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Dendritic Cells and Humoral Immunity in Humans

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Summary

Dendritic cells (DCs) orchestrate the innate and adaptive immune systems to induce tolerance and immunity. DC plasticity and subsets are prominent determinants in the regulation of immune responses. Our recent studies suggest that humoral and cellular immunity is regulated by different myeloid DC subsets with distinct intrinsic properties in humans. While antibody response is preferentially mediated by $CD14^+$ dermal DCs, cytotoxic T cell response is preferentially mediated by Langerhans cells (LCs). Thus, mechanisms whereby DCs induce humoral and cellular immunity appear to be fundamentally distinct. In this review, we will focus on the role of DCs in the development of humoral immunity. We will also discuss the mechanisms whereby DCs induce $CD4^+$ T cells associated with the help of B cell response, including T follicular helper (Tfh) cells, and why human LCs lack this ability.

Introduction

Dendritic cells (DCs) induce/maintain tolerance to self and immunity to non-self by integrating the innate and adaptive immune systems[1, 2]. Generating the right type of immune response can be a matter of life and death. In leprosy, for instance, the tuberculoid form of the disease is characterized by a Type 1 response which keeps the disease in check, while the lepromatous form induces an often fatal Type 2 response[3].

DCs are endowed with enormous functional plasticity, which permits them to induce different immune responses according to the microenvironment. In addition, The DC system is composed of subsets associated with the induction of different types of immunity. We have recently demonstrated that two myeloid DC subsets in human skin, i.e., Langerhans cells (LCs) and $CD14^+$ dermal DCs, are engaged in the induction of different types of adaptive immunity[4]. While LCs are very efficient at inducing CTL responses, $CD14^+$ dermal DCs display a unique property to promote the development of antibody responses (Fig. 1). In this review, we will briefly summarize the phenotypical and functional differences between human LCs and $CD14^+$ dermal DCs, and discuss how human DCs are involved in the regulation of humoral responses.

Epidermal LCs and $CD14^+$ dermal DCs

Human skin hosts at least three different mDC subsets. $CD1a^{high}CD14^-HLA\text{-}DR^+$ Langerhans cells (LCs) reside in epidermis, while $CD1a^{dim}CD14^-HLA\text{-}DR^+$ DCs ($CD1a^+$ dermal DCs) and $CD1a^-CD14^+HLA\text{-}DR^+$ DCs ($CD14^+$ dermal DCs) are present in dermis [4]. $CD14^+$ dermal

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DCs express CD163 and FXIIIa, which are also expressed by dermal macrophages. However, $CD14^+$ dermal DCs express CD11c, while dermal macrophages do not[5].

$CD14^+$ dermal DCs express a broad spectrum of surface C-type lectins including DC-SIGN, DEC-205, LOX-1, CLEC-6, Dectin-1, and DCIR[6]. In contrast, LCs express a more limited set, including Langerin and DCIR. Neither of the two dermal DC subsets express Langerin, an observation that contrasts with the presence of $Langerin^+$ dermal DCs in mice[7-9]. $CD14^+$ dermal DCs also express multiple TLRs recognizing bacterial components, such as toll like receptor (TLR)1, 2, 4, 5, 6, 8, and 106, 10, suggesting their involvement in the induction of anti-bacterial immunity. LCs have been reported to express TLR1, 2, 3, 6, (7) and 1010-12, and to respond to ligands of TLR2 (peptideglycan11 and Pam3CysSerLys4 (Pam3CSK4)13) or TLR3 (Poly I:C11, 12). In contrast, a study showed that LCs poorly respond to TLR-ligands derived from bacteria, including TLR2, TLR4, and TLR510. Our microarray studies using of highly purified LCs failed to show much TLR expression6, while $CD14^+$ dermal DCs showed significant expression.

LCs promote CTL responses

Human LCs are remarkable at inducing CTL responses in vitro. For example, upon loading with tumor-derived peptides, LCs effectively prime peptide-specific naïve $CD8^+$ T cells, and induce their differentiation into CTLs that express high levels of cytotoxic molecules and are accordingly efficient at killing tumor cells[4]. Notably, induction of CTL response by LCs does not appear to be dependent on IL-12 or IFN-α, as neither CD40 nor TLR stimulation do not induce LCs to secrete these cytokines[4, 11, 12, 14]. Instead, CD40-stimulation induces LCs to secrete IL-15[4, 14], which we surmise responsible for their capacity to induce potent CTL responses. This hypothesis is partly supported by the observation that externally added IL-15 enhances the ability of $CD14^+$ dermal DCs to develop CTLs with high levels of cytotoxic granules[6].

