

Keywords: immunodeficiency; T follicular helper cells; T-dependent B cell activation; T–B cell interactions; humoral immunity; XLP

$CD4^+$ T cell subsets and effector function

It has been known for some time that T cells are required for the generation of intact immune responses. Some of the earliest evidence for this originated from experiments performed in thymectomized mice, where the absence of T cells abrogated antibody (Ab)- and cell-mediated immune responses (i.e., delayed type hypersensitivity) following immunization with specific antigens (Ag).[1–3] In the setting of humoral (i.e., Ab-mediated) immunity, $CD4^+$ T cells provide "help" in the form of cell–cell contact and cytokine secretion to support Ab production by cognate B cells. The wealth of research that subsequently followed these seminal studies revealed that naïve $CD4^+$ T helper (Th) cells can differentiate into multiple distinct subsets with unique helper functions. Mosman and Coffman's original Th1–Th2 hypothesis proposed that IFN-γ–producing Th1 cells were involved in immunity against intracellular pathogens, while IL-4–producing Th2 cells protect against extracellular pathogens and may regulate Ab production by B cells.[4] The cytokine environment present at the time of T cell activation was found to dictate these differentiation pathways, because specific cytokines activate distinct transcription factors to induce polarization to a particular fate. In the case of Th1 and Th2 cells, this involves the cytokines IL-12 and IL-4 stimulating expression of the transcription factors *TBX21* (encoding T-bet) and *GATA3*, respectively.[5] In more recent times, the list of distinct $CD4^+$ Th cell subsets has grown to include regulatory T cells, Th9, Th17, Th22, and T follicular helper (T_{FH}) cells.[6–8] Since the topic of this review is T–B cell interactions in primary immunodeficiencies (PIDs), we will focus predominantly on the latter subset, whose defining function is B cell helper activity.

T follicular helper cells

While the obligate role of T cells in generating intact Ab responses has been known for decades, it was not until 2000 that a subset of $CD4^+$ T cells believed to function primarily in providing help to B cells in lymphoid follicles was described.[9,10] These $CD4^+$ T cells were termed T follicular helper (T_{FH}) cells and could be identified by expression of the

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B cell follicle homing chemokine receptor CXCR5, which allows them to migrate to the B cell follicle where they are positioned to provide help to Ag-activated B cells.[6,11–13] In addition to their precise positioning, T_{FH} cells have specialized attributes that are important for their survival, differentiation, and/or function. These include secretion of the B cell-trophic cytokine IL-21 and expression of costimulatory molecules such as CD40 ligand (CD40L), ICOS, CD200, OX40; members of the SLAM family of cell surface receptors (CD84, NTBA); and the cytoplasmic adaptor protein SLAM-associated protein (SAP)[14,15] required for intracellular signaling downstream of SLAM receptors.[16–18] Furthermore, T_{FH} cells can also be identified by elevated expression of the activation markers PD-1 and BTLA, the transcription factor BCL6, and lack of expression of CCR7, CD127, and CD62L.[13–15,19,20]

Function of T_{FH} cells

Many of the molecules expressed by T_{FH} cells, including CD40L and various cytokines, allow them to function as potent helpers of B cell differentiation. For example, engagement of CD40 alone is sufficient to induce B cell activation and proliferation.[21–23] Furthermore, mice in which CD40–CD40L interactions are disrupted show abortive T-dependent (TD) B cell responses and lack long-term humoral memory (reviewed in Refs. 24 and 25), demonstrating that CD40L is a critical component of $CD4^+$ T cell help to B cells. It is interesting to note, however, that in addition to its role in activating B cells, T cell-expressed CD40L also plays a role in activating dendritic cells (DCs), which may contribute to the initial priming of $CD4^+$ T cells.[24,25]

While CD40L is a potent activator of B cells, other signals, such as cytokines, play important roles in supporting B cell activation and differentiation. For instance, IL-21, which is highly expressed by T_{FH} cells, is one of the most potent differentiation factors for human B cells, being able to induce isotype switching and the generation of Ab-secreting cells.[26–29] The use of *Il21* or *Il21r* gene-targeted mice has demonstrated *in vivo* that this cytokine also influences B cell expansion as well as the generation of germinal centers and memory B cells.[30–32] The degree of the defects observed in the absence of IL-21/IL-21R signaling, however, varied significantly, suggesting other factors may compensate for the loss of IL-21. It is interesting to note, therefore, that T_{FH} cells also express other cytokines such as IL-4,[15,33–37] IL-10,[9,15] IL-17,[37,38] and IFN-γ,[34,35,37–39] which are all capable of modulating isotype switching and Ab secretion by B cells.[21,23,40]

Regulation of T_{FH} cell formation

Recent work has significantly expanded our knowledge of the signals required for the generation and maintenance of T_{FH} cells. These include signals delivered via the TCR, as well as those provided by soluble mediators, such as cytokines, and costimulatory molecules engaged by ligands expressed by Ag-presenting cells (APCs), such as DCs and B cells (Figs. 1B and 1C).

