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A brief history of T cell help to B cells

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Abstract

In celebration of the 50th anniversary of the discovery of B cells, I take a look back at the history of T cell help to B cells, which was discovered 47 years ago. In addition, I summarize and categorize the distinct molecules that are expressed by $CD4^+$ T cells that constitute 'help' to B cells, and particularly the molecules expressed by T follicular helper (T_{FH}) cells, which are the specialized providers of help to B cells.

A timeline of B cell help discoveriess

Providing help to B cells was one of the earliest discovered functions of T cells, resulting in the coining of the term 'T helper (T_H) cell'. The first indications came from Claman and colleagues in 1966 (REF. 1), but an unambiguous demonstration of a role for thymus-derived helper cells in antibody responses was made in a trio of back-to-back papers by Miller and Mitchell in 1968 (REFS 2–4) (FIG. 1). Using cell transfer experiments, they showed that transfer of neither thymus (T) cells nor bone marrow (B) cells to irradiated mice was sufficient to result in the development of an antibody response after immunization of mice with sheep erythrocytes. However, co-transfer of both bone marrow-derived and thymus-derived cells led to robust antibody responses[2,3]. These experiments showed that the cells from the thymus were necessary for the antibody response to the immunogen but that the thymus-derived cells did not produce the antibodies themselves. Thus, two different cell types — B cells and T cells — were required to collaborate to induce an antibody response. The T cells were recognized as a form of supporting cell type and termed 'antigen-reactive cells' by the authors[2]. The definitive nature of these papers resulted from a series of careful and clever controls — including using T cell-depleting antiserum, thymectomies and chromosomal markers[2–4]. In one experiment, Miller and Mitchell transferred thoracic duct cells from CBA mice crossed with C57BL/6 mice (consisting of predominantly mature T cells obtained by cannulation) into adult thymectomized and irradiated CBA mice that had been reconstituted for 2 weeks with CBA bone marrow and then immunized. They made use of strain-specific antiserum (H2-specific serum) to deplete CBA or C57BL/6 cells *in vitro* from spleen cell preparations from the immunized mice. Splenocyte preparations depleted of C57BL/6-derived cells (eliminating the thoracic duct-derived transferred cells but not the

Competing interests statement

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bone marrow-derived cells) did not lose antibody-secreting cells, whereas splenocyte preparations depleted of CBA-derived cells (in which the thoracic duct-derived cells and bone marrow-derived cells were eliminated) lost 97% of all antibody-secreting cells[3].

A rapid flurry of confirmatory studies were published showing the requirement of T cell help for antibody responses against many types of antigens in a plethora of experimental systems[5], including the important hapten-carrier systems that enabled B cell and T cell antigens to be distinguished at the molecular level[5,6]. One compelling experimental approach made use of T cell-depleting antiserum (θ-specific serum) to eliminate T cells[7] and thereby to prevent T cell help to B cells and antibody responses to immunogens[8]. However, of note, T cell help was not required for antibody responses to *Salmonella adelaide* flagellin, which is the antigen that is used in the seminal and brilliant 1958 ‘one cell — one antibody specificity’ paper by Nossal and Lederberg[9]. By 1972, the term ‘helper T cells’ was widely used to describe the thymus-educated cells that provide help to B cells[5,8].

