Review

Follicular dendritic cells: origin, phenotype, and function in health and disease

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Follicular dendritic cells (FDCs) were originally identified by their specific morphology and by their ability to trap immune-complexed antigen in B cell follicles. By virtue of the latter as well as the provision of chemokines, adhesion molecules, and trophic factors, FDCs participate in the shaping of B cell responses. Importantly, FDCs also supply tingible body macrophages (TBMs) with the eat-me-signaling molecule milk fat globule-EGF factor 8 (Mfge8), thereby enabling the disposal of apoptotic B cells. Recent studies have provided fundamental insights into the multiple functions of FDCs in both physiological and pathophysiological contexts and into their origin. Here we review these findings, and discuss current concepts related to FDC histogenesis both in lymphoid organs and in inflammatory lymphoneogenesis.

FDCs: origin and functions

Follicular dendritic cells (FDCs) (see Glossary) were originally identified by their striking morphology and by their ability to trap immune complexes (ICs) of antigen and antibodies in B cell follicles. Owing to their location within lymphoid organs and their dendritic appearance, FDCs were mistakenly assumed to be a subset of conventional dendritic cells (DCs). However, FDCs are stromal in origin and develop from vascular mural cells [1], unlike conventional DCs, which are hematopoietic. Functionally, FDCs also differ from DCs. DCs activate naive T cells by presentation of processed antigen via major histocompatibility complex (MHC) molecules, whereas FDCs appear to present unprocessed antigen in the form of ICs. This feature, along with the provisioning of chemokines, adhesion molecules, and trophic factors, enables FDCs to shape B cell responses and mold the local microenvironment.

Here we review the role of the FDC as a bridging cell between innate and adaptive (B cell) responses. The sensing of innate stimuli by FDCs via toll-like receptors (TLRs) amplifies adaptive responses. In addition, FDCs control the removal of apoptotic germinal center (GC) B cells by secretion of the 'eat-me' signaling molecule Mfge8. This FDC-mediated ingestion of dying B cells plays a crucial role in preventing autoimmunity. However, FDCs can also contribute to autoimmune disorders. Auto-IC deposition on FDCs and FDC-mediated recruitment of self-reactive follicular helper T cells (T_{FH} cells) may lead to the selection of autoreactive B cells. Finally, FDCs can act as extraneuronal sanctuaries of prions and facilitate their neuroinvasion. This feature sparked the interest of prion researchers, and important insights into FDC biology in recent years was obtained through experiments involving prion infection.

Origin and development of FDCs

Functional B cell follicles are based on the mutually dependent collaboration of B cells and FDCs: while the FDC provides signals to sequester and maintain B cells within B cell follicles, B cells are essential for FDC development and maintenance by providing tumor necrosis factor (TNF) and

Glossary

Cognate B cell: a B cell that has a BCR with specificity for the antigen.
Follicular B cell (Fo B): a naïve (antigen inexperienced), mature B cell present in primary B cell follicles.
Follicular dendritic cell (FDC): the predominant stromal cell type of primary and secondary (GC) B cell follicles, able to bind ICs.
Fibroblast reticular cell (FRC): a stromal cell mainly present in the T cell zone (TZ), therefore also known as T cell zone reticular cell (TRC).
Germinal center (GC): a specialized microenvironment of lymphoid organs and ectopic lymphoid tissues where B cells differentiate to enhance their affinity to antigens, and switch the class of their antibodies.
GC B cell (GC B): an antigen-experienced, mature B cell that enters the GC to undergo antibody affinity maturation.
Immune complex (IC): a complex made of antigen and antibody, antigen and complement, or antigen, antibody, and complement.
Marginal reticular cell (MRC): a stromal cell underneath the marginal sinus engaged in connections with B cell follicles and the T cell zone.
Myofibroblast: a cell that shares the expression of markers associated with vascular mural cells as well as fibroblasts (SMA, PDGFRβ). Unlike vascular mural cells, they do not surround endothelial cells.
Secondary lymphoid organs (SLOs): organs, such as spleen, lymph nodes, or Peyer's patches, where adaptive immune responses are mounted.
Tertiary lymphoid tissues (TLTs): *de novo* generated lymphoid tissues in nonlymphoid organs and tissues such as kidney, liver, or joints, appearing as a result of impaired clearance of antigen, as is the case in chronic inflammations.
Vascular mural cells: vascular smooth muscle cells (vSMC) and pericytes surrounding $CD31^+$ blood endothelial cells. vSMC and pericytes express the mural markers PDGFRβ and can express NG2, vSMC, and also SMA.

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lymphotoxin (LT). Lymphoid organs lacking B cells or either of these cytokines are also devoid of FDCs [2,3]. While both LT and TNF are needed for FDC development, LT is required to maintain FDCs in mature lymphoid organs [4]. FDCs are thus a constitutive part of B cell follicles in secondary lymphoid organs (SLOs), which continuously monitor blood and lymph for incoming pathogens. Crucially, FDCs can also be generated *de novo* in nonlymphoid organs during chronic inflammatory conditions. The persistent presence of antigen (e.g., in chronic viral hepatitis) can elicit tissue reorganization into tertiary lymphoid tissues (TLTs) containing GCs and fully differentiated FDCs [5].

Several studies of splenic cells showed that FDCs arise from stromal, mesenchymal, radioresistant, and most likely locally-residing precursors [6]. However, TLTs can almost arise everywhere in the body – implying that FDC precursors are either sessile and ubiquitous, or possess considerable motility. Indeed, using kidney transplants, our group found that FDC precursors reside within their target organs prior to TLT formation. Detailed histological analysis and cell lineage tracing experiments in the spleen showed that FDC precursors express molecules associated with vascular mural cells [platelet-derived growth factor receptor-beta (PDGFRβ) and alpha smooth muscle actin (SMA)] and localize to the perivascular space [1]. Finally, stromal vascular (SV) fractions from adipose tissues transplanted into the kidney capsule can generate artificial lymphoid structures containing FDCs. These results showed that FDCs emerge from perivascular precursors, and provide an explanation as to how FDCs can quickly arise from ubiquitous tissue-intrinsic vasculature and participate in the newly assembling TLTs.

