# Follicular Dendritic Cells (B Lymphocyte Stimulating)

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**Introductory article**

**Article Contents**



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Follicular dendritic cells (FDCs) are unique immune system cells that contribute to the maintenance of humoral (i.e. antibody) immune responses. These cells are located in the follicles of secondary lymphoid tissues (e.g. lymph nodes and spleen), where they trap and retain antigens in the form of highly immunogenic immune complexes (ICs). FDC-ICs are composed of antigen plus specific antibody and/or complement proteins. These trapped antigens, combined with other soluble and membrane-bound signals contributed by FDCs, are essential to the development and maintenance of the germinal centre reaction and IgG and IgE responses respectively. FDCs also appear to contribute to initial IgM responses. In addition to their positive effects on humoral immunity, FDCs may promote diseases including HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome), prion diseases and follicular lymphomas. A better understanding of FDCs should permit better regulation of antibody responses and may also allow the amelioration of some disease states.

## Introduction

Antigen (Ag) persists on cells within the follicles of secondary lymphoid organs (e.g. lymph nodes and spleen) for years after Ag challenge. These Ag-retaining cells are called follicular dendritic cells (FDCs) because of their follicular location and dendritic morphology. The characteristics that distinguish FDCs from other cells of the immune system are their ability to retain Ag-Antibody (Ab) complexes (i.e. immune complexes [ICs]) long-term on their surfaces and their follicular localization. Unlike other immune accessory cells, FDCs lack phagocytic activity, lysosomes, lysozyme and Birbeck granules. A number of monoclonal Abs are available that selectively recognize FDCs and these Abs are useful in the enrichment of these cells. The monoclonal Abs DRC-1, HJ2 and KiM4 recognize human FDCs, whereas FDC-M1 and FDC-M2 recognize murine FDCs.

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## FDC Morphology

Studies of FDCs using light and electron microscopy (EM) have revealed structural details that help clarify FDC functions. As illustrated, FDCs are slightly larger than lymphocytes and possess many fine dendritic processes. These dendrites extend and intimately interact with neighbouring cells, creating a unique microenvironment. This intimate interaction with surrounding lymphocytes appears to be important for FDCs to provide potent Ag-dependent and Ag-independent signals that promote humoral immune responses (**Figure 1**).

EM revealed that FDCs have irregular, sometimes bilobed, euchromatic nuclei (sometimes there are multiple nuclei) containing distinct nucleoli. FDCs possess a scanty cytoplasm with few mitochondria, a rough endoplasmic reticulum, a Golgi apparatus and vesicles. The dendritic processes of FDCs appear in two general forms: some are attenuated, with folds and intermittent thickenings that form a variety of differently shaped cytoplasmic extensions, while others form more uniform, highly convoluted,

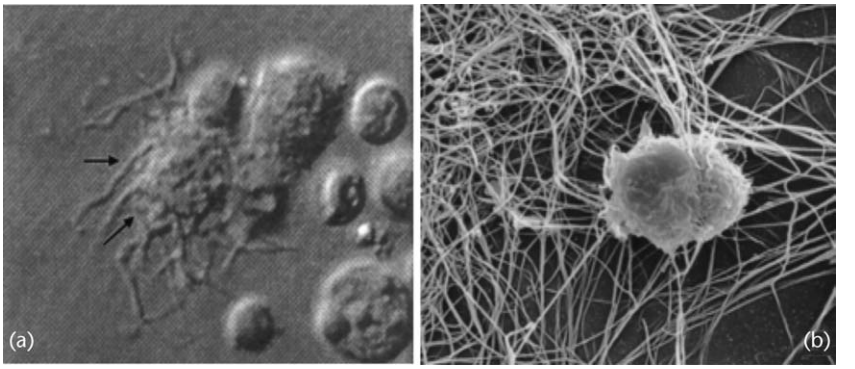


**Figure 1** Light and electron micrographs of isolated FDCs. (a) Light micrograph of an FDC in suspension. Note the long dendritic processes emanating from the cell body. These processes allow intimate interactions with surrounding lymphocytes. The arrows indicate an FDC. (b) Scanning electron micrograph of an isolated FDC cultured on collagen type 1 illustrating the extensive dendritic networks generated *in vitro*. This micrograph was contributed by Dr. Andras K Szakal, Richmond, VA. It can also be viewed at: http://commons.wikimedia.org/wiki/File:Follicular_dendritic_cell.jpg