Discovery of interleukin-4

The nature of the ‘help’ was not immediately apparent[5]. Indeed, even today we are still trying to understand the process of T cell help to B cells. One early model was that helper T cells may secrete one or more cytokines that are the molecular embodiment of the ‘help’ to B cells. In 1982, interleukin-4 (IL-4) was discovered as the first B cell help factor[10,11] (FIG. 1). The role of IL-4 was identified on the basis of its secretion from the mouse thymoma EL4 cell line and the *in vitro* ability of IL-4 in combination with B cell receptor (BCR) signalling to increase the number of B cells. With the development of the T_H1 cell–T_H2 cell paradigm in 1986 (REF. 12), it was generally inferred that as there were two types of $CD4^+$ T cells and only T_H2 cells expressed IL-4, these must be the $CD4^+$ T cells that help B cells. Although the initial T_H1 cell–T_H2 cell paper had more refined conclusions, the simple interpretation that T_H2 cells are the providers of B cell help became the standard interpretation, ingrained in textbooks and scientific papers alike. That deduction based on *in vitro* data was erroneous, but it was many years before the correct $CD4^+$ T cell type would be identified. Along the way, there were sporadic publications showing that deletion of T_H2-associated genes did not result in a loss of germinal centres *in vivo*[13,14]; these studies revealed a major gap in the understanding of T cell help to B cells. Germinal centres are microanatomical structures within the B cell regions of the lymph nodes and the spleen. The germinal centres are the active sites of large-scale antigen-specific B cell proliferation and mutation. It is primarily in germinal centres that B cells evolve high-affinity BCRs via mutation and selection by $CD4^+$ T cells, and it is almost mainly via germinal centres that B cells develop memory in the form of long-lived plasma cells and memory B cells[15]. Germinal centres depend on $CD4^+$ T cells for their development and maintenance, and for the production of plasma cells. Of particular note, germline deletion of *Il4* in mice resulted in no significant reduction of germinal centres or of total IgG in response to immunizations; the effects of loss of *Il4* were generally restricted to loss of IgE and IgG1, and a bias in the ratios of different IgG subtypes[13,16]. These results indicated that IL-4 uniquely contributes to IgE class-switch recombination but that most other aspects of T cell help to B cells primarily depend on other molecules.

Discovery of CD40

In the meantime, the importance of CD40 and CD40 ligand (CD40L) was discovered, creating interest in the help to B cells that occurs via direct interactions between $CD4^+$ T cells and B cells, in addition to the role of the secretion of cytokines (which may act at a distance). The first step to recognizing the role of CD40 came in 1986 with the generation of an antibody specific for human CD40, which induced B cell proliferation when combined with BCR signals[17]. Furthermore, stimulation of human germinal centre B cells with a CD40-specific antibody prevented apoptosis[18]. Clearly, CD40 was an important molecule on the surface of B cells, but what was the ligand? CD40L was cloned in 1992 and was found to be highly expressed by activated $CD4^+$ T cells[19]. Strikingly, treatment of naive mouse or human B cells with a CD40L–Fc fusion protein could induce B cell proliferation in the absence of any additional co-stimulation, which indicates that CD40L signalling to CD40 is a dominant mechanism of T cell help to B cells[19]. Shortly thereafter, it was determined by several research groups that the severe human genetic immunodeficiency X-linked hyper-IgM syndrome is frequently caused by mutations in *CD40LG* (the gene encoding CD40L)[20–24], which reinforced the concept that CD40L signals from $CD4^+$ T cells are a primary component of T cell help to B cells. Individuals with X-linked hyper-IgM syndrome who had mutations in *CD40LG* lacked germinal centres. In 1994, it was shown that a CD40L-specific monoclonal antibody could prevent the formation of germinal centres in mice[25]. In addition, germinal centres were known to contain $CD4^+$ T cells[25,26], which implied that $CD4^+$ T cells provide help to germinal centre B cells, and at least one component of that T cell help was contact-dependent CD40L.

Discovery of the role of IL-21

In 2000, the cytokine IL-21 was cloned and shown to help B cell proliferation[27,28]. IL-21 has since been shown to be the most potent cytokine for stimulating plasma cell differentiation[29,30]. Mice that are deficient for both IL-4 and the IL-21 receptor ($Il4^{-/-}Il21r^{-/-}$ mice) were found to have severe defects in antibody production, class-switch recombination and germinal centres, which indicated that the combination of these two cytokines was important for help to B cells[31]. However, the source of the IL-4 and IL-21 remained unclear.

Contact dependency

At this time, the evidence for additional contact-dependent help functions of T cells to B cells was also accumulating. Both inducible T cell co-stimulator (ICOS) and SLAM-associated protein (SAP; also known as SH2D1A) are expressed by $CD4^+$ T cells and deletion of the corresponding genes (*Icos* or *Sh2d1a*, respectively) results in severe defects in germinal centres and B cell memory[32–35]. Mutations in *SH2D1A*[36] (which result in the clinical disorder X-linked lymphoproliferative disease)or *ICOSL* (which encodes ICOS ligand)[37] result in immunodeficiency. A mutation in *SH2D1A* frequently leads to child mortality as a result of increased susceptibility to certain infections[36]. As SAP binds cytoplasmic tails of signalling lymphocytic activation molecule (SLAM) family receptors, it was proposed that SAP was involved in adhesion and/or co-stimulation of B cells by T cells[38]. Nevertheless, discovering the importance of ICOS and SAP in T cell help to B cells