White adipose SV fractions contain undifferentiated preadipocytes [7], and the precursor within the SV pool is a glycoprotein (GP)38^{+}CD31^{-} cell [8]. LTβR signaling acts as a fate determinant: when preadipocytes experience LTβR activation, adipose development is blocked and cells enter a lymphoid stromal pathway. Whether FDC precursors also exist within the pool of GP38^{+}CD31^{-} cells or are derived from a different subtype of SV cells remains to be shown. However, as discussed below, recent observations imply that different stromal cells of SLOs – FDCs, fibroblastic reticular cells (FRCs), and marginal reticular cells (MRCs) – are generated from one and the same precursor.

FDCs, FRCs, and MRCs share the expression of certain markers [LTβR, tumor necrosis factor receptor 1 (TNFR1), vascular cell adhesion molecule 1 (VCAM1), intercellular adhesion molecule 1 (ICAM1), and BP3 (also know as bone marrow stromal cell antigen 1, BST1)], indicating that they are closely related, even though they are distinguishable by morphology, localization, and expression of cell type-associated molecules such as complement receptors (FDCs), GP38 and chemokine (C–C motif) ligand 19 (CCL19; FRCs), as well as mucosal vascular addressin cell adhesion molecule 1 (MadCAM1; MRCs) [1,6,9,10]. FDCs stem from PDGFRβ-expressing precursors, and FRCs and MRCs actively express PDGFRβ, a molecule associated with mural cells of the vasculature and myofibroblasts [1,11]. A recent report on FRC development in the LN identifies its precursor using CCL19–Cre driven reporter gene expression. When LTβR signaling in CCL19^{+} precursor cells is abolished, terminally differentiated FRCs expressing GP38 do not develop and CCL19^{+} precursors are found in the T cell zone reticular network (termed myofibroblasts) or surround high endothelial venules [12]. Their location and increased levels of SMA and PDGFRβ suggest developmental similarities with FDC [1]. Only recently was genetic evidence for a common ancestor to splenic FRCs, FDCs, MRCs, and mural vascular cells brought forward. Using reporter genes it was shown that they all develop from embryonic splenopancreatic mesenchymal cells of the NK2 homeobox 5 (Nkx2.5)$^{+}$Islet1^{+} lineage [13]. Transplantation of embryonic Nkx2.5^{+}Islet 1^{+} cells, or of adult PDGFRβ^{+} adipose SV cells [1], leads to the generation of lymphoid stromal cell subsets and of *de novo* lymphoid tissues. Hence the transplanted cell fractions not only contain stromal precursors but also include the stromal organizer (SO) cell, a cell type essential for the induction of lymphoid tissues [14].

Thus, various lymphoid stromal cells including FDCs, FRCs, MRCs, myofibroblasts, perivascular mural cells, and SO cells originate from common progenitors located in the perivascular space (Figure 1). Through collaboration with specific sets of hematopoietic cells, precursors may mature into their terminally differentiated status and adapt the phenotypes appropriate for their respective niche.

FDCs and lymphoid follicle microarchitecture maintenance

The generation and maintenance of FDCs depends crucially on the continuous supply of LT and TNF provided by B cells [2–4]. Mice lacking these cytokines, their respective receptors, or factors essential for their downstream signaling not only fail to develop FDCs, but are also unable to establish B cell follicles as part of the sophisticated lymphoid structure. This suggests that FDCs exert a pivotal role in sequestering B cells.

A direct result of LT provision is the upregulation of the FDC-derived chemokine (C–X–C) motif ligand 13 (CXCL13), whose recognition via chemokine (C–X–C motif) receptor 5 (CXCR5)-expressing follicular B cells (and T_{FH} cells) leads to their migration into B cell follicles (Figure 2A). In a positive feedback loop, CXCL13 also signals the B cell to further augment LT production [15]. S1PR2, a receptor for the chemokine sphingosine 1 phosphate (S1P), is upregulated in GC B cells and is mandatory for entering the GC area [16]. Interestingly, FDCs produce particularly low amounts of S1P compared to surrounding tissues. Indeed binding of S1P to S1PR2 inhibits the attracting effect of CXCL13 on GC B cells. This suggests that S1PR2 signaling on GC B cells is necessary to actively exclude them from S1P^{+} areas outside the GC, simultaneously facilitating access to CXCL13-producing GC FDCs [16,17].

FDC express the adhesion molecules ICAM1 and VCAM1, ligands for integrins αLβ2 (lymphocyte function associated antigen 1, LFA-1) and α4β1 (very late antigen 4, VLA-4), respectively, expressed by follicular and GC B cells. Surprisingly, disturbing the interaction of these ligands with their cognate receptors (using blocking antibodies) does not affect the localization of follicular B cells within their follicles, even though seeding with new B cells is reduced [18]. Therefore, FDC-derived adhesion