LCs also induce a potent proliferation of allogeneic naïve $CD4^+$ T cells. Naïve $CD4^+$ T cells primed by LCs secrete larger amounts of Type 2 cytokines than those primed by two dermal DCs[4]. A recent report showed that human LCs also promote the development of IL-22-secreting $CD4^+$ T cells, which do not co-express Th1, Th2 or Th17 cytokines[15]. Interestingly, IFN-γ-secreting $CD4^+$ T cells are induced at a similar level by LCs and other dermal DC subsets. However, the developmental mechanism of Th1 cells induced by these DC subsets appears be distinct. Consistent with their inability to secrete IL-12, induction of Th1 cells by epidermal LCs was shown to be independent of IL-12 or IL-23[12]. Considering the potent capacity of LCs to induce CTL responses, such Th1 cells primed by LCs might be efficient helpers for the development of CTL responses.

Role of plasmacytoid DCs in antibody response

In vitro studies with plasmacytoid DCs (pDCs) isolated from human blood and tonsils demonstrate that pDCs are also directly involved in the help B cell responses. Upon stimulation with influenza virus, pDCs promote the differentiation of memory B cells towards antibody-secreting plasma cells through sequential steps. Type I intereferon secreted by pDCs promotes the differentiation of CD40-stimulated B cells into non-antibody-secreting plasmablast. Similar to mDCs, IL-6 secreted by pDCs further induces the transition of non-secreting plasmablasts into antibody-secreting plasma cells[16]. pDCs activated with TLR9 ligand are also capable of inducing TLR9-triggered naïve B cells to differentiate into IgM-producing plasma cells17.

pDCs also contributes to the humoral immunity through cross-talk with mDCs. Type I IFN secreted by pDCs induces mDCs and monocytes to express BAFF and APRIL[18], which

promotes B cell survival, proliferation, and class-switching[19]. Furthermore, a mouse study showed that mDCs exposed to Type I IFN in vivo promote the differentiation of naïve $CD4^+$ T cells towards helper $CD4^+$ T cells which promote antibody responses [20], i.e., T follicular helper (Tfh) cells.

$CD14^+$ dermal DCs directly promote plasma cell development via IL-12

A decade ago, in vitro studies with $CD14^+$ DCs generated from $CD34^+$ hematopoietic precursor cells have shown that $CD14^+$ DCs induce the differentiation of CD40-activated naïve B cells into IgM-producing plasma cells through direct interactions[21]. In contrast LCs, both in vitro-generated and ex-vivo isolated, lacked this capacity[21, 22]. Mechanistic studies revealed that IL-12 secreted by $CD14^+$ DCs is critical for the first step of plasma cell differentiation. Co-operation of IL-12 and IL-6 further induces transition from a non-secreting plasmablast to IgM-producing plasma cells[23]. Indeed, $CD14^+$ DCs, both in vitro-generated and skin-derived, secrete multiple proinflammatory cytokines such as IL-1β, IL-6, IL-10, IL-12, TNFα and GM-CSF in response to stimulation through CD40, while LCs do not[4, 11, 12], Thus, the lack of secretion of IL-12 and IL-6 appears to explain the inability of LCs to help naïve B cells through direct interactions.

$CD14^+$ dermal DCs induces development of helper T cells

$CD14^+$ dermal DCs also promote antibody responses indirectly through skewed differentiation of naïve $CD4^+$ T cells. Both in vitro-generated $CD14^+$ DCs and skin-derived $CD14^+$ dermal DCs induce naïve $CD4^+$ T cells to differentiate into effectors capable of helping B cell responses. There, $CD4^+$ T cells primed by $CD14^+$ dermal DCs are efficient at inducing naïve B cells to become antibody secreting plasma cells producing IgM, as well as to switch isotypes towards IgG and IgA[4]. In contrast, in spite of Th2 cytokine secretion, $CD4^+$ T cells primed by LCs lack the capacity to induce B cells to differentiate into antibody-secreting cells. These observations indicate that $CD4^+$ T cells primed by LCs or $CD14^+$ dermal DCs functionally differ in their ability to help B cells.