Cytokines

Like other helper lineages, the generation of T_{FH} cells has also been linked to production of specific cytokines. Activation of naive $CD4^+$ T cells *in vitro* in the presence of either IL-6 or IL-21 has been shown to generate IL-21–expressing cells capable of inducing increased Ab production by B cells.[41–44] Some studies have further shown that mice deficient in IL-6[41] or IL-21[30,41,45] have decreased numbers of T_{FH} cells. More recent studies, however, have not observed reduced T_{FH} cell numbers when either IL-6[46,47] or IL-21[30,31,46–49] signaling is disrupted. Given that both IL-6 and IL-21 activate STAT3, such discrepancies likely reflect redundancy between these cytokines for STAT3 activation. Consistent with this idea, ablation of signaling by both IL-6 and IL-21 results in a significant decrease in numbers of T_{FH} cells.[47] Indeed, the level of redundancy among cytokines may be even greater, as IL-27, another STAT3-activating cytokine, has also been implicated in the generation of T_{FH} cells.[50] Interestingly, the cytokines that direct the differentiation of human T_{FH} cells appear to be different to those required for murine T_{FH} cells. Although IL-6, IL-21, and IL-27 could induce IL-21 production from human naive $CD4^+$ T cells, IL-12 was found to be much more potent.[15,50,51] This was also associated with an increased ability of these cells to support Ab secretion by cocultured B cells.[15,51]

Cell surface molecules

Multiple cell surface molecules have been identified to be involved in $CD4^+$ T cell–APC interactions and to regulate T_{FH} cell generation, function, and maintenance. Initial activation of $CD4^+$ T cells is