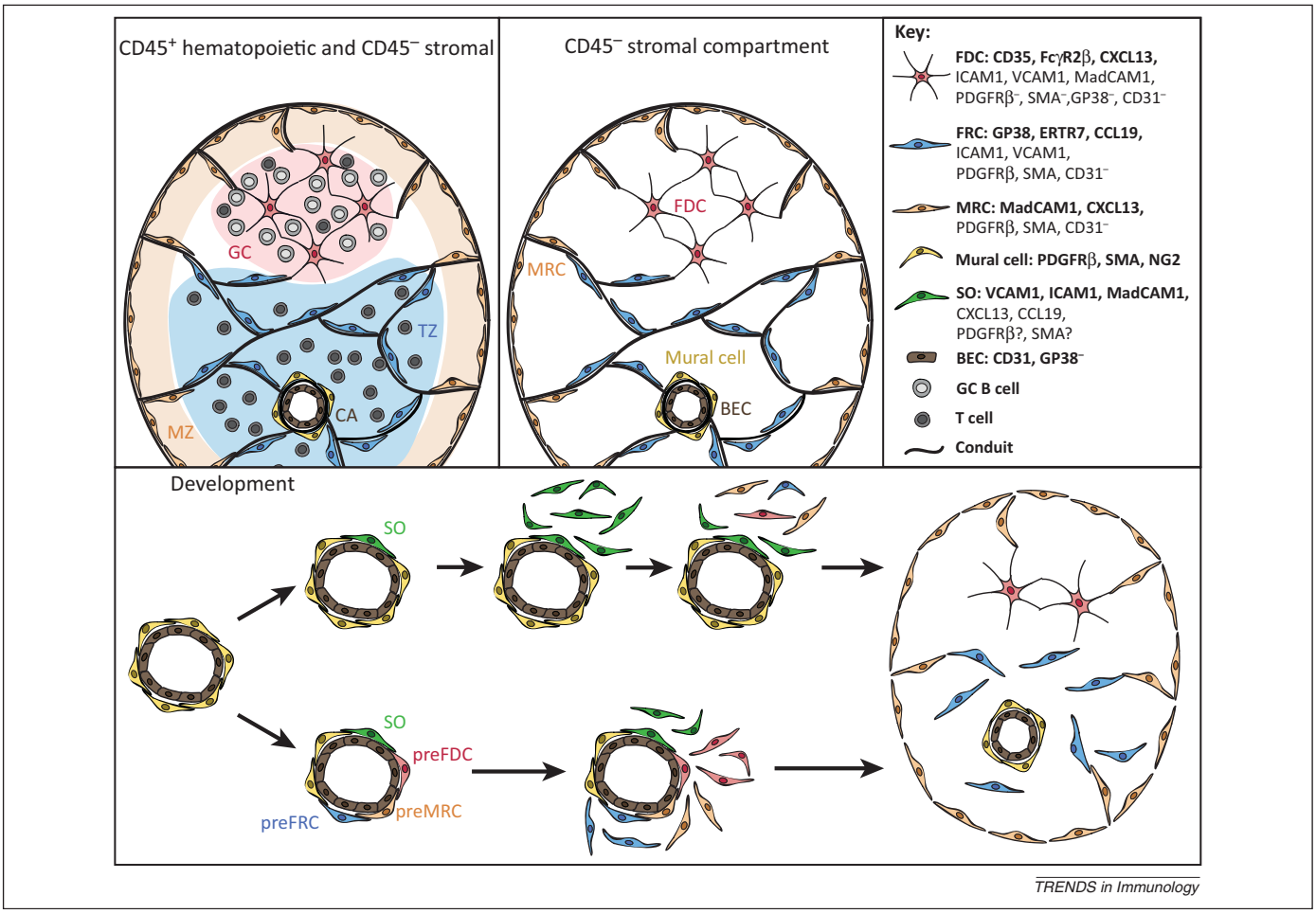

Figure 1. Stromal cells of the splenic white pulp. Upper panel, left and middle: organization of the splenic white pulp. GC: germinal center; MZ: marginal reticular zone underneath the marginal sinus; TZ: T cell zone surrounding the central arteriole (CA). Middle panel: anatomical localization of stromal cell populations. FDC: follicular dendritic cell; FRC: fibroblast reticular cell; MRC: marginal reticular cell; BEC: blood endothelial cell; and vascular mural cell. Right: expression of molecules typically associated with distinct stromal cells. SO: stromal organizer; Conduit: a structural element of the lymphoid organ facilitating lymphocyte and antigen trafficking. The proteins that are used to identify a stromal cell subset are highlighted in bold; –: molecules absent in this cell type, but used as a distinctive marker for one or more of the other stromal cells. Lower panel: two possible models of stromal cell development. Both models assume that FDCs, FRCs, MRCs, and vascular mural cells are derived from a common sessile and mesenchymal precursor, which may reside in blood vessel walls. In the spleen, this common precursor is an Nkx2.5^{+} Islet 1^{+} cell. In the upper model, FDCs, FRCs, and MRCs develop from the SO cell. This model is supported by the notion that the different cell types appear successively during lymphoid organ development; SO cells develop first and locate around blood vessels, where they initiate lymphoid organs. SO cells express molecules characteristic of FDCs, FRCs, and MRCs, suggesting derivation from secondary lymphoid organs (SLOs). The lower model suggests that each stromal cell subset (SO, FDC, FRC, and MRC) has a distinct precursor located in, or around, the blood vessel wall.

molecules are not essential to maintain naïve follicular B cells within B cell follicles.

During the GC response, LT and TNF-dependent nuclear factor-kappa-B (NFκB) signaling induces the adhesion molecules ICAM1, VCAM1, and MadCAM1 on FDCs [2,19]. Also, co-culture of GC B cells with FDCs, or culture of GC B cells with ICAM1 and VCAM1, promotes their survival in an integrin-dependent fashion [20,21]. While these changes may promote adhesion of GC B cells and FDCs, *in vivo* microscopy showed that GC B cells are highly mobile. Hence, integrin upregulation may subtly modulate their interaction with FDCs rather than foster firm and stable adhesion. *In vitro*, ICAM1/VCAM1/integrin are important components of the B cell synapse and enhance signaling in B cells [22]. Several studies support the notion that integrins alter GC outcomes *in vivo*. Mice lacking LT on GC B cells or IκB kinase 2 (IKK2), a molecule involved in the canonical pathway of NFκB signaling, develop FDCs in primary follicles and GCs but do not show GC-mediated upregulation of VCAM1 and ICAM1 and suffer from reduced affinity maturation despite proper recruitment of GC B cells [19,23]. Mutations in the guanine exchange factor dedicator of cytokinesis 8 (DOCK8) cripple the formation of immunological synapses in B cells, resulting in aberrant clustering of ICAM1/LFA-1 in the peripheral synapse. Antibody affinity maturation fails in DOCK8-deficient mice, supporting the notion that FDC-derived adhesion molecules affect the outcome of the GC reaction [21,24] (Figure 2B).