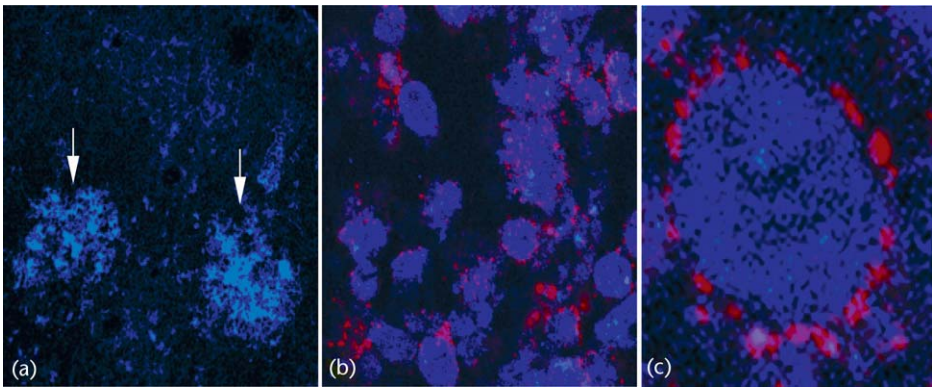


**Figure 2** FDCs trapping fluorescently labelled ICs *in vivo* and *in vitro*. (a) Photomicrograph of FDCs *in vivo* demonstrating trapping of ovalbumin ICs (ovalbumin+anti-ovalbumin). The ICs on FDCs are detected using goat antibody directed against the anti-ovalbumin present in the immune complexes (i.e. goat-anti-IgG [blue]). The arrows designate two FDC networks containing trapped fluorescent ICs. (b) FDC-trapping of fluorescent antigen *in vitro*. Ovalbumin ICs were incubated with highly enriched FDCs in culture. Detection of the FDC-trapped antigen is performed using goat, antibody specific for the IgG in the ovalbumin–anti-ovalbumin complexes (red) and the FDCs are labelled using FDC-M1 (blue). (c) Higher magnification of an isolated FDC with ICs labelled as in panel b.

labyrinthine configurations. These dendritic processes interdigitate with one another and form a vast network or reticulum on which ICs are trapped. This trapping can be clearly visualized using fluorescently labelled Abs (**Figure 2**).

Two morphological types of FDCs have been identified with scanning EM: one having filiform or finger-like processes, and one with 'beaded' dendrites. Intermediate forms have also been observed, suggesting that one form may 'mature' into the other. The transition from one form of FDC into another appears to be related to the formation of a specialized Ag-delivery system. The resulting 'beads' are called 'iccosomes' to denote that they consist of immune complex-coated bodies or 'somes'.

## Phylogeny and Development

Information available on FDCs is based primarily on studies using humans and rodents. However, FDCs are present and functional in birds and if FDCs are defined broadly as cells with the ability to trap and retain ICs, they appear to exist in all jawed vertebrates, including amphibians, reptiles and fish. The origin of FDCs remains unclear. FDCs are radiation resistant making it difficult to study development using adoptive transfer models. At present there are some data supporting a haematopoietic origin while even more data support a stromal cell origin.

## Immunoregulatory Mechanisms Involving FDCs

### IC trapping, periodicity and iccosomes in the germinal centre (GC) reaction

In primary Ab responses to thymic dependent (TD) Ags, ICs form as soon as Ab is produced and, by four days after Ag challenge, ICs may be found on splenic FDCs. The

kinetics of recall responses are dramatic. Ags are almost instantaneously converted into ICs by Ab persisting from prior immunization and by one min after challenge, labelled Ags can be detected on cells in a 'chain' transporting ICs to FDCs deeper in the lymph node cortex. IC retention is localized and Ag injection into a single limb of an immune mouse will be restricted to the draining lymph nodes and to a lesser extent to the spleen. With time, FDC-Ag becomes more and more focused to lymph nodes nearest the site of Ag injection and by one year, persisting Ag and specific Ab-forming cells are almost exclusively confined to the most proximal lymph node.

FDCs trap ICs in a periodic manner, a phenomenon that was discovered using scanning EM with Ag trapped *in vivo*, revealing an orderly, spiralling, arrangement of ICs made up of alternating light and dark bands. The same periodicity was observed in recent *in vitro* studies where ICs were arranged on FDCs with a 200–500 Å spacing between epitopes. This spacing correlates with the 95–675 Å spacing originally described by Dintzis as optimal for B-cell receptor for Ag (BCR) cross-linking and activation in thymic independent (TI) Ab responses.