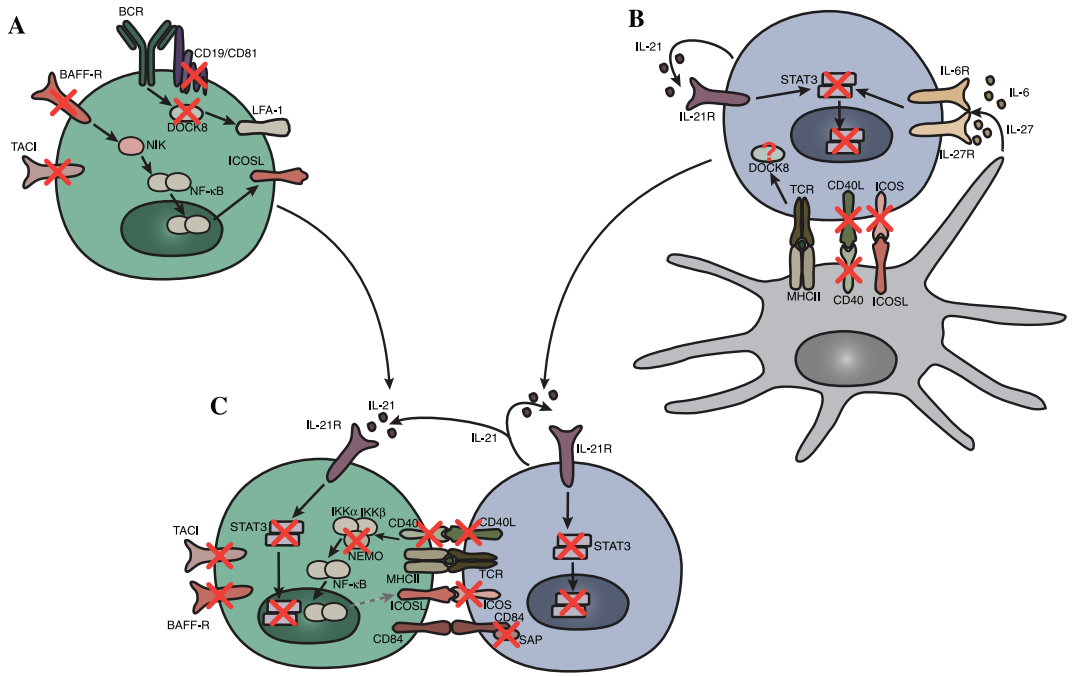

Figure 1. Interactions required for the generation of T-dependent Ab responses. Molecules known to be affected in PIDs are marked with red crosses. (A) B cell survival is regulated by signaling through BAFF-R. BAFF-R signaling also maintains constitutive expression of ICOSL on B cells via a NIK-dependent pathway. B cell activation occurs in response to Ag binding by the BCR. CD19, CD21, and CD81 are also required as components of the BCR coreceptor complex. DOCK8 is required for polarization of LFA-1 to the immune synapse. (B) $CD4^+$ T cells are activated following interactions with DCs. CD40–CD40L interactions at this stage lead to activation and "licensing" of the DC. ICOS–ICOSL interactions are required for differentiation of T_{FH} cells. STAT3-activating cytokines such as IL-6, IL-21, and IL-27 can also support T_{FH} cell generation/survival. DOCK8 may also play a role in synapse formation and adhesion in $CD4^+$ T cells, thus contributing to T cell activation and differentiation into T_{FH} cells. (C) Following activation, $CD4^+$ T cells and B cells migrate to the T–B border and interfollicular regions within secondary lymphoid tissues, allowing the two cell types to interact. Homotypic interactions between CD84 (and possibly Ly108 [human NTB-A]) and subsequent downstream SAP signaling are required to promote T–B adhesion. ICOS–ICOSL signals are required to maintain T_{FH} cells. STAT3 signaling downstream of cytokine receptors, such as IL-21R, probably also contributes to T_{FH} cell maintenance. CD40L on T cells binds CD40 on B cells resulting in NF-κB activation downstream of NEMO. This CD40L signal is critical to the activation and survival of B cells. NF-κB activation may also contribute to the maintenance of ICOSL on the B cell surface. IL-21 produced by T_{FH} cells stimulates activation and differentiation of B cells via a STAT3-dependent pathway. TACI also contributes to B cell differentiation.

thought to occur primarily via interactions with DCs. This requires engagement of the TCR and CD28 by peptide:MHC II and B7.1/B7.2, respectively, expressed by DCs. In the absence of signaling through CD28, $CD4^+$ T cells fail to upregulate CXCR5,[52] resulting in reduced numbers of T_{FH} cells.[53] Similarly, OX40–OX40L interactions between $CD4^+$ T cells and DCs are thought to play a role in inducing CXCR5 expression.[52,54–56] This initial activation and upregulation of CXCR5, coupled with a downregulation of CCR7, allows the $CD4^+$ T cells to migrate toward the B cell follicle where they are able to interact with B cells.[11–13]

The ensuing interactions with B cells are important not only in order for the T cells to provide helper signals to the B cells but also for regulating T_{FH} cell responses. Thus, mice in which B cells are absent, or where T–B cell interactions are disrupted, show decreased T_{FH} cell numbers.[13,19,36,39,46] Similar to DC-mediated T cell activation, T–B cell interactions involve both TCR and co-stimulatory signals. However, it appears that the main co-stimulatory signal provided by B cells is not via CD28, but rather through the related receptor ICOS. Disruption of ICOS–ICOSL signaling in mice results in decreased numbers of T_{FH} cells and impaired germinal

center (GC) responses.[19,38,53,57,58] Although ICOS–ICOSL co-stimulation predominates at the stage of T–B cell interactions, ICOSL is widely expressed on other hematopoietic cells, including DCs, and studies suggest that optimal T_{FH} cell formation requires ICOS–ICOSL signaling during both initial DC–T cell interactions and later T–B cell interactions (Figs. 1B and 1C).[41,59]

Another important set of molecules involved in $CD4^+$ T–B cell interactions are the SLAM family of receptors, several of which—CD229, NTB-A (Ly108 in mice), CD84—are highly expressed on activated B and T cells, including T_{FH} cells.[14,15,17–19,35,60–62] These molecules signal via SAP, and $CD4^+$ T cells lacking SAP fail to support TD B cell responses.[16–18] This is because SAP is required downstream of CD84 (and potentially Ly108) to promote adhesion between $CD4^+$ T cells and B cells (Fig. 1C).[60,63] Thus, in the absence of SAP or CD84, the resultant short-lived interactions between $CD4^+$ T and B cells not only prevent the delivery of help to B cells but also preclude the B cells from providing the signals necessary to maintain the differentiation and/or survival of T_{FH} cells.[19,35,60,63–65]