Therefore, CXCL13 secreted by FDCs is essential for sequestering CXCR5 expressing B cells into the follicles of SLOs. The provision of integrin ligands positively influence intercellular adhesion between GC B cells and FDCs, and may shape the B cell synapse ensuring optimal activation of the GC B cell [25].

FDC contributions to GC B cell activation via BCR and IC receptors

FDCs have a unique ability to capture and retain ICs over a long period of time [15]. FDCs bind ICs either via the

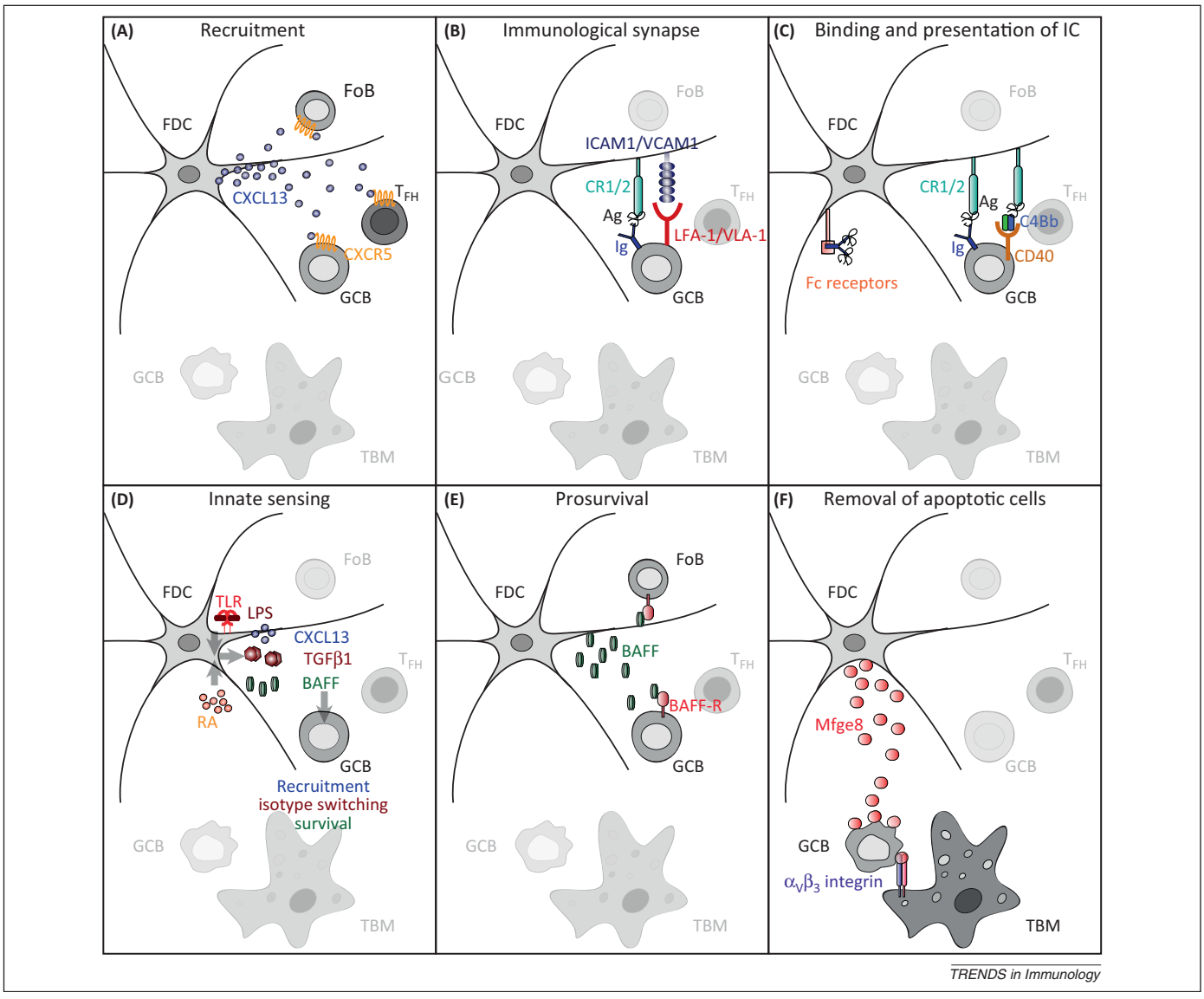

Figure 2. FDC functions. FDCs secreting CXCL13 recruit CXCR5 expressing FoB cells, GC B cells, and T_{FH} cells into primary and secondary B cell follicles **(A)**. Via the interaction with the B cell integrins αLβ2 (LFA-1) and α4β1 (VLA-4) FDC-derived ICAM1/VCAM1 mediate adhesion and contribute to a functional immunological synapse involving BCR signaling **(B)**. FDCs bind antigen in the form of ICs via Fc and complement receptors (CR1 and CR2). This leads to antigen-specific signaling in GC B cells bearing cognate BCR (Ig) as well as complement C4BP-mediated activation of CD40 **(C)**. TLR stimulation via bacterial constituents (LPS) and detection of retinoic acid induces upregulation of CXCL13, BAFF, and TGFβ in FDCs. These factors are involved in the recruitment, survival, and isotype switching of GC B cells, respectively **(D)**. Secretion of BAFF by FDCs supports the survival of follicular and GC B cells **(E)**. FDCs secrete Mfge8, which binds to PS exposed on apoptotic GC B cells. Mfge8-opsonized apoptotic cells are then recognized and cleared by TBMs in an $\alpha_v\beta_3$ integrin-dependent manner **(F)**. BCR: B cell receptor; CXCL13: chemokine (C–X–C) motif ligand 13; CXCR5: chemokine (C–X–C motif) receptor 5; FDCs: follicular dendritic cells; FoB cells: follicular B cells; GC: germinal center; ICAM1: intercellular adhesion molecule 1; ICs: immune complexes; LFA-1, lymphocyte function associated antigen 1; LPS: lipopolysaccharide; Mfge8, milk fat EGF-factor 8; PS: phosphatidylserine; TBM: tingible-body macrophage; T_{FH} cells: follicular helper T cells; TGFβ: transforming growth factor β1; TLR: toll-like receptor; VCAM1: vascular cell adhesion molecule 1; VLA-4, very late antigen 4.

complement receptors 1 (CR1/CD35) and 2 (CR2/CD21) or via the Fc receptors for IgG [FcγR2β (CD32)], IgE [FcεR2 (CD23)], IgA, and IgM (Fcα/μR) [3] (Figure 2C).

Evidence for the functional relevance of ICs to GC responses comes from *in vitro* experiments where ICs deposited on FDCs stimulate B cells and induce somatic hypermutation as well as immunoglobulin class switching. Moreover, mice deficient in stromal CR1 and CR2 have reduced T-dependent antibody responses, particularly with low doses of antigen and in the absence of adjuvants [3,26]. In mice, CR1/2 are splice variants of the same gene, and FDCs express high levels of CR1, suggesting an important role for CR1 during antibody responses. This notion was confirmed in elegant experiments wherein the coding sequence for CR1 was ablated without affecting expression of the CR2 protein. These mice had decreased T-dependent antibody responses and reduced GC size [27].

Advanced *in vivo* imaging techniques have answered longstanding questions related to the delivery of ICs to FDCs. LN afferent lymphatic ducts were found to deliver ICs to LN subcapsular sinus (SCS) macrophages. Blood-borne antigen enters the spleen via the marginal sinus. Incoming ICs are rarely immediately bound by cognate B cells, whereas mostly marginal zone B cells or noncognate follicular B cells pick up opsonized antigen in a CR-dependent way and then shuttle to the B cell follicle, where ICs are deposited onto FDCs [28–30]. FDC–IC then stimulate cognate follicular B cells via the B cell receptor (BCR), and