FDC receptors specific for the Fc fragment of immunoglobulins (IgG and IgE) and complement fragments are used to trap Ag in ICs. Trapping of ICs by phagocytic cells is mediated by similar receptors, yet, these ICs are rapidly degraded. In contrast, FDC-Ags in ICs persist and these can be detected in lymphoid follicles for over a year. FDC-Ags persist in picogram quantities and are maintained in their native or 'unprocessed' form. Remarkably, once Ags are trapped on FDCs, they remain relatively unaffected by a variety of manipulations including gamma-irradiation, stress and treatment with a number of anticancer drugs. However, injection of cortisone acetate results in the loss of a significant portion of persisting Ag (although the reason for this remains unclear).

Interestingly, requirements for Ag trapping by FDCs vary with respect to the secondary lymphoid organ involved. FDCs in the spleen trap Ags via complement fragments and trapping is markedly decreased in the absence of complement. Furthermore, gamma-irradiation (400 rad) inhibits IC trapping in the spleen. In marked contrast, Ag trapping on FDCs in lymph nodes can occur in the absence of complement and even after a high dose of gamma-irradiation (1800 rad). The reasons for these differences are not clear, but suggest heterogeneity in Ag transport mechanisms or in FDC populations.

## Delivery of primary and secondary signals to B cells in TD GC responses

### FDCs and presentation of TD Ags to B cells

FDCs retain Ags for very long periods, and serve as a repository to help maintain TD B-cell responses associated with GCs. Antigens retained on FDCs are delivered to B cells in the form of iccosomes, which are highly immunogenic. Iccosomes are readily endocytosed by GC B cells, which process the Ag and present it to T cells. Finally, the T cells respond by generating cytokines that stimulate B-cell proliferation and differentiation.

### FDC contributions to Ag presentation

Since FDC-trapped Ags are ICs, and ICs are poorly immunogenic, an interesting paradox arises. In secondary responses, Ags are rapidly converted into ICs and one might predict that it would require high Ag doses to induce good Ab responses. However, potent recall responses may be induced with minute quantities of Ag, suggesting that Ags trapped as ICs on FDCs are highly immunogenic. In fact, picogram quantities of FDC-Ag may induce microgram levels of specific Ab *in vivo*. The features of FDC-associated Ags that may contribute to this remarkable immunogenicity are discussed below and diagrammed in **Figure 3**.

#### Ag-dependent contributions

It has been reported that Ags with epitopes periodically arranged between 120 and 670 Å apart are optimal for B-cell stimulation, and FDC-Ag has an average periodicity of approximately 350 Å. In addition, FDCs "display" Ags even in the presence of high levels of specific Ab. This is striking because high concentrations of Ab might be expected to 'mask' epitopes and thus block successful Ag presentation. However, B cells cluster with FDCs forming a synapse at the point of FDC-B cell contact and Ag-specific B cells recognize FDC-Ag via their BCRs in the synapse even in the presence of high levels of Ab in the environment.

#### Ag-independent contributions

In addition to specific Ag, FDCs provide secondary signals that enhance the activation/proliferation of B cells. This occurs via soluble and/or membrane-bound molecules including C4-binding protein (C4BP), CD21L, IL-6 and B-cell-activating factor of the tumour necrosis factor (TNF) family (BAFF). These and other molecules that promote FDC–B cell interactions are described in **Table 1**.

## Delivery of primary and secondary signals in T independent B-cell activation

The ability of FDCs to convert TD Ags into TI Ags was recently reported. TD-Ags in ICs on FDCs are spaced 200–500 Å apart, which is consistent with the recurring epitopes 95–675 Å apart on the flexible backbone of TI type-2 (TI-2) Ags. Moreover, FDCs provide BAFF and C4BP, which are known to support TI B-cell activation. Nude (athymic) mice challenged with ICs produce specific IgM in 48 h, while challenge with free Ag in adjuvant fails to induce IgM even after many weeks. Moreover, the draining lymph nodes of IC-challenged nude mice exhibit well-developed GCs associated with FDC Ag retaining reticula and plasmablasts within 48 h. In contrast, no GCs or plasmablasts develop in Ag immunized nude mouse controls. Normal mice challenged with Ag in adjuvant induce detectible IgM