Antibody defects in PIDs

Defects in humoral immunity, recognized by reductions in the levels of serum Ig and/or of Ag-specific Ab, represent one of the most common immunedeficient conditions. Indeed, common variable immunodeficiency (CVID) affects ~1 in 25,000 individuals.[66] The molecular cause of the vast majority of cases of CVID remains enigmatic.[66] However, mutations in *ICOS*,[67] *CD19*,[66,68,69] *CD81*,[70] *TNFRSF13B*,[71–75] and *TNFRSF13C*[76] (encoding TACI and BAFF-R/BR3, respectively) have been identified in a small number of patients diagnosed with CVID (Table 1). Several other molecularly defined PIDs are also characterized by dysregulated levels of serum Ig and/or defects in humoral immune responses to TD and T-independent Ags. These include X-linked and autosomal recessive (AR) hyper IgM syndrome (HIGM), X-linked anhidrotic ectodermal dysplasia with immunodeficiency (XL-EDA-ID), X-linked lymphoproliferative disease (XLP), and the autosomal dominant (AD) and AR hyper-IgE syndromes (HIES),[77] conditions caused by mutations in *CD40LG*,[78–80] *CD40*,[85] *IKBKG* (encoding NEMO),[86,87] *SH2DIA* (encoding SAP),[90] *STAT3*,[100,101] and *DOCK8*,[106,107] respectively (Table 1). Thus, although the earliest identified Ab deficiencies were found to result from profound intrinsic defects in B cell development,[110] it is now becoming clear that humoral immunodeficiency often results from defects in T–B cell interactions. However, the mechanisms underlying these defects differ significantly and can be primarily T cell-intrinsic, B cell-intrinsic, or a combination of both.

Ab defects due to impaired T_{FH} cell formation, function, and/or survival

Patients with HIGM,[81–83] ICOS-deficient CVID,[67,97] or XLP[91–95] display obvious defects in humoral immune responses, including reductions in the numbers of circulating memory B cells and levels of neutralizing Ag-specific serum Ab (Table 1). Further, they display an absence of well-formed GCs in their secondary lymphoid tissues.[82–84,96,97] However, previous studies have established that B cells from patients with X-HIGM or XLP respond normally to *in vitro* stimulation with mimics of T cell help,[88,93,94,11] suggesting that these defects may be T cell-intrinsic. Consistent with this idea, CD40L, ICOS, and SAP are predominantly expressed by T cells and NK cells, but are particularly highly expressed by T_{FH} cells.[6,15] T_{FH} function and generation was analyzed in these patients by quantifying the frequency of $CD4^+CXCR5^+$ T cells in peripheral blood of affected individuals or examining the ability of these mutant $CD4^+$ T cells to acquire features of T_{FH} cells *in vitro*, such as providing help to B cells for their differentiation into Ab-secreting cells.[57,93] This revealed that $CD4^+$ T cells from individuals with loss-of-function mutations in *CD40LG*, *ICOS*, and *SH2D1A* had impaired formation, effector function, and/or maintenance of T_{FH} cells,[57,93] paralleling what was observed in gene-targeted mice (Figs. 1B and 1C). These studies highlighted the pivotal roles of signaling through CD40/CD40L, ICOSL/ICOS, and members of the SLAM family expressed by B cells and T_{FH} cells for the generation of effective long-lived humoral immune responses in humans. However, these defects can probably be divided into two different categories. Thus, defects seen in ICOS deficiency are probably due to a failure in production of T_{FH} cells from naive precursors following interactions with APCs, such as DCs and B cells. In contrast, the defects observed in the

Table 1. Defects in B cells and CD4$^+$ T cells underlying impaired humoral immunity in primary immunodeficiencies