$CD4^+$ T cells associated with B cell help

The requirement of T cell help in the development of antibody responses was first described in 1960s[24]. $CD4^+$ T cells were found to be necessary to develop germinal centers (GCs), a discrete structure in secondary lymphoid organs where selection of high-affinity B cells and development of B cell memory occur[25, 26]. In vitro studies in 80s, mostly using $CD4^+$ T cell clones and recombinant cytokines, had concluded that Th2 is the major Th subset engaged in the help of B cells, through the secretion of IL-4 and IL-10[27, 28]. Recent extensive studies on $CD4^+$ T cells present in GCs in mice and humans have established a novel Th subset, named T helper follicular (Tfh) cells, representing $CD4^+$ T cells specialized for the help of humoral responses[29-32]. Tfh cells express the chemokine (C-X-C motif) receptor 5 (CXCR5) [29, 33, 34, which drives their migration into B cell follicle, as the ligand, CXCL13, is produced by follicular stromal cells including follicular DCs 35, 36]. Several factors have been identified to be essential for Tfh cells to provide help to B cells. These include surface molecules such as CD40 ligand (CD40L) [27] and ICOS 37. In particular, Tfh cells secrete the cytokine IL-21 [33, 38, which drives the growth, differentiation, and isotype switching of B cells [39, 40]. Tfh cells secrete larger amounts of IL-21 than other conventional Th subsets, including Th1, Th2, and Th17 cells.

Human DCs induce IL-21-producing helper $CD4^+$ T cells via IL-12

In mice, IL-21 itself is critically involved in the generation of Tfh cells[41, 42]. IL-21 provides a positive feedback loop to $CD4^+$ T cells and induces human [43] and mouse [41, 42, 44-47] naïve

$CD4^+$ T cells to secrete more IL-21. However, as naïve $CD4^+$ T cells or DCs do not secrete IL-21, IL-21-producing $CD4^+$ T cells need to be induced through interaction with DCs. In mouse, IL-6 derived from DCs appears to be the major cytokine involved in the induction of mouse $CD4^+$ T cells to secrete IL-21 [20, 44, 48, 49]. In contrast, in humans, we and others showed that IL-12 is the major cytokine by which DCs promote the development of IL-21-producing $CD4^+$ T cells[50, 51]. Similar to Tfh cells[52], $CD4^+$ T cells induced by activated human DCs help B cell responses through IL-21[50]. IL-12 is the most potent DC-derived cytokine at inducing naïve human $CD4^+$ T cells to become IL-21^+ $CD4^+$ T cells[50]. Consistently, activated DCs induce IL-21-producing helper $CD4^+$ T cells via IL-12, as blocking IL-12 during DC-T coculture potently inhibit their development[50]. The induction of IL-21^+CD4^+ T cells by DCs might represent the first key step in the development of human Tfh cells. Alternatively, the induced IL-21-producing helper $CD4^+$ T cells might be also associated with plasma cell differentiation at extrafollicular sites.

Notably, human naïve $CD4^+$ T cells stimulated with activated DCs differentiate into two different types of IL-21^+CD4^+ T cells: IFN-γ^+IL-21^+ Th1 cells expressing T-bet, and IFN-γ^-IL-21^+ non-Th1 cells. Both IL-21^+CD4^+ T cells are dependent on signal transducers and activator of transcription (STAT)4 for their development by IL-12. IL-21 and IL-23 also contribute to the development of IL-21^+CD4^+ T cells, but at a much lesser extent. IL-21 and IL-23 induce the development of IFN-γ^-IL-21^+ non-Th1 cells in a manner dependent on STAT3[50] (Fig. 2). Thus, in humans, both STAT4 and STAT3 pathways contribute to the development of IL-21^+CD4^+ T cells. DCs regulate the balance of IFN-γ^+IL-21^+ Th1 cells and IFN-γ^-IL-21^+ non-Th1 cells through multiple pathways. For example, naïve $CD4^+$ T cells primed in the presence of IL-12 and IL-23 promote the development of IFN-γ^-IL-21^+ non-Th1 cells (Schmitt et al. Unpublished observation). Whether which types of IL-21+CD4+ T cells, IFN-γ^+IL-21^+ Th1 cells or IFN-γ^-IL-21^+ non-Th1 cells, display more potent capacity to help B cells is under investigation.