provide additional signals through the complement and Fc receptors, as elegantly discussed in a recent review [26]. Complement-containing ICs also recruit complement 4b-binding protein (C4BP), which in turn interacts with CD40 in B cells. This process was shown to be particularly important for thymus-independent GC responses [31,32].

Although antigen shuttling from noncognate B cells into the GC was visualized as early as 2009, the direct transfer of ICs onto FDCs was not visualized until very recently [33]. In this study, antigen was shown to traffic between B cells and stromal $CR2^+$ cells, presumably FDCs, and the transfer of ICs from noncognate B cells to FDC was confirmed in *in vitro* co-culture experiments. After transfer, ICs underwent rapid endocytosis and recycling to the FDC surface, whereupon they activated cognate B cells. In contrast to endocytosis of ICs in macrophages, internalization by FDCs was not associated with degradation, and ICs were maintained over many days *in vivo* as well as under *in vitro* culturing conditions.

The contribution of IC formation to the overall humoral response was assessed in mice immunized with sheep red blood cells (RBCs) [34]. Challenge with suboptimal doses of antigen did not yield anti-RBC IgG titers, yet co-delivery of anti-RBC IgM during the immunization process rescued these poor responses. Amelioration of the humoral response was dependent on CR expression by FDCs. B cell-resident CR also contributed, maybe because increased amounts of antibody lead to enhanced IC trapping by (noncognate) B cells and subsequent deposition on FDCs.

Using mathematical predictions, which were subsequently confirmed experimentally, Zhang *et al.* showed that antigen-specific antibodies do not coercively enhance the humoral response [35]. Their model incorporated the effect of antibody availability and affinity on antigen retention, as well as antigen masking. Accordingly, newly formed ICs deposited on FDCs first increase antigen availability for GC B cells, therefore augmenting the response. Hence the steep increase of secreted high-affinity antibodies during the GC response increases the competitive pressure for high-affinity B cells by preventing low-affinity B cells from gaining antigen access. Eventually, antigen masking by emerging higher-affinity antibodies brings the selection process – and thus the immune response – to a halt. Accordingly, treatment of mice undergoing a GC response with high affinity antibodies led to reduced GC numbers, whereas in agammaglobulinemic mice, which lack such an antibody-mediated feedback loop, GCs were maintained over a prolonged period of time [35]. Hence antigen availability on the surface of FDCs can become limiting during the GC reaction. This finding supports the prevailing model of GC B cell selection: only B cells bearing a relatively higher-affinity receptor engage FDCs, receive sufficient BCR stimulation, and are provided with other activating molecules.

Modulation of the GC response through TLR signaling

Pattern recognition receptors, such as the TLRs, trigger and shape the adaptive immune response to pathogens and stress-associated signals. FDCs express TLR4, which detects lipopolysaccharide (LPS) from Gram-negative bacteria. TLR4 expression is upregulated during GC responses, suggesting that FDCs directly sense microbial ligands through innate receptors and thereby influence adaptive immune responses [36–38]. Indeed, when TLR4 is ablated in the stromal compartment, affinity maturation is diminished and GC size is reduced [37].