Primary Immune deficiency	Affected gene/protein	Antibody defect	B cell defect	Mechanism of humoral deficiency	References
X HIGM	*CD40LG* (CD40L)	• normal/ ↑ serum IgM • ↓ serum IgG/A/E • ↓ functional (i.e., Ag-specific) Ab response	• ↓ IgM+ memory B cells • absent IgG, IgA memory B cells	• impaired CD40L-mediated B-cell activation • impaired development and/or function of T_{FH} cells • absence of GCs	57, 77-80, 81–83, 84
AR HIGM	*CD40* (CD40)	• normal/ ↑ serum IgM • ↓ serum IgG/A/E • ↓ Ag-specific Ab response	• ↓ IgM+ memory B cells • absent IgG, IgA memory B cells	• *reduced T_{FH} cells due to impaired ICOS-L expression downstream of CD40/CD40L signaling*	77, 85
XL-EDA-ID	*IKBKG* (NEMO)	• ↓, normal, or h serum IgM • normal or ↓ serum IgG • ↑ or ↓ serum IgA • ↓ Ag-specific Ab response	• ↓ memory B cells	• impaired NEMO-dependent CD40-mediated B-cell activation • *reduced T_{FH} cells due to impaired ICOS-L expression downstream of CD40/NEMO signaling*	77, 86–89
XLP	*SH2D1A* (SAP)	• hypogammaglo-bulinemia • ↓ Ag-specific Ab response	• ↓ IgM+ memory B cells • absent IgG, IgA memory B cells	• impaired development and/or function of T_{FH} cells • reduced GCs	90–96
CVID	*ICOS*	• normal/ ↓ serum IgM • ↓ serum IgG/A/E • ↓ Ag-specific Ab response	• ↓ IgM+ memory B cells • absent IgG, IgA memory B cells	• impaired development and/or function of T_{FH} cells • absence of GCs	57, 67, 97
	CD19	• ↓ serum IgM/G/A/E • ↓ isohemagglu-tinins • ↓ Ag-specific Ab response	• ↓ memory B cells	• impaired signaling through the CD19/CD81/CD21 BCR co-receptor complex	13, 68, 69
	CD81	• normal serum IgM • ↓ serum IgG • normal/i serum IgA • ↓ isohemagglu-tinins • ↓ Ag-specific Ab response	• ↓ memory B cells	• *reduced T_{FH} cells secondary to impaired B cell activation*	70

Continued

Table 1. ***Continued***

Primary Immune deficiency	Affected gene/protein	Antibody defect	B cell defect	Mechanism of humoral deficiency	References
	TNFRSF13B (TACI)	• ↓/normal serum IgM • ↓ serum IgG, IgA	• ↓/normal memory B cells	• impaired survival of B cells and plasma cells (BAFF/APRIL dependent)	72, 74, 75, 98, 99
	TNFRSF13C (BAFF-R)	• ↓ serum IgM, IgG • normal serum IgA • impaired response to TI (pneumococcal) Ag • variable response to TD (tetanus toxoid) Ag	• ↓ total B cells • ↓/normal memory B cells	• impaired B cell survival • *reduced T_{FH} cells due to impaired ICOS-L expression downstream of BAFF-R signaling*	76, 98, 99
AD-HIES	*STAT3*	• normal serum IgM, IgG, A • ↓ Ag-specific Ab response • hyper IgE	• ↓ memory B cells	• intrinsic inability of STAT3 mutant B cells to respond to STAT3-activating cytokines, particularly IL-21 • *reduced T_{FH}-like function due to impaired production of IL-21 in response to IL-6, IL-21, IL-23 and IL-27*	41, 50, 51, 77, 100–105
AR-HIES	*DOCK8*	• reduced serum IgM • normal/↑ serum IgG, A • ↓ Ag-specific Ab response • hyper IgE	• ↓ memory B cells	• intrinsic inability of DOCK8 mutant B cells to polarise LFA-1, resulting in impaired responses to BCR signalling • *reduced formation of T_{FH} cells due to impaired LFA-1-dependent interactions with DCs*	77, 106–109

Abbreviations: X-HIGM: X-linked hyper IgM syndrome; AR-HIGM: autosomal recessive hyper IgM syndrome; XL-EDA-ID: X-linked ectodermal dysplasia with immunodeficiency; XLP: X-linked lymphoproliferative disease; CVID: common variable immunodeficiency; AD-HIES: autosomal dominant hyper IgE syndrome; AR-HIES: autosomal recessive hyper IgE syndrome. Mutations/polymorphisms in *TNFRSF13B* and *TNFRSF13C* are believed to represent susceptibility loci, rather than disease causing alleles.[66,77] The italicized text under the "Mechanism of humoral deficiency" column are predictions of possible defects in these conditions; they have not actually been documented in patients with the indicated PID.

absence of CD40L or SAP probably reflect not only the compromised generation of T_{FH} cells but, more importantly, their inability to adequately deliver help to B cells due to the central role of CD40L and the requirement for long-lasting T–B cell interactions, respectively, in this process.