Distinct immune-modulatory capacity of IL-12 between mice and humans

Of note, the IL-12-IL-21 axis for helper T cell development does not appear to be operate in the mouse immune system, as IL-12 does not induce mouse naïve $CD4^+$ T cells to secrete IL-21. Conversely, IL-6, a potent inducer of IL-21 in mouse $CD4^+$ T cells, does not induce IL-21 expression in human naïve $CD4^+$ T cells[50]. Thus, DC subsets and their activation paths involved in the development of IL-21^+CD4^+ T cells might differ between mice and humans. Accordingly, the in vivo biological effect of IL-12 might also differ between mice and humans. Mouse studies have demonstrated that IL-12, when administered as vaccine adjuvant, enhances the development of tumor-specific CTL and Th1 responses in vivo[53, 54]. In humans, the systemic administration of IL-12 has thus far shown only very modest clinical efficacy[55, 56]. The injection of IL-12 into tumor sites of head and neck cancer patients resulted in the activation of B cells in the draining lymph nodes[57]. Thus, IL-12 and adjuvants that promote the secretion of IL-12 might improve vaccines aimed at induction of neutralizing antibodies in humans.

Taken together, IL-12, a cytokine traditionally viewed as a potent inducer of Type 1 response, also contributes to humoral responses in humans. It acts through two independent paths: a direct path in DC-B cell interaction, and an indirect path through DC-T cell interaction by developing IL-21^+ helper $CD4^+$ T cells (Fig. 3). These two paths might act simultaneously in vivo, through the “ménage à trois” formation of antigen-presenting DCs with antigen-specific T cells and B cells at extrafollicular sites, as recently illustrated through in vivo imaging in mice[58, 59].

Role of DCs in the development of Tfh cells

Tfh cells express the transcription factor, B cell lymphoma 6 (Bcl-6)[60], which is essential for the development of germinal center B cells 61› 62. Recent mouse studies indicated that Bcl-6 is necessary and sufficient for the development of Tfh cells in vivo63-[65]. On the contrary, Blimp-1, a transcription factor repressing the function of Bcl-6, inhibits the generation of Tfh cells[65]. Furthermore, down regulation of Blimp-1 in $CD4^+$ T cells promotes their differentiation into Tfh cells. Thus, development of Tfh cells is reciprocally regulated through two transcription factors, Bcl-6 and Blimp-1. However, Bcl-6 does not regulate IL-21 secretion in mouse $CD4^+$ T cells[64, 65], in contrast to other transcription factors engaged in the differentiation of other Th subsets, Th1, Th2, and Th17 cells, regulating the secretion of cytokines typical of each subset. How Bcl-6 expression leads to the generation of Tfh cells remains to be established.

Another key question is when and how naïve $CD4^+$ T cells primed by DCs regulate the expression of Bcl-6 and Blimp-1, and commit to the Tfh developmental pathway. Differentiation of naïve $CD4^+$ T cells towards other conventional Th subsets is mainly regulated by the signals that they receive from DCs during cognate interactions. If the generation of Tfh cells shares the same mechanism, which signals from DCs favor the upregulation of Bcl-6 in naïve $CD4^+$ T cells rather than transcription factors associated with other Th subsets? Cytokines inducing IL-21 in $CD4^+$ T cells, i.e., IL-6 in mice[64] and IL-12 in humans[51, 66], have been shown to upregulate Bcl-6 mRNA expression in activated naïve $CD4^+$ T cells. However, as the induction of Bcl-6 mRNA by these cytokines appears to be transient, other factors derived from DCs might be involved in the regulation of Bcl-6 expression. It is also possible that acquisition of IL-21-producing ability and expression of Bcl-6 are regulated through independent processes, but not consequent events.