FDCs that reside in gut-associated tissues [Peyer's patches (PP) and mesenteric LN] display mRNA expression profiles that indicate activation of TLR and retinoic acid pathways, which differs from the profile seen in FDCs resident in peripheral LN, suggesting that exposure to bacterial products and vitamin A metabolites can alter the FDC phenotype [38]. PP FDCs express increased levels of chemokines (CXCL13), survival factors [B cell activating factor (BAFF), discussed in the next section], and adhesion molecules, and exhibit enhanced secretion of transforming growth factor β1 (TGFβ1), the cytokine principally responsible for IgA class switching in B cells in this locale [38,39] (Figure 2D). In line with this observation, abolishing TLR signaling by deleting the downstream signaling molecule myeloid differentiation primary response protein 88 (Myd88), or by depleting vitamin A, results in fewer FDCs, smaller GCs, and reduced levels of IgA.

FDCs provide cytokines important for the GC reaction

Signaling mediated by the cytokine BAFF is required for B cell homeostasis in developing as well as mature B cells [40]. FDCs are a source of BAFF [38], and may in this manner impact the survival of follicular and GC B cells. Mice deficient in either BAFF or its receptor (BAFFr) initially develop GC responses, but GCs are not sustained [41,42] (Figure 2E).

FDCs also produce the pro-inflammatory cytokine interleukin-6 (IL-6), and GCs in mice devoid of this cytokine are reduced in size. These mice exhibit defective upregulation of complement factor 3, a central member of the complement signaling pathway upon which the classical and the alternative arms of the complement cascade converge. The reduced complement-mediated signaling associated with this defect is thought to cause the altered GC phenotype [43,44].

Analysis of human tonsillar FDCs identified FDC-SP as an FDC-derived secreted protein binding to B cell lymphoma cells [45]. The precise function of FDC-SP is unknown, but the protein shares similarities with inflammatory regulators. Overexpression of FDC-SP in mice resulted in small GCs, indicating that endogenous FDC-SP might regulate adaptive immune responses [46].

Hence, by providing cytokines FDCs maintain GCs, although the mechanisms of how this is achieved are incompletely understood. As discussed below, FDCs also impact GC maintenance and dynamics through other signaling cascades.

FDCs provide a variety of factors with putative roles in the GC reaction

The Notch, Wnt, and Sonic hedgehog (SHH) signaling cascades are highly conserved pathways that function in the regulation of cell fate decision processes in multiple tissues. Human tonsillar FDCs express ligands for Notch, and *in vitro* experiments using FDC cell lines and GC B cells, showed reduced GC B cell survival upon blocking Notch signaling using gamma-secretase [47]. The secreted signaling protein Wnt5a has various immunoregulatory

properties and also regulates B cell proliferation [48]. Wnt5a is expressed by FDCs in culture, and has a positive effect on GC B cell survival *in vitro* by inducing Wnt/Ca^{2+}-dependent activation of nuclear factor of activated T cells (NFAT), NFκB, and B cell leukemia/lymphoma 6 (BCL6) [49]. SHH is found on FDCs, and both FDCs and GC B cells express SHH receptors. *In vitro* treatment of GC B cells with anti-SHH antibodies or with the steroidal alkaloid cyclopamine, which inhibit SHH signaling, results in increased apoptosis [50]. Thus, three signaling cascades known for their key roles in cell fate decisions are likely involved in the interaction of FDCs and GC B cells. The exact mechanisms by which these FDC-derived signals alter GC outcome *in vivo* remain poorly understood.

Human tonsillar FDCs express cyclooxygenase 2 (COX2) and prostacyclin synthetase, enzymes mandatory for the synthesis of prostaglandin (PG) and its derivative prostacyclin [51], and FDC lines were shown to secrete prostanoids [52,53]. However, *in vitro* experiments performed using slightly different culturing conditions (co-culture of GC B cells or B cells with human or murine FDCs, with or without other cytokines) attested both pro- as well as antisurvival effects of prostanoids on B cells [53,54]. *In vivo* experiments only attest a minor role of prostanoids thus far. A combination of COX inhibitors and PG E2 receptor antagonists resulted in a small decrease in number of apoptotic GC cells, and total GC numbers remained unaffected [53].

In an attempt to better characterize FDC phenotype and function, Wilke *et al.* and Huber *et al.* analyzed the transcriptome of the FDC [9,15,55]. The identified transcripts included well-established FDC markers, such as CXCL13, Mfge8 (FDC-M1), or MadCAM1, as well as molecules that had previously not been associated with FDCs such as Serpina1, Cochlin, Perostin, the prion protein (Prnp) (Box 1), Cilp, Lrat, Glycam1, and Enpp2. How the function of these proteins impacts GC reactions has not yet been examined in detail. Some insight into the function of one of these proteins – cochlin, an extracellular matrix protein – was reported recently. Cochlin is involved in modulating innate responses [56]: upon inflammation, cochlin is cleaved and released into the blood stream, where it impacts cytokine production, recruitment of innate immune effectors, and bacterial clearance. Thus, cochlin production by FDCs may be a way in which these cells participate in innate immunity.

Even though prostaglandins and cochlin have important immunoregulatory roles, the importance of FDCs in supplying these factors has not yet been specifically examined. Furthermore, the FDC-specific functions of many genes identified by different transcriptomic screens are still largely unknown. Therefore, more experiments are needed that use FDC-specific deletion or FDC-restricted expression of these genes to unravel unidentified immunoregulatory roles of FDCs.