B cell-intrinsic and -extrinsic effects of gene mutations associated with humoral immunodeficiencies

In contrast to the examples provided above, humoral deficiency characteristic of patients with mutations in *CD40*, *CD19*, *CD81*, *STAT3*, *DOCK8*,

IKBKG, *TNFRSF13B* (TACI), and *TNFRSF13C* (BAFF-R) results primarily from intrinsic B cell defects (Fig. 1A; Table 1). This is based on the well-established, and critical, roles of CD40 and the B cell coreceptor complex comprising CD19, CD21, and CD81 (and Leu13), in activating B cells[25] and fine-tuning signals elicited through the BCR,[112] respectively. Similarly, STAT3 and DOCK8 are required for integration of signals downstream of receptors for IL-6, IL-10, and IL-21 (among others),[113] and those delivered through the BCR itself,[108] respectively, for the generation of optimal humoral immune responses. The B cell-intrinsic requirement for STAT3 and DOCK8 in humoral immunity has also been established from analysis of mice that selectively lack expression of these genes in the B cell lineage. Thus, *Stat3*$^{flox/CD19cre}$ mice exhibited reduced production of Ag-specific Ab following immunization with TD Ags.[114] In an analogous manner, mice harboring an ENU-induced mutation in *Dock8* exhibit reduced primary and secondary immune responses to TD Ag, and transfer of *Dock8* mutant B cells into wild-type (WT) mice revealed B cell-intrinsic defects in their ability to form GCs and undergo affinity maturation.[108] It has also been demonstrated that B cells from patients with XL-EDA-ID due to mutations in *IKBKG* are unable to undergo Ig isotype switching *in vivo* or *in vitro* due to impaired CD40L-induced NF-κB activation.[87–89] Lastly, impaired signaling through BAFF-R and TACI, which are receptors for BAFF and/or APRIL, are likely to directly compromise B cell survival and differentiation.[98,99]

Despite this evidence for B cell-intrinsic functions for these genes, it is also likely that mutations in *STAT3*, *DOCK8*, *CD19*, *CD81*,*TNFRSF13C*, *CD40,* and *IKBKG* compromise the function of non-B cells. Such defects will arise either directly as a consequence of these genes being expressed in $CD4^+$ T cells or manifest secondarily to defects in B cells that subsequently influence $CD4^+$ T cell function, thereby contributing to Ab defects in PIDs. We speculate on these possibilities below.

STAT3

STAT3 is ubiquitously expressed and has important functions in regulating many aspects of cellular function.[115] It is thus not surprising that germline deletion of *Stat3* is embryonically lethal.[115] To circumvent this problem, and to ascertain lineage-specific functions of STAT3, conditional STAT3-deficient mice have been generated.[115] Mice lacking STAT3 only in B cells are unable to generate normal titers of Ag-specific IgG to TD Ags. However, they do generate intact GCs, Ag-specific memory B cells, and serum levels of Ag-specific IgA and IgE.[114] This contrasts with some of the features of humans with AD-HIES due to germline mutations in *STAT3* who also have a reduced capacity to generate Ag-specific IgG responses,[102–105] but additionally have reduced memory B cells[105,116] and Ag-specific IgA[103] (and aberrantly high levels of IgE[100,101,113]). Although the differences between STAT3-deficient humans and mice may reflect species-specific functions of STAT3, it is probable that the more severe phenotype in STAT3-deficient humans results from impaired function of $CD4^+$ T cells, specifically T_{FH} cells (Figs. 1B and 1C). This is based on the findings that STAT3 is required for induction of IL-21 production by murine and human $CD4^+$ T cells *in vitro* following stimulation with IL-6, IL-21, IL-23, and IL-27,[15,41–44,50,51] and that T_{FH} cells[41] or T_{FH}-like function[43] can be reduced in mice whose T cells lack STAT3 or receptors for IL-6, IL-21,[41,45] or IL-27.[50] The percentages of circulating $CD4^+CXCR5^+$ T cells are also reduced in the peripheral blood of patients with STAT3 mutations compared to normal donors (C.S. Ma, unpublished). Thus, the *in vivo* functional Ab deficiency characteristic of AD-HIES probably results from an intrinsic B cell defect that is compounded further by the compromised generation and/or function of T_{FH} cells (Table 1).

