Follicular dendritic cells: dynamic antigen libraries

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Abstract | Follicular dendritic cells (FDCs) are essential for high-affinity antibody production and for the development of B cell memory. Historically, FDCs have been characterized as ‘accessory’ cells that passively support germinal centre (GC) responses. However, recent observations suggest that FDCs actively shape humoral immunity. In this Review, we discuss recent findings concerning the antigen acquisition and retention functions of FDCs, and relevant implications for protective immunity. Furthermore, we describe the roles of FDCs within GCs in secondary lymphoid organs and discuss FDC development within this dynamic environment. Finally, we discuss how a better understanding of FDCs could facilitate the design of next-generation vaccines.

Follicular dendritic cells (FDCs) are a unique population of cells that is essential for efficient germinal centre (GC) formation and for the production of high-affinity antibodies\textsuperscript{b} (FIG. 1a). They are centrally located within B cell follicles in secondary lymphoid organs and, as shown by Aguzzi and colleagues in an elegant study\textsuperscript{c}, they develop from perivascular precursors of stromal cell origin that are seeded throughout the body. FDC maturation requires lymphotixin and tumour necrosis factor (TNF) signalling through B cells, and the disruption of these pathways leads to the loss of FDCs\textsuperscript{3–5}. In the spleen and lymph nodes, FDCs are just one stromal cell type within a network of stromal cells (FIG. 1b,c). Although incompletely defined, the interplay between these different stromal cell populations may have substantial effects on the generation of protective immunity.

First identified in 1965 as ‘antigen-retaining reticular cells’, FDCs are now known to support GC responses through a variety of functions\textsuperscript{6} (FIG. 2 (TIMELINE)). FDCs maintain an organized follicular structure by producing CXC-chemokine ligand 13 (CXCL13), which signals via CXC-chemokine receptor 5 (CXCRI5) to attract B cells and specific subsets of T cells to the follicles\textsuperscript{7}. Interestingly, during selective ablation of FDCs, follicles lose their typical round shape and become disorganized ‘bands’ of cells. These B cell bands retain CXCL13-expressing stromal cell populations, which indicates that FDCs are not the only stromal source of this chemokine\textsuperscript{8}. FDCs also express an array of adhesion molecules that are thought to stabilize their interactions with cognate GC B cells, and they promote B cell survival in GCs through the production of interleukin-6 (IL-6) and B cell-activating factor (BAFF; also known as TNFSF13B)\textsuperscript{9,10}.

FDCs have the unique ability to retain intact antigen for extended periods. Indeed, this is required for GC maintenance, robust B cell somatic hypermutation (SHM) and the promotion of long-term immune memory\textsuperscript{11}. Activated B cells that participate in a GC reaction interact with antigen on the surface of FDCs in order to receive survival signals and undergo affinity maturation, which leads to the formation of memory B cell populations\textsuperscript{12–15}. Oyster and colleagues\textsuperscript{14} have excellently reviewed the multiple functions of FDCs in the GC reaction. In short, activated B cells migrate to the T cell–B cell border of the follicle where they present antigen to T helper cells and receive co-stimulation. Selected B cells then migrate to the centre of the follicle, where they start a cycle of proliferation and hypermutation in the dark zone before undergoing antigen-driven selection by FDCs in the light zone. After selection by the FDC, the B cell can re-enter the GC or, with the help of T follicular helper (TFH) cells, can exit the GC as a memory B cell or as a plasma cell (FIG. 3).

FDCs express high levels of complement receptor 1 (CR1; also known as CD35) and CR2 (also known as CD21; B.A.H. and M.C.C., unpublished observations), which are essential for antigen retention. In the absence of complement component C3 or following the deletion of the Gr2 locus (which encodes CR1 and CR2 in mice) FDCs are unable to retain antigen and GCs are reduced\textsuperscript{15}. Although affinity maturation can occur outside of GCs,
Somatic hypermutation (SHM). B cells diversify their B cell receptor by mutating the variable regions of immunoglobulin genes, thus creating a more specific repertoire. This occurs within the germinal centre and requires follicular dendritic cell-mediated help.

Affinity maturation
The process by which B cells produce antibodies with increased affinity for antigen during the course of an immune response. Follicular dendritic cells repeatedly present the same antigens to B cells and this leads to the production of antibodies with successively greater affinities.