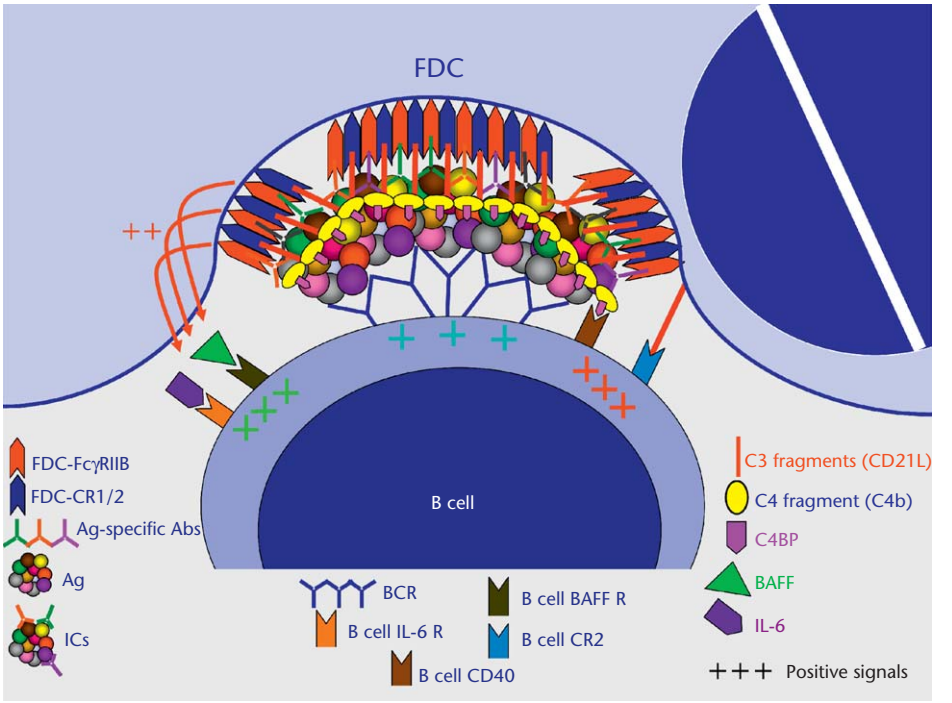


**Figure 3** Important FDC-membrane associated signalling molecules. In experimental animals with specific Abs, ICs form instantaneously upon Ag challenge and are trapped by FDC-FcγRIIB and CR1/2. The engagement of FDC-FcγRIIB with ICs, provides signals to FDCs that result in the production of BAFF and IL-6. These same ICs also activate complement and generate C3 and C4 fragments that are covalently bound to FDC-ICs and can also be seen 'decorating' the FDC membranes. C3 fragments (CD21 ligand) engage FDC-CR1/2, whereas C4BP binds C4b and localizes on the FDC-ICs. The periodically arranged FDC-ICs engage BCRs, and extensive BCR cross-linking delivers an Ag-specific stimulatory signal. FDC-CD21-ligand binds B cell CD21, FDC-C4BP ligates B cell CD40, FDC-BAFF engages B cell BAFF-R and FDC IL-6 binds B cell IL-6R delivering additional co-stimulatory signals that promote B-cell activation, proliferation and differentiation.

in 4 days, but normal mice challenged with ICs produce specific IgM in just 48 h. These *in vivo* studies are supported by *in vitro* experiments where highly purified IC-bearing FDCs and naïve B cells from humans or mice were co-cultured in the absence of T cells or T-cell factors. B cells stimulated with IC-bearing FDCs in these cultures produce specific IgM in 48 h whereas no response is observed when ICs are replaced with free Ag. Both the kinetics of the response and the IgM production are consistent with TI responses.

The ability to induce FDC-dependent, TI IgM responses may have practical application. IgM is the first class of antibodies produced during primary Ab responses and it plays important roles in host protection. We reason that individuals who fail to respond to a vaccine, as a consequence of problems with Ag-presenting cells or the effect of T regulatory cells, should mount rapid specific IgM responses when immunized with appropriate ICs. The ICs should be trapped on FDCs and bypass limitations imposed by major histocompatibility complex Ags and T cells. Similarly, specific IgM responses should be inducible in animals or people with congenital and/or acquired T cell insufficiencies including human immunodeficiency virus (HIV) infected, aged, diabetic, uremic and neonatal subjects. Major FDC-molecules (receptors, cytokines, chemokines, etc.) with known functions are listed in **Table 1**.