FDCs contribute to autoimmunity by display of autoantigens

In light of the role of FDCs in the selection of high-affinity antibodies, it is not surprising that FDCs have also been associated with autoimmune diseases in which autoantibodies contribute to pathology such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [57–59]. FDCs do not just present foreign antigen to GC B cells, but also trap autoantigen–IC and even recruit autoreactive T_{FH} cells, thus supporting the selection of autoreactive B cells [60]. This has been shown in a model of RA where mice develop high levels of anti-glycosylphosphatidylinositol (GPI) autoantibodies targeting GPI-anchored surface proteins. Accordingly, drugs interfering with FDC integrity, such as decoy receptors for TNF and LT, ameliorate RA in mice and humans [59,61].

Natural IgM, which in contrast to immune IgM, is present in the serum in the absence of an antigenic stimulus, has a polyreactive character, and shows a certain propensity for low affinity self-reactivity [62]. In obesity-associated inflammation, levels of natural IgM as well as levels of apoptosis inhibitor of macrophages (AIM) are increased [63,64]. AIM protein inhibits internalization of

Box 1. FDCs and prions

The ability of FDCs to trap and accumulate opsonized particles plays an important role in the pathogenesis of prion diseases. Prions are infectious protein aggregates consisting of a misfolded variant of the physiological protein PrP^C, which is highly expressed by FDCs [78]. Prions cause incurable spongiform encephalopathies in many different species (e.g., cattle, sheep, deer, and humans) [79]. The immune system delivers crucial support for the spread of prions to the CNS, and B cell-deficient mice are protected from extraneurally administered prions [80]. B cells were initially suspected to transfer prions from the site of injection to lymphoid organs, but we now know that B cells play an indirect role, consisting primarily in provisioning survival factors for FDCs [81,82].

Prion inoculation experiments have unambiguously shown that FDCs are the main cell type responsible for lymphoid prion replication and accumulation. Accordingly, mice lacking mature FDCs (deficient in LT or its receptor LTβR) do not show any lymphoid prion replication [81]. In addition, transient depletion of FDCs by injection of the soluble decoy receptor LTβR-Fc, substantially impairs peripheral prion replication [82]. The accumulation of PrP^{Sc} in the GC can be visualized by blotting spleen sections onto membranes, followed by proteinase K treatment to remove cellular prion protein and staining with anti-PrP antibodies (a technique called 'histoblotting'). Histoblots have clearly shown that lymphoid PrP^{Sc} invariably colocalizes with FDCs [83].

The fact that FDCs are so efficient in accumulating prions has important consequences. Chronic inflammation, which is very common in farmed and free-ranging animals, can alter the organ tropism of prions. Mastitis and nephritis with occurrence of FDC-containing tertiary follicles lead to prion secretion via milk and urine, respectively, thereby potentially contributing to horizontal spread of prions within flocks [84,85].

The complement system plays a major role in targeting prions to FDCs. Deficiency in complement factors C1q, C3, and C4, or pharmacological depletion of C3, impairs peripheral prion replication [86,87]. These observations suggest that the complement system targets prions for FDC uptake by directly opsonizing PrP^{Sc}. This idea is supported by studies that show direct binding of C1q to PrP^{Sc} oligomers or immobilized PrP^C [88,89]. FDCs may acquire complement-opsonized prions via their abundant complement receptors. Indeed, lack of complement receptors CR1/2 on FDCs significantly impaired splenic prion replication and neuroinvasion [90]. Once trapped on FDCs, prions efficiently replicate in FDCs, which express high levels of PrP^C [78]. The presumptive longevity and the slow turnover of FDCs might contribute to their function as efficient prion sanctuaries, because *in vitro* experiments suggest that high mitotic activity may contribute to prion clearance [91]. After relatively long periods of asymptomatic prion replication in lymphoid tissues, neuroinvasion occurs primarily via sympathetic nerves, some of which are in close proximity to FDCs [92].

IgM–ICs by FDCs and thus increases IC display in the GC. It is thought that augmented IgM and presentation of autoreactive IgM–IC seen in mice under a high fat diet results in the generation of isotype-switched pathogenic autoantibodies [64,65]. Accordingly, AIM-deficient mice have reduced levels of self-reactive IgG [64].

Autoantibodies directed against intracellular components, such as double-stranded DNA are prevalent in many SLE patients. GCs of SLE patients accumulate apoptotic cells whose impaired removal leads to the release of intracellular components and immune activation [66,67]. Because these proteins are normally hidden from the immune system, they might not be available for thymic negative selection of T cells. Hence, some T cells reacting to nuclear proteins might escape the thymus. Indeed, autoreactive T cells can be found in SLE patients [68]. As in RA, natural IgM could also bind to nuclear proteins released from dying cells resulting in IC deposition on FDCs and subsequent selection of autoreactive GC B cells.

FDCs prevent autoimmunity by regulating the clearance of apoptotic cells

The vast majority of B cells generated in the GC reaction do not achieve higher antigen affinity, and some even acquire self-reactivity. These cells do not pass the selection process, undergo cell death through apoptosis, and are cleared by highly specialized macrophages of the GC, the TBMs. FDCs not only control GC B cells survival, but also 'license' TBMs for phagocytosis, thereby ensuring that the accumulating apoptotic B cell bodies are properly disposed of [69] (Figure 2F).

Little was known about how TMBs exert their scavenging function, until the Nagata group reported that Mfge8-deficient TBMs show impaired uptake of apoptotic cells in the GC [70]. When cells undergo apoptosis, they expose phosphatidylserine (PS) on their surface. Mfge8 is a secreted PS-binding protein that acts as a bridging molecule between the apoptotic cell and the macrophage, where it binds to surface integrin ($\alpha_v\beta_3$) [71]. Because certain macrophage populations can produce Mfge8, it was assumed that TBMs are the source of Mfge8 in the GC [69–71]. However, *in situ* hybridization visualizing Mfge8 mRNA showed unequivocally that the sole sources of Mfge8 are radiation-resistant FDCs and their precursors [1,69].