raised more questions than answers about B cell–T cell interactions. The crucial importance of colocalization of $CD4^+$ T cells and B cells for T cell help was highlighted when technological advances in microscopy enabled intravital microscopy imaging. Intravital microscopy studies revealed extensive cognate interactions between $CD4^+$ T cells and B cells in the border region between the T cell zone and the B cell follicle early during antigen-specific immune responses[39–41] and later in germinal centres[42]. Later, it would become clear that ICOS has roles in T follicular helper (T_{FH}) cell differentiation[43], migration[44] and cytokine production[45].

Defining T_{FH} cells

Although the T_H1 cell–T_H2 cell paradigm held sway for many years, cracks in that oversimplification emerged over time and, ultimately, discoveries showed that the catalogue of $CD4^+$ T cell types included many more than just T_H1 cells and T_H2 cells. This started with the firm establishment of regulatory T (T_{Reg}) cells in 2000–2003 — catalysed by the discovery of forkhead box P3 (FOXP3)[46]. The catalogue of $CD4^+$ T_H cell types then expanded to include T_H17 cells in 2005–2006 (REF. 47). These revelations opened the door for serious consideration that there may be a subset of $CD4^+$ T cells that are specialized in B cell help. T_{FH} cells were first proposed in 2000 and 2001 (REFS 48–50) (FIG. 1). However, that proposal was mainly ignored as shown by the lack of mention of T_{FH} cells in almost all $CD4^+$ T cell reviews and textbook chapters in the years thereafter. Nevertheless, some savvy scientists recognized the importance of the T_{FH} cell concept and forded key areas[51–57]. T_{FH} cells were not widely accepted until 2009 when the transcriptional repressor B cell lymphoma 6 (BCL-6) was identified as a lineage-defining transcription factor of T_{FH} cells[58–60]. A range of experiments — including the use of *Bcl6*$^{-/-}$ $CD4^+$ T cells, constitutive expression of BCL-6 in antigen-specific $CD4^+$ T cells and manipulation of the expression of B lymphocyte-induced maturation protein 1 (BLIMP1; a potent antagonist of BCL-6) in $CD4^+$ T cells — showed that the expression of BCL-6 by $CD4^+$ T cells is necessary for T_{FH} cell differentiation and that T_{FH} cells are the unique providers of T cell help to B cells for the development of germinal centres and for the generation of most class-switched antibodies[58–60]. A central marker of T_{FH} cells is CXC-chemokine receptor 5 (CXCR5), which was shown a decade earlier to be required by B cells for entry into follicles[61] and therefore it was logical that T_{FH} cells would need to express the same chemokine receptor. It was also determined that T_{FH} cells express IL-21 (REF. 50) and that T_{FH} cells are the primary producers of IL-4 in lymphoid tissue[62,63]. The regulation of *Il4* differs between T_{FH} cells and T_H2 cells — in T_{FH} cells *Il4* is regulated by SAP and protein kinase Cθ (PKCθ), and in T_H2 cells it is regulated by GATA-binding protein 3 (GATA3) — and it is the IL-4 secreted from T_{FH} cells that is necessary for class-switch recombination[64–67].

Following the identification of BCL-6, the study of T_{FH} cells and T cell help to B cells has markedly increased. Stages of T_{FH} cell differentiation, inductive signals, migration patterns, memory, associations with human autoimmune diseases, and BCL-6^+ T_{Reg} cells (also known as T follicular regulatory (T_{FR}) cells) have since been discovered and have recently been reviewed[68]. Briefly, T_{FH} cell differentiation is independent of the differentiation of T_H1 cells, T_H2 cells or T_H17 cells[54], and induction of BCL-6 expression and T_{FH} cell differentiation can occur within the first 48 hours of $CD4^+$ T cell priming, by the second cell

division[43,69–71], by dendritic cells or by other myeloid antigen-presenting cells[43,72]. Furthermore, our understanding of the nature of T cell help to B cells has become more refined.

What is T cell help?