**See also**: Major Histocompatibility Complex (MHC)

## Consequences of FDC-activation and FDC-deficits (e.g. in the Elderly) on Humoral Responses

### FDC-activation

FDC-phenotypes in primary and secondary lymphoid follicles are very different. In secondary follicles (i.e. germinal centres), FDCs bear high levels of FcγRIIB (Fc gamma receptor IIB), ICAM-1 (intercellular adhesion molecule 1 (CD54)) and VCAM-1 (vascular cell adhesion molecule 1), which are involved in converting poorly immunogenic ICs into a highly immunogenic form as well as facilitating FDC–B cell interactions. In contrast, FDC–FcγRIIB, FDC–ICAM-1 and FDC–VCAM-1 levels are low and difficult to detect in primary follicles. Expression of FDC accessory molecules is subject to regulation, and engagement of ICs, toll-like receptor (TLR) ligands or collagen type 1 induces FDC activation and upregulation of these accessory molecules. Similarly, FDC-FCγRIIB-mediated

**Table 1** FDC Immuno-regulatory molecules

| FDC molecules | Immunoregulatory role |
|---|---|
| FcγRIIB (CD32) | 1. *Conversion of poorly immunogenic ICs into a highly immunogenic form*: FDCs express high levels of FcγRs relative to GC B cells and these receptors bind immunoglobulin-Fc in ICs and minimize binding to B cell FcγRIIB. Thus, cross-linking of BCR and B cell-FcγRIIB via ICs is minimized, ITIM signalling is reduced and B cells are productively signalled<br>2. *FDC activation*: Both wild-type (WT) and FcγRIIB$^{-/-}$ mice trap ICs but only WT mice respond to ICs by upregulating FcγRIIB, ICAM-1 and VCAM-1. Similarly, blockade of FDC-FcγRIIB results in inhibition of IC-induced FDC-IL-6 and FDC–BAFF production indicating the importance of FDC-FcγRIIB in FDC activation and cytokine production<br>3. *IC periodicity*: In the absence of complement, ICs are trapped by FDC-FcRs and are periodically arranged on FDC dendrites. ICs trapped via complement receptors do not induce the B-cell activation characteristic of periodically arranged Ags<br>4. *Long term IC retention*: Complement-mediated IC trapping in the draining lymph nodes of FcγRIIB$^{-/-}$ mice is normal. However, long-term retention of ICs is reduced in FcγRIIB$^{-/-}$ mice suggesting the importance of this receptor in the long-term retention of ICs<br>5. *Regulation of serum IgG levels*: High IgG levels feedback on Ag retained on FDC dendrites and 'zip' them together thus hiding the ICs within 'ball-of-yarn'-like dendritic convolutions. When Ab levels decline, Ab dissociates from Ag-epitopes, the dendrites unravel and the persisting Ag is exposed to memory B cells. This exposure initiates a rebound in Ab and memory B-cell production, thereby maintaining humoral immunity |
| FcεRII (CD23) | *Immune complex retention and regulation of IgE levels*: Serum IgE is suppressed in CD23 transgenic (Tg) mice where FDC-CD23 and B cell-CD23 are elevated. Adoptive transfer studies indicated that IgE production is suppressed when normal lymphocytes are used to reconstitute Tg mice with high levels of FDC-CD23. Furthermore, isolated Tg-FDCs augment IgG production normally but IgE production is reduced suggesting that a high level of FDC-CD23 selectively suppresses IgE |
| Fcα/μR | *Immune complex retention*: In humans FDCs are the predominant cell type expressing Fcα/μR. This Fc receptor can bind Abs of both IgM and IgA isotypes and may function in Ag presentation and B-cell selection in the GC response in systemic and mucosal immunity |
| CR1/2 (CD21/35) | *Immune complex retention (especially in the spleen)*: Splenic IC retention does not occur without complement |
| CD21L (iC3b, C3d or C3dg) | *B cell co-stimulation via CD21*: Engagement of CD21 in the B-cell co-receptor complex by complement derived FDC-CD21L delivers a critical co-signal. Co-ligation of BCR and CD21 facilitates association of the two receptors and the phosphorylation of the cytoplasmic tail of CD19 by a BCR-complex-associated tyrosine kinase. This co-signal augments stimulation delivered by Ag and blockade of FDC-CD21L reduces B-cell proliferation, activation induced cytidine deaminase and Ab production from 10- to 1000-fold |
| FDC-M1 (Mfge8) | *Clearance of apoptotic bodies*: Milk fat globule epidermal growth factor 8 (Mfge8) 'licenses' tingible body macrophages to engulf apoptotic bodies in GCs and helps minimize autoimmunity |
| FDC-M2 (C4b eptiope) | *Binds C4b localized with FDC-ICs*: C4b-binding protein (C4BP) binds C4b and co-localizes with ICs on FDCs. FDC-C4BP has been shown to signal B cells via CD40, independent of T-cell CD40L (CD154). Injection of mice with FDC-M2 inhibits C4BP localization and TI-GC development |
| ICAM-1 (CD54)<br>VCAM-1 (CD106)<br>MadCAM-1 | *Stability of the FDC-B cell synapse*: Abs reactive with murine ICAM-1 and/or Leukocyte Functional Ag-I (LFA-I) interfere with FDC-B cell clustering resulting in reduced B-cell proliferation. In addition, VLA-4 and VCAM-1 have been observed in GCs and likely also play a role in FDC–B cell interactions. These adhesion molecules are thought to stabilize the FDC–B cell synapse and promote interaction of FDC-Ag and FDC-costimulatory molecules with B cells |
| CXCL13 | *B-cell homing to lymphoid follicles via CXCR5*: CXCL13 is secreted by FDCs and acts as a chemoattractant for B cells via the CXCR5 chemokine receptor. FDC development and |