FDCs produce large quantities of Mfge8, which accumulates around their dendrites [69]. Hence GC B cells, while interacting with FDCs to receive survival signals, are drenched in Mfge8. Given the importance of rapid removal of dying cells to prevent autoimmunity, it is likely that Mfge8 ensures instantaneous opsonization of dying B cells exposing PS on their surface [70–72]. The clearance process is highly efficient, and in healthy individuals apoptotic cells within the GC can only be detected inside TBMs [73]. Selective lack of Mfge8 in FDCs, brought about by reconstituting Mfge8-deficient mice with wild type bone marrow, resulted in impaired engulfment of apoptotic cells and in subsequent accumulation of apoptotic cells on the surface of TBMs. Accordingly, Mfge8-deficient mice develop an SLE-like pathology [69,70].

The cascade delineated above implies that TBMs are the executioners of debris removal, yet their clearing activity necessitates 'licensing' by Mfge8. In the absence of Mfge8, TBMs are still able to bind apoptotic cells, but do not phagocytose them, and unengulfed cell debris accumulates on the surface of TBMs [70]. Indeed, local provisioning of Mfge8 for the purpose of TBM licensing may be one of the most important physiological functions of FDCs.

FDCs might not only acquire apoptotic cell-derived antigens upon impaired clearance from the GC, but also from the marginal zone (MZ) [74]. Li *et al.* showed that aged BXD2 mice that develop lupus-like autoimmunity have strongly reduced MZ macrophage numbers. In these mice, apoptotic debris accumulated in the MZ and was transferred onto MZ B cells, which have been shown to shuttle antigen in the form of ICs into the follicle and deposit them onto FDCs [29]. The release of apoptotic material in proximity of or inside the GC is thus likely to drive selection of autoreactive GC B cells and result in the development of SLE.

FDCs mediate tolerance outside the GC

Despite their involvement in antibody-mediated autoimmune responses, FDCs may also have a role in maintaining peripheral tolerance through the elimination of autoreactive naïve B cells. Yau *et al.* restricted membrane-bound autoantigen selectively to FDCs [75]. Mice expressing a membrane-bound form of duck egg lysozyme (DEL) under the CD21-promoter were reconstituted with hematopoietic cells from hen egg lysozyme (HEL) BCR transgenic mice. HEL BCRs show cross-reactivity with DEL at moderate affinity and FDC-restricted expression of autoantigen efficiently eliminated self-reactive HEL-BCR B cells, resulting in tolerance [75].

Another intriguing study reported an involvement of FDCs in tolerizing T cells: wild type females carrying mouse fetuses expressing a membrane-bound version of the model antigen ovalbumin (OVA) generated anti-OVA antibodies against fetal/placental OVA. OVA–ICs became deposited on FDCs and were maintained for several weeks postpartum [76]. DCs then sampled FDC-displayed antigen and successfully presented antigen–peptide; intravenously transferred OVA peptide-specific CD8 (OTI) T cells underwent an antigen-dependent proliferative burst, but subsequently were deleted. These findings suggest that in this context, DC presenting peptides derived from ICs presented by FDCs are tolerogenic. This was not only the case for placenta-derived OVA antigen because the same effect was also seen in wild type mice treated with OVA–ICs 3 weeks prior to OTI CD8 transfer. Although this mechanism might contribute to preventing anti-fetal T cell responses, the latter experiment suggests that this might be a more general approach to suppressing T cell responses.

The studies described above highlight a dual role for FDCs in autoimmunity. FDCs contribute to autoimmunity through the presentation of self-IC and the recruitment of self-reactive T_{FH} cells. Therefore, FDCs drive the selection and affinity maturation of self-reactive B cells. Conversely, FDCs are important gatekeepers of tolerance ensuring the timely removal of dying cells, negatively selecting naïve self-reactive B cells and inducing the generation of tolerogenic DCs unable to stimulate T cells.

Concluding remarks and outlook

Recent advances in understanding the cell lineage of FDCs and other lymphoid stromal cells have changed our perception of how secondary lymphoid organs develop. The existence of common perivascular progenitors implies their ubiquity because most tissues and organs are vascularized. However, it remains to be formally proven that vascular founder cells exist in tissues other than lymphoid organs and fat – the tissues investigated thus far. The ubiquity of vascular progenitors implies that TLT can arise in any place, yet this is far from clear. Might this indicate that the multipotency of perivascular cell differs from one tissue to another? Also, do FDC progenitors exist in nonvascularized tissues such as the cornea of the eye? This issue is important because corneal transplants have resulted in transmission of human prion diseases [77], suggesting the existence of corneal prion sanctuaries.

Transcriptomic analysis of FDCs revealed an immense number of molecules associated with this cell type [9,55]. Many of these molecules may influence follicular and GC B cells as well as T cells, possibly even altering innate responses. FDC-specific gene targeting studies will help determine the contribution of single factors to immunity and autoimmunity. In addition, the characterization of FDCs from select SLOs suggests that mature FDC populations may be more heterogeneous than previously thought [38], and these differences could reflect distinct roles in the GC of various lymphoid tissues. It will be interesting to determine the functional impact of this heterogeneity on the GC.

In summary, FDCs may not be able to retain their mysterious nature for much longer. Although many questions remain, recent studies have provided important insights into their histogenesis and broad range of functions. The pivotal involvement of FDCs in prion infections has rekindled intense studies of these cells and has brought about significant progress. Far from simply providing scaffolds to lymphoid tissues, FDCs help shape immune responses, and are crucial for the removal of cell debris from GCs and in preventing autoimmunity. Although these discoveries fall into the realm of basic immunology, they may someday be translated into diagnostic and therapeutic principles.

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