'Help' to B cells is not a single product of T_{FH} cells and not even a single process. T cell help to B cells can be divided into seven distinct functions, as illustrated in FIG. 2: proliferation, survival, plasma cell differentiation, somatic hypermutation, class-switch recombination, adhesion and attraction. These seven different forms of help are all contributors to T_{FH} cell–B cell interactions, and each process consists of multiple pathways, with only a minority shown in FIG. 2 for simplicity. Furthermore, some molecules have a role in several different forms of help.

The simplest B cell help function that is provided by T_{FH} cells is the induction of B cell proliferation. CD40L is the most prominent protein expressed by T_{FH} cells that contributes to pro-mitotic signalling in B cells[64]. Survival signals from T_{FH} cells are also crucial, as germinal centre B cells are exquisitely pro-apoptotic[73]. IL-4 produced by T_{FH} cells triggers pro-survival signals to germinal centre B cells via the IL-4 receptor complex[64]. Somatic hypermutation is central to germinal centre biology and the primary purpose of germinal centres is to facilitate affinity maturation of B cells via sequential rounds of immunoglobulin gene mutation and selection[68,74,75]. The enzyme activation-induced cytidine deaminase (AID; which is encoded by *Aicda*) induces the DNA damage in the immunoglobulin genes that is then converted into mutations by DNA repair enzymes[73]. BCL-6 must be co-expressed with AID by the germinal centre B cell to repress the DNA damage response programme that would otherwise trigger self-destruction of the cell[76]. The signals that induce AID and BCL-6 expression by B cells are not entirely defined, but CD40L, IL-4 and IL-21 contribute[77]. Indeed, the combination of CD40L, IL-4 and IL-21 in different ratios seems to be the primary mix of T cell help signals that control B cell proliferation, somatic hypermutation and differentiation. Class-switch recombination can also be induced by instructive signals from T_{FH} cells to B cells. AID is necessary for class-switch recombination, but the specific target of the heavy chain constant region gene recombination depends on additional factors that are selectively activated by different cytokines, which predominantly, but not exclusively, come from $CD4^+$ T cells. Human IgM to IgG class-switch recombination is most efficiently induced by IL-21, whereas IgE recombination is induced by a high IL-4 to IL-21 ratio[78,79].

B cell help crucially depends on cell contact, probably because of a mixture of cell-surface co-stimulatory ligand interactions and directional cytokine production during cognate interactions. Therefore, adhesion molecules expressed by T_{FH} cells and B cells (FIG. 2) are necessary components of T cell help to B cells, as they regulate the overall duration of the '*pas de deux*'. The most dramatic example of this requirement is SAP, which is described above. SAP binds to the intracellular domains of SLAM family surface receptors, which are involved in cell–cell adhesion. In the absence of SAP, the duration of B cell–T cell adhesion is short and inadequate for the T_{FH} cell to provide sufficient help signals to the B cell. This leads to a general defect in SAP-dependent T cell help to B cells and thus a loss of antigen-

specific B cell proliferation and survival, as well as a complete loss of germinal centres and of most memory B cells and long-lived plasma cells[32,57,80].

Finally, chemoattraction is another component of T cell help to B cells (FIG. 2). CXC-chemokine ligand 13 (CXCL13) is the ligand for CXCR5 and human germinal centre T_{FH} cells constitutively secrete copious quantities of CXCL13 (REFS 81,82), which probably recruits B cells to colocalize with the T_{FH} cells and to facilitate confinement of the B cells to the germinal centre. Notably, CXCL13 signalling via CXCR5 also modifies B cell adhesion and lymphotoxin synthesis, which shows that CXCL13 also has cytokine-type functions[83,84]. Thus, chemoattraction is another form of T cell help to B cells.

Conclusions and perspectives

T cell help to B cells is a complex interplay of many factors and processes. Particularly in the germinal centre, many signals (both stimulatory and inhibitory) are exchanged between T_{FH} cells and germinal centre B cells (and other cells in the microenvironment) in an iterative manner, over many rounds of rapid B cell division, mutation and selection. These integrated interactions remain poorly understood at the molecular and temporal levels, as the features of the cells change and the availability of antigen becomes more and more limiting. Furthermore, fundamental gaps remain in defining the signals that induce or that inhibit T_{FH} cell differentiation[68]. Finally, it is important to better understand T_{FH} cells in humans who have been immunized with vaccines to learn how to better boost vaccine responses, and an increased understanding of T_{FH} cells in individuals with autoantibody-associated autoimmune diseases or allergies is important for learning how to ameliorate or how to block these T_{FH} cell responses. There is much to be learned in the next 47 years about T cell help to B cells!