Alternatively, $CD4^+$ T cells primed by DCs might regulate the expression of Bcl-6 and Blimp-1 after they encounter with B cells. Mouse studies showed that interaction of primed $CD4^+$ T cells and B cells is essential for the development of Tfh cells in vivo[65, 67]. Furthermore, mouse $CD4^+$ T cells deficient of the expression of SAP do not differentiate into Tfh cells in vivo, due to the lack of stable interaction with B cells[68]. This mechanism might also operate in humans, as SAP deficiency results in human X-linked lympho-proliferative disease, where GC formation and humoral immunity is profoundly impaired[69, 70]. Thus, the major role of DCs in the development of Tfh cells might be the induction of Tfh precursors capable of forming long-lasting interaction with antigen-presenting B cells. There, the location of migratory sites of DCs in secondary lymphoid organs will be critical. Notably, mouse studies showed that dermal DCs upon activation migrate into the outer paracortex just beneath the B cell follicles, whereas LCs migrate into the T cell rich inner paracortex[71] (Fig. 1). This observation further supports that dermal DCs, rather than LCs, are the major DC subset associated with the development of humoral immunity.

Future directions

Considerable progresses in the knowledge of human DC biology clearly open the avenues for development of novel strategies in clinical interventions. The capacity of LCs and $CD14^+$ dermal DCs to preferentially prime cellular immunity and humoral immunity respectively has significant implications, most particularly in the context of novel human vaccines. Targeting LCs will be important for the design of vaccines that aim at eliciting strong CTL responses, while targeting $CD14^+$ dermal DCs will be optimal to induce strong antibody responses.

Understanding the role of DCs in the regulation of humoral immunity is an underdeveloped research area. Further phenotypical and functional characterization of Tfh cells and their precursors will provide a fertile ground to understand how DCs regulate antibody responses

through their development. Of note, Tfh cells appear to be composed of subsets secreting different sets of cytokines[72-76], which differentially regulate isotype-switching of B cells. Subsets within Tfh cells are also present in humans (Morita et al. Unpublished observations). Accordingly, DCs stimulated through different paths might induce different Tfh subsets. Establishing the mechanisms whereby the DC system induces Tfh cells with different functions will facilitate the design of novel vaccines. In particular, establishing how DC system generates Tfh subsets associated with the induction of mucosal homing plasma cells will provide a significant insight in the development of novel mucosal vaccines.

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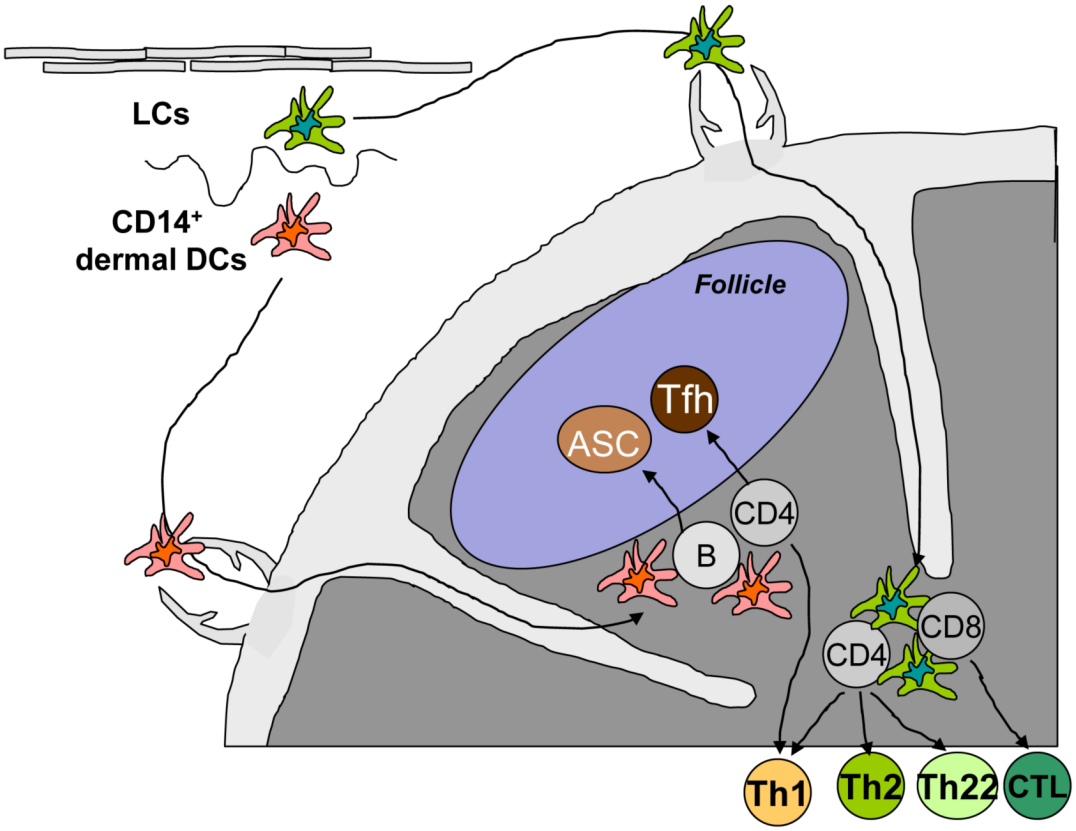