(*Continued*)

**Table 1** Continued

| FDC molecules | Immunoregulatory role |
|---|---|
| | expression of this chemokine depend on $LT\alpha_1\beta_2$, TNFα and related molecules. A persistent $LT\alpha_1\beta_2$ stimulus is important for both the induction and the maintenance of FDC networks. Further studies suggest that the maintenance of the primary lymphoid follicle structure is mediated by a positive feedback loop: CXCL13 stimulates B cells to express high levels of $LT\alpha_1\beta_2$ and in turn$LT\alpha_1\beta_2$ stimulates FDCs to produce CXCL13 |
| IL-6 | *GC development and terminal-cell differentiation*: FDCs are the source of IL-6 in GCs. Engaging FDC-FcγRIIB by ICs activates FDCs and enhances FDC-IL-6 production. FDC-IL-6 promotes GC development, IgG production and somatic hypermutation |
| IL-15 | *Enhancement of GC B cell proliferation*: IL-15 is produced by FDCs and is captured by IL-15Rα on the surface of FDCs. Surface IL-15 is active and promotes GC B-cell proliferation. GC B cells have the signal-transducing components (IL-2/15Rβγ), but not a receptor for binding of soluble IL-15 (IL-15Rα) and the IL-15 signal may be delivered by trans-presentation from FDCs to GC-B cells via cell–cell contact |
| 8D6 (CD320) | *B cell anti-apoptosis*: The 8D6 molecule inhibits apoptosis and influences both proliferation and Ab secretion by GC B cells. Moreover, GC B cells that are induced to differentiate into pre-plasma cells are the most sensitive to the neutralizing effects of anti-8D6 |
| BAFF | *Enhancement of T-independent B-cell proliferation*: FDC-BAFF has the ability to support TI B-cell activation. The outcome of BAFF signalling is multifaceted and different receptors mediate different functions. Peripheral B-cell survival, plasma cell survival, MZ B-cell integrity, GC maintenance, CD21 and CD23 expression, T independent B-cell responses and Ig class switching may be influenced by BAFF |
| CD40 | *Regulation of FDC-CD23*: FDCs express CD40 and when incubated with either CD40L trimer or agonistic anti-CD40 Ab; the expression of FDC-CD23 is increased both at the mRNA and protein levels. As explained earlier, FDC-CD23 helps regulate IgE levels |
| Toll-like receptors (TLRs) (2, 3 and 4) | *Engagement of Pathogen-associated molecular patterns (PAMPs) and FDC activation*: Dramatic upregulation of FDC-ICAM-1, VCAM-1 and FcγRIIB is observed after injecting LPS into animals expressing wild-type TLR4 but not in animals with mutated TLR4. Incubation of FDCs with LPS *in vitro* upregulates FcγRIIB, ICAM-1 and VCAM-1. FDC activation by TLR agonists has been largely studied with LPS. However, FDCs express mRNA for TLR2, 3, 4 and 9 as well, and injection of poly I:C increases FDC-FcγRIIB to levels comparable with LPS |
| CD44<br>CD29 | *Interaction with ECM proteins, regeneration of FDC dendrites and B cell anti-apoptosis*: FDCs express CD44 and CD29 and FDC binding to collagen type I *in vitro* induces the regeneration of FDC processes and networks. CD44 also enhances B-cell adherence to FDCs allowing delivery of the FDC-derived B-cell survival signals including 8D6 and BAFF |
| TNFα | *T-cell stimulation*: FDCs produced soluble tumour necrosis factor alpha (TNFα) that increases transcription and production of HIV in GC T cells |
| IL-7 | Interleukin 7 has been found in isolated tonsillar FDCs using RT-PCR and intracellular staining. IL-7 signalling coupled with cross-linking of surface immunoglobulin receptors results in B-cell proliferation |
| LT-R (and TNFα) | FDC development and maturation |