DOCK8

The exact function of DOCK8 in immune cells, and how inactivating mutations compromise immune cell function, remains to be completely defined. However, DOCK8 clearly has an important role in mediating synapse formation between immune cells via an LFA-1–dependent manner. Specifically, in response to specific Ag, transgenic B cells and $CD8^+$ T cells from *Dock8*-mutant mice were unable to efficiently polarize LFA-1 to the immune synapse for optimal interactions with other cell types, such as follicular DCs or APCs.[108,117] In the case of B cells, this appeared to be central to the defects in GC formation and affinity maturation in DOCK8-mutant mice.[108] Since DOCK8 is also expressed in $CD4^+$ T cells, it can be envisaged that compromised immune synapse formation involving interactions between LFA-1 on DOCK8-deficient $CD4^+$ T cells and

counter structures on APCs could also contribute to impaired humoral immunity in DOCK8-deficient humans and mice (Fig. 1B). While this remains to be formally tested, the concept of defective help by DOCK8-deficient $CD4^+$ T cells is supported by several independent observations. First, differentiation of $CD4^+$ T cells into T_{FH} cells occurs in a multistep process, with the initial stages involving interactions between integrins, including LFA-1, expressed by $CD4^+$ T cells and DCs.[60] Thus, impaired polarization of LFA-1 by DOCK8-deficient $CD4^+$ T cells may impair T–DC interactions and subsequent T cell activation and T_{FH} cell formation. Second, a recent report detailed the long-term outcome of treating a patient with AR-HIES due to a *DOCK8* mutation by allogeneic stem cell transplant (SCT).[109] Although the conditioning regime was sufficient to achieve >95% donor T cells, chimerism within the B cell compartment was split, with only ∼35% being donor-derived. Despite the predominance of host (i.e., mutant) B cells, reconstituting the T cell compartment in this DOCK8-deficient individual with normal cells was sufficient to completely reverse the humoral defects observed pre-SCT.[109] Specifically, while immunization with standard vaccines was ineffective prior to SCT, protective Ab responses against such vaccines were elicited post-SCT.[109]

It is certainly possible that the small number of engrafted normal B cells is responsible for the restored Ab responses in this DOCK8-deficient patient. However, analysis of chimeric mice generated by reconstituting irradiated recipients with equal proportions of bone marrow from WT or *Dock8*-mutant mice demonstrated that DOCK8-deficient B cells compete very poorly with WT B cells during Ag-specific Ab responses, constituting only 2–5% of responding B cells.[108] Thus, if the humoral defect in DOCK8-deficient humans resulted exclusively from B cell-intrinsic defects, the frequency of donor-derived B cells would be predicted to dominate over time; however, even seven years post-SCT they represented only ∼one-third of all B cells. Thus, it would be reasonable to conclude that defects autonomous to DOCK8-deficient $CD4^+$ T cells significantly contribute to impaired humoral immunity in this form of AR-HIES (Table 1).

CD19–CD81

CD19 physically associates with the complement receptor CD21, as well as the tetraspanin molecule CD81, to form the B cell coreceptor complex.[112] CD19 acts as the signal transducing component for CD21, but also enhances BCR signaling.[112] Interestingly, CD81 is required for expression of CD19 at the B cell surface.[118] The importance of the coreceptor complex to B cell activation and effector function is apparent from the phenotype of mice lacking CD19, CD21, or CD81 (Fig. 1A); while T and B cell development is intact in these mice, they all exhibit impaired GC formation, Ab production, and memory B cell differentiation in response to TD Ags.[112,118]

While mutations of CD19 or CD81 would clearly affect B cell activation in an intrinsic manner (Fig. 1A), *Cd19*-deficient mice also lack T_{FH} cells.[13] This reflects the requirement for interactions between $CD4^+$ T cells and appropriately activated B cells during T_{FH} cell formation.[6] It is therefore highly likely that the generation of T_{FH} cells may be impaired in humans with mutations in *CD19* or *CD81*, that latter of which phenocopies CD19-deficiency due to the requirement of CD81 for CD19 expression (Fig. 1; Table 1).[68,70]

BAFF-R (TNFRSF13C), NEMO (IKBKG), and CD40

A recent study revealed an interesting link between NF-κB signaling in B cells and T_{FH} cell development. Specifically, mice lacking NF-κB–inducing kinase (NIK) displayed reduced levels of ICOSL expression on B cells, and this manifested as a reduction in T_{FH} cells following immunization with TD Ags.[119] NIK is a component of the noncanonical NF-κB signaling pathway that is activated in response to engagement of BAFF-R and CD40 by their specific ligands (i.e., BAFF, CD40L). Remarkably, signaling through BAFF-R is required to maintain constitutive expression of ICOSL on B cells, while BAFF- and anti-CD40 mAb–mediated activation of murine B cells further upregulates ICOSL expression.[119] Although NEMO is a component of the canonical NF-κB pathway, it is also possible that it contributes to optimal ICOSL expression on CD40-activated B cells. Based on these findings, T_{FH} cell formation may also be compromised in individuals with mutations in *TNFRSF13C* (encoding BAFF-R), *CD40,* or *IKBKG* as a result of deficient ICOSL–ICOS interactions between B cells and T cells, recapitulating the phenotype of ICOS-deficient CVID patients (Fig. 1A; Table 1). This lack of T_{FH} cells could then

potentially compound the B cell-intrinsic effects of these gene mutations, resulting in a more severe phenotype.