Figure 1. CD14$^+$ dermal DCs preferentially induce humoral immunity, while Langerhans cells induce cellular immunity

Upon activation, epidermal LCs and CD14$^+$ dermal DCs migrate to the secondary lymphoid organs through afferent lymphatics. Dermal DCs migrate into the outer paracortex, just beneath the B cell follicles, whereas LCs migrate into the T cell rich area. LCs are efficient at inducing high avidity-cytotoxic CD8$^+$ T cell and Th1, Th2, and Th22 responses. In contrast, CD14$^+$ dermal DCs are efficient at inducing the differentiation of naïve B cells into antibody-secreting cells (ASC) and at promoting the development of T follicular helper (Tfh) cells. CD4$^+$ T cells primed by LCs might be efficient at helping the development of CTL responses.

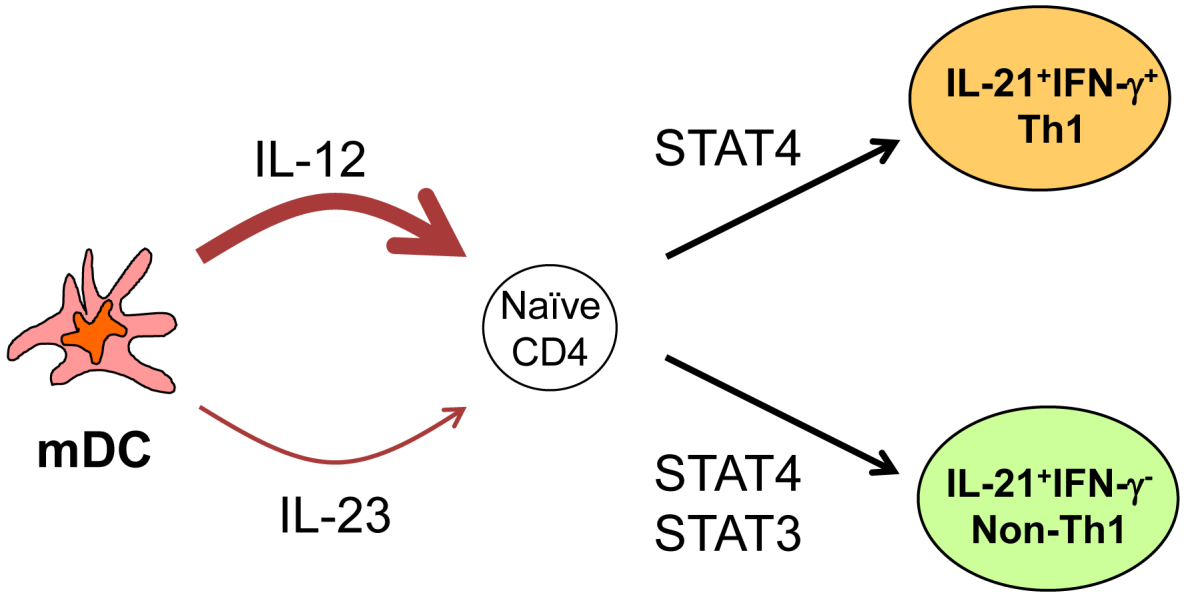

Figure 2. Human activated DCs induce IL-21-producing T follicular helper (Tfh)-like cells via IL-12