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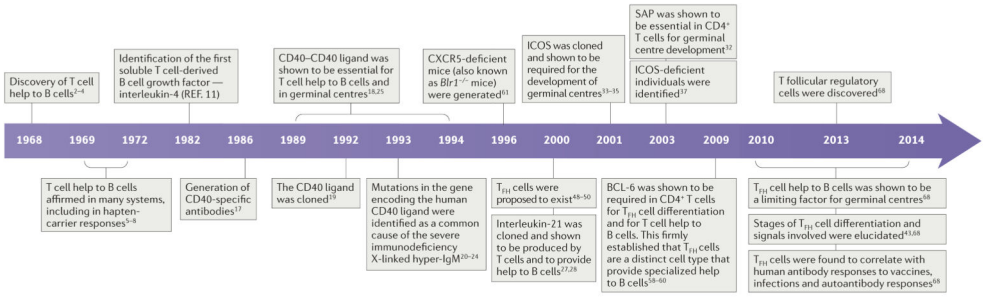

Figure 1. A timeline of discoveries about T cell help to B cells

T cell help to B cells was discovered only a few years after the discovery of B cells. Subsequent discoveries lead to coining of the term T follicular helper (T_{FH}) cells ~30 years later. BCL-6, B cell lymphoma 6; CXCR5, CXC-chemokine receptor 5; ICOS, inducible T cell co-stimulator; SAP, SLAM-associated protein.

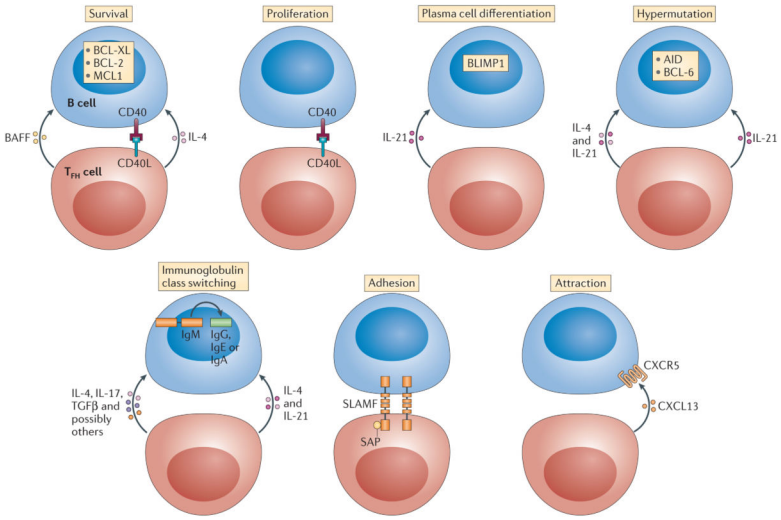

Figure 2. Categories of T cell help to B cells

Help can come in many different forms and can have different consequences for different processes. T follicular helper (T_{FH}) cells provide seven main forms of T cell help to B cells: signals that promote survival, proliferation, plasma cell differentiation, hypermutation, class-switch recombination, adhesion and chemoattraction (cell migration). For simplicity, only a few examples of factors that are important for each process are shown, although many more molecules are involved in the regulation of the processes. Several of these pathways are reviewed in detail elsewhere[64,73,85]. Some molecules have pleiotropic effects, resulting in combinatorial possibilities and functional redundancies between molecules. AID, activation-induced cytidine deaminase; BAFF, B cell-activating factor; BCL, B cell lymphoma; BLIMP1, B lymphocyte-induced maturation protein 1; CD40L, CD40 ligand; CXCL13, CXC-chemokine ligand 13; CXCR5, CXC-chemokine receptor 5; IL, interleukin; MCL1, myeloid cell leukaemia 1; SAP, SLAM-associated protein; SLAMF, signalling lymphocytic activation molecule F; TGFβ, transforming growth factor-β.