Impaired T–B interactions underlie XLP disease pathogenesis

Studies in mice suggested that T_{FH} cell formation and function is impaired in SAP-deficient $CD4^+$ T cells due to inefficient interactions between these cells and cognate B cells.[17,63,65] Such impaired conjugate formation compromises the ability of T_{FH} cells to productively provide help for the differentiation of B cells into memory and plasma cells,[17,65] which may explain the humoral immune defects in XLP patients (Fig. 1C).[16] Although TD Ab responses come to mind when considering T–B interactions, lessons from PIDs have also demonstrated a crucial role for T–B interactions in controlling pathogen infections. Thus, the inability of B cells and SAP-deficient T cells to interact sufficiently may also explain another key feature of XLP—the extreme sensitivity to infection with the herpes virus Epstein–Barr virus (EBV).[16,17] EBV is a B cell trophic virus that infects more than 90% of the population.[120] Although infection with EBV is asymptomatic in the vast majority of healthy individuals, it causes severe and often-fatal fulminant infectious mononucleosis in XLP patients.[16,120] An unanswered question has been why XLP patients exhibit such exquisite susceptibility to EBV infection but not other viruses, including related herpes viruses. We recently showed that the vulnerability of XLP patients to EBV results from the inability of SAP-deficient cytotoxic $CD8^+$ T cells to specifically respond to B cell targets, while they could efficiently respond to viral antigens presented on other APCs such as monocytes, DCs, and fibroblasts.[121,122] This paralleled the ability of SAP-deficient murine $CD4^+$ T cells to form stable conjugates with DCs, but not B cells.[17,60,63]

Interestingly, the role of relevant SLAM family receptors, and the consequence of SAP signaling, in interactions between $CD4^+$ and $CD8^+$ T cells with B cells appears to be quite distinct. Receptors such as CD84 and Ly108/NTBA appear to be important for inducing long-lasting interactions between $CD4^+$ T cells and B cells (Fig. 1C).[17,60] In contrast, SAP appears to be required in $CD8^+$ T cells to prevent the delivery of inhibitory signals through the SLAM receptors NTB-A and 2B4 (CD244), whose ligands (NTB-A, CD48) are highly expressed on EBV-infected B cells.[121,122] This conclusion is based on the complimentary findings that (1) the poor response of SAP-deficient $CD8^+$ T cells to Ag-presenting B cells can be improved when 2B4–CD48 and NTB-A–NTB-A interactions are prevented [121,122] and (2) recognition of Ag presented on fibroblasts by SAP-deficient $CD8^+$ T cells was reduced when these APCs expressed ectopic NTB-A.[122] The problem with SAP-deficient $CD8^+$ T cells in recognizing B cell targets is not restricted to EBV-infected B cells; indeed, SAP-deficient $CD8^+$ T cells were also compromised in responses to EBV-negative, activated B cells.[121] This defect may explain the increased incidence of B cell lymphoma in XLP patients.[16,17,92]

Conclusions

Although the incidence of PIDs is infrequent, they are nonetheless excellent "experiments of nature." They provide opportunities to not only determine the nonredundant functions of specific genes during the development and acquisition of effector function of immune cells, but also to elucidate the cellular and molecular mechanisms underlying defects in lymphocyte function and the clinical features of these conditions. As discussed here, the study of several monogenic PIDs has crystallized the importance of T–B cell interactions during the generation of helper and lytic effector functions of $CD4^+$ T_{FH} cells and $CD8^+$ cytotoxic T cells, respectively. These advances provide a foundation to further dissect cell- and Ab-mediated protective immunity in health and disease states. Continued studies of PIDs will identify novel molecules and signaling pathways as critical regulators of immune cell function and potentially facilitate the translation of these discoveries of basic research into therapies in cases of immune dysregulation such as immunodeficiencies and autoimmunity, in addition to improving Ab responses during vaccination.

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Conflicts of interest

The authors declare no conflicts of interest.

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