IL-12 induces human naïve $CD4^+$ T cells to differentiate into two different types of IL-21-producing $CD4^+$ T cells: IFN-γ^+IL-21^+ Th1 cells expressing T-bet, and IFN-γ^-IL-21^+ non-Th1 cells. Both IL-21-producing $CD4^+$ T cells develop in a manner dependent on STAT4. IL-23 induces only IFN-γ^-IL-21^+ non-Th1 cells through STAT3. The induction of IFN-γ^-IL-21^+ non-Th1 cells by IL-12 appears to be partially dependent on STAT3 as well.

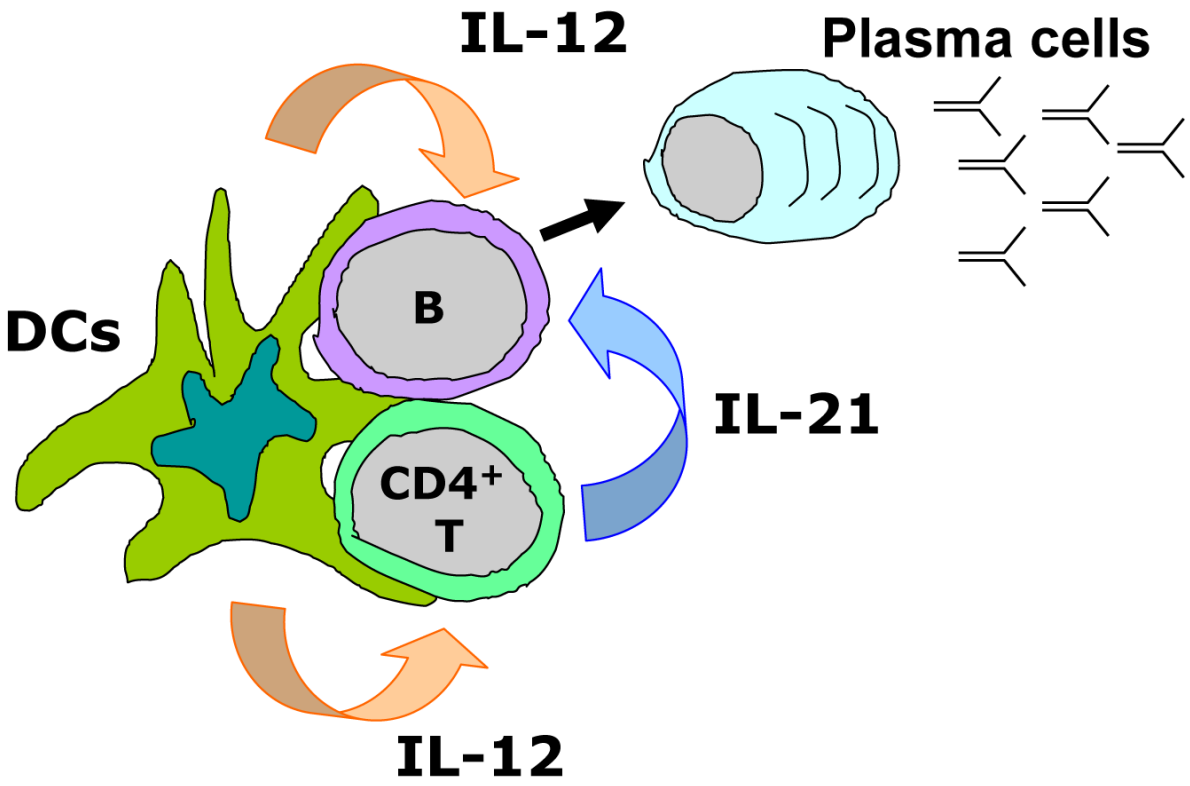

Figure 3. Possible involvement of IL-12 secreted from DCs in the development of antibody responses during DC-T cell-B cell "ménage à trois" complex

When DCs form the complex with T cells and B cells at extrafollicular sites, IL-12 derived from activated DCs promotes B cells to differentiate into antibody-secreting cells (ASCs) by two different paths: a direct path via DC-B interaction, and an indirect path through induction of IL-21-producing helper cells.