trapping of ICs *in vitro* induces the secretion of BAFF and IL-6 (interleukin 6). FDC-activation by TLR agonists was generally done using lipopolysaccharide (LPS). However, FDCs express mRNA (messenger ribonucleic acid) for TLR2, 3, 4 and 9 and injection of polyinosinic:polycytidylic acid (poly I:C; an immunostimulant) increases FDC-FcγRIIB in draining lymph nodes similar to results for LPS. FDCs also express CD44 and CD29 and FDC binding to collagen type I *in vitro* induces regeneration of FDC processes and networks with features in common with networks *in vivo* (see **Figure 1b**). A major consequence of activation is a marked increase in accessory activity. For example, the number of FDCs needed for IgG responses *in vitro* could be reduced 4-fold and somatic hypermutation could be increased if FDCs were activated. **See also**: Fc Receptors

## FDC-deficits

FDCs from $Fc\gamma RIIB^{-/-}$ mice do not retain and present ICs to WT B cells effectively either *in vivo* or *in vitro*. Similarly, FDC-FcγRIIB is dramatically reduced in GC

reactions in aged mice and the reduction correlates with reduced Ag retention. Germinal centre B cells rapidly proliferate in response to Ag in young mice but in aged mice GC reactions are limited. Since 'aged' FDCs lose their capacity to retain ICs and present Ag to B cells, we are not surprised that their GC reactions and Ab responses are reduced. Thus, FDCs in aged animals appear to represent a 'bottle-neck' in the induction of Ab responses.

## The Negative Impact of FDCs

In addition to their contributions in immunity, FDCs also play important roles in pathological states, including HIV/AIDS, prion diseases and B-cell lymphomas.

### FDCs in HIV/AIDS

Shortly after infection, enormous quantities of intact HIV particles are trapped on FDC dendritic processes. Just as Ags, these virus particles are trapped as ICs containing Ab and/or complement proteins. Quantitative image analysis estimates that FDC-trapped HIV contains $1.5 \times 10^8$ copies of viral RNA per gram of lymphoid tissue making this one of the largest HIV repositories in humans. Moreover, because HIV does not infect FDCs, therapeutic drugs designed to target actively propagating virus fail to affect HIV on FDCs. Just as FDCs retain conventional Ag for long periods, they also retain virus particles for long periods. In fact, as long as FDCs are present in infected individuals, HIV can be found associated with them. Studies examining the half-life of HIV on FDCs in patients suggest that the virus decays (i.e. is lost from FDCs) with a half-life of approximately 2 weeks (compared with the decay of virus in the blood that is estimated to have a half-life of 2 h or less). However, this estimated loss of infectious virus may be misleading in that it only requires one infectious virus particle to come in contact with a susceptible host cell to transmit infection.

Because FDC-trapped HIV persists for months, it prompted the postulate that these unique cells are an important 'reservoir' of virus. Reservoirs are defined as tissue sites and cells where virus persists with a half-life longer than virus in productively infected cells. Additionally, in reservoirs, virus must remain infectious and possess a greater genetic diversity than virus found elsewhere. Recent testing indicates that FDC-trapped HIV fulfills these criteria and that drug-resistant virus can be found on FDCs that is not present elsewhere. Thus FDC-trapped HIV persists for long periods and can reignite infection and perpetuate the disease. **See also**: Human Immunodeficiency Viruses (HIV)

Just as FDC signalling is important to immune reactions, these cells also provide a microenvironment that is highly conducive to HIV transmission. HIV ICs remain infectious for months and just as ICs containing conventional Ag can be 'presented' to B cells in the presence of Abs, HIV on FDCs is 'presented' to T cells resulting in infection, even if the HIV-ICs are composed of potent neutralizing Abs. FDC-signalling also contributes to HIV pathogenesis. FDC-secreted TNFα increases the rate of HIV transcription by approximately 3-fold in infected T cells resulting in a significant increase in virus production. FDCs also increase the T-cell expression of the HIV co-receptor CXC-chemokine receptor 4 (CXCR4) and these cells become highly susceptible to infection with small quantities of virus (i.e. X4-tropic HIV-1) that do not infect other cells with lower levels of CXCR4. FDC-produced CXCL13 also contributes to HIV pathogenesis by attracting HIV-susceptible T lymphocytes into the lymphoid follicle. Remarkably, FDCs induce T-cell expression of two inhibitory signalling molecules, regulators of G-coupled protein signalling 13 and 16 (RGS13 and RGS16) that markedly decrease the ability of the T cells to migrate to the chemokine CXCL12, that is found outside the germinal centers and may help the T cells migrate away from the FDC reservoir of HIV. Thus, the contributions of FDCs to HIV pathogenesis include the storage of a large and diverse reservoir of infectious virus, including drug resistant variants, in an activated microenvironment where CD4T cells targets are attracted but impaired in their ability to leave, thereby increasing the likelihood of their infection.

### FDCs in prion disease

Prion diseases involve neurodegeneration that ultimately results in death. These diseases occur in both animals and humans and are caused by misfolded proteins that form aggregates. The proteins involved are encoded by the Prnp gene and consist of a normal form ($PrP^c$) and its aberrant counterpart ($PrP^{Sc}$). Without the normal $PrP^c$ protein, whose function is still unknown, the diseases are not manifest. Examples of prion-mediated diseases or transmissible spongiform encephalopathies (TSE) include bovine spongiform encephalitis (BSE) of cattle, Scrappie (a disease of sheep) and Creutzfeldt-Jakob disease (CJD) of humans. FDCs appear to play an important role in most TSEs as evidenced by the finding that in experimental models where FDCs are not present, the TSEs do not typically appear. On exposure to prions (e.g. in the gastric mucosa following ingestion), the agents are transported into secondary lymphoid tissues where the proteins accumulate and replicate on FDCs. Although the mechanism of prion transport to the lymphoid tissues is not well understood, $PrP^c$ is involved and the FDC is a major source of this protein. Antibodies do not appear to play a seminal role in FDC-trapping of prions but complement proteins do. After prion replication in the secondary lymphoid tissues, the $PrP^c$–$PrP^{Sc}$ complexes are transported to the central nervous system where neurodegeneration occurs, although the mechanism of transport remains to be elucidated. When experimental animals have been injected with high concentrations of TSE agents (i.e. Scrapie), FDCs are not needed for disease development; however, most exposure to prions is thought to occur at lower doses. Because FDCs appear to be required for disease pathogenesis in

most cases, attempts have been made to destroy these cells. The use of blocking agents to the lymphotoxin beta receptor (LTβR) pathway, needed for FDC development and maintenance, results in impaired development of disease suggesting the potential of this approach for therapy. Mice deficient for the inflammatory cytokine TNFα, are also less susceptible to disease and clinically approved TNFα inhibitors are currently available. A further understanding of the role of FDCs in TSE generation should provide additional new information that may help in alleviating or ameliorating this type of neurodegenerative disease. **See also**: Prions

### FDCs in B-cell lymphomas

Some 20% of non-Hodgkin lymphomas are follicular lymphomas. The morphology of these lymphomas resembles that of conventional germinal centers having T cells, macrophages and FDCs. Recent genetic studies of follicular lymphomas suggest that the microenvironment in which the malignant cells reside is an important determinant in the nature of the disease and its progression. The malignant cells appear to require the contributions of T cells, macrophages and FDCs as evidenced by the observation that in the absence of these cells, the malignant cells are difficult to culture. In addition, to provide signals important to tumour cell growth, FDCs also can provide signals that spare malignant B cells from undergoing apoptosis or programmed cell death, including that induced by chemotherapeutic agents such as busulfan, etoposide and cyclophosphamide. Thus, the contributions of FDCs may provide a microenvironment that not only 'supports' B-cell lymphomas but also establishes a protective sanctuary for malignant cells from otherwise effective drugs.

## Concluding Comments

FDCs represent a unique accessory cell that is critical in the induction of germinal centres and in optimizing humoral immune responses. These cells provide both Ag-dependent and Ag-independent signals that contribute to the ability of B cells to proliferate and produce optimal levels of specific Ab. In addition to their positive contributions to immunity, they can have a negative impact by contributing to disease progression in HIV/AIDS, prion diseases and follicular lymphomas. As our understanding of FDCs increases, we may gain the ability to better regulate and control immune responses and to ameliorate the progression of some diseases.

## Further Reading


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