Immune complexes
Structures that are formed by the binding of an antibody to a soluble antigen and subsequent complement deposition.

the depletion of FDCs, the disruption of antigen binding, or the ablation of CR1 or CR2 on FDCs results in the loss of GC maintenance and severely impairs SHM responses\(^2^,\(^3^,\(^4^,\(^5^\)). To preserve antigen for long time periods, FDCs trap immune complexes in recycling endosomal compartments, thereby protecting the antigen from degradation\(^6\). This observation suggests a mechanism by which FDCs may control antigen availability and regulate the humoral immune response.

In this Review, we detail recent developments in FDC biology and discuss how FDC interactions with other stromal cells may affect humoral immunity. We also explain how the regulation of antigen cycling by FDCs may be beneficial to the host by promoting the generation of high-affinity antibodies but may be disadvantageous during HIV infection.

Development and maintenance of FDCs
Within the lymph node environment, there is a heterogeneous population of stromal cells that are characterized, in part, by their differential expression of CD31 (also known as PECAM1) and podoplanin (also known as gp38 in mice and gp36 in humans)\(^7\) (FIG. 1c). The five major stromal cell types that can be distinguished on the basis of their morphology and function are fibroblastic reticular cells (FRCs), marginal reticular cells (MRCs), lymphatic endothelial cells (LECs), blood endothelial cells (BECs) and FDCs. The descriptions of FRCs, MRCs, LECs and BECs, and their contributions to immunity have recently been reviewed in detail\(^8\). This Review focuses on the development and maintenance of FDCs, and on their interactions with other components of the stroma.
FDCs mature from ubiquitous vascular mural cells that are seeded throughout the body. This becomes evident when one takes a closer look at human FDC sarcoma, in which there is a rare deregulation of FDC proliferation. This very uncommon neoplasm can occur anywhere in the human body, which is in line with recent studies that have identified FDC precursor localization in the mouse. Lineage-tracing experiments have shown that splenic FDCs, FRCs and MRCs originate from precursors that express homeobox protein NKX2-5 and insulin gene enhancer protein ISL1 (ISL1; also known as islet 1); however, lymph node stromal cells are derived from other precursors that are as yet unknown. When precursor cells were implanted under the kidney capsule of mice, normal lymphoid structures developed, which indicates that the implanted cell population contained lymphoid tissue organizer cells, as well as stromal precursors for FRCs, MRCs and FDCs. In contrast to in vitro FDC cultures that are derived from lymph nodes, cultures that are derived from the spleen do not form B cell clusters (B.A.H. and R.C.M., unpublished observations). These observations suggest a developmental and functional distinction between lymph node-derived and spleen-derived FDCs.

FDCs develop as part of a stromal network. During prenatal development, retinoic acid (converted from vitamin A) triggers lymphoid tissue organizer cells to produce CXCL13, which attracts early lymphoid tissue inducer cells (LTi cells) to sites of lymph node formation. In response to lymphotixin-β receptor (LTβR; also known as TNFRSF3) signalling in LTi cells, lymphoid tissue organizer cells express various adhesion molecules and chemokines that promote the clustering of haematopoietic cells, which leads to the expansion and differentiation of the stromal network. MRCs are among the first subset of stromal cells to appear. They are present in the lymph nodes at birth and are morphologically similar to lymphoid tissue organizer cells. MRCs differentiate in response to lymphotixin that is produced by LTi cells and subsequently localize just below the lymph node subcapsular sinus (SCS). Here, they produce CXCL13, further supporting stromal organization and the trafficking of leukocytes into the developing lymph node. Although the exact sequence of events is not clear, FRCs and MRCs are thought to develop during the same period and to require similar developmental signals. At birth, FRCs are found throughout the parenchyma, where they ensheath a dense conduit network that they generate through the secretion of extracellular matrix components. During the first week of postnatal development, the lymphocyte compartment within the lymph node is almost entirely composed of T cells, and this corresponds with the appearance of conduits. Incubation of CD4+ T cells with lymph node-derived stromal cell lines induces the production of an extracellular matrix in vitro, which suggests that this influx of T cells into the early lymph node leads to conduit formation through interactions between T cells and FRCs. In the absence of B cells during initial lymph node formation, conduit networks throughout the paracortex are dense and have an extensive branching pattern. However, once B cell follicles are fully formed, the conduits are sparser and branching is reduced within the B cell area. In adult μMT mice, which lack mature B cells, the lymph node paracortex contains an abundant web of conduits that is surrounded by ERTR7+ FRCs. Following the adoptive transfer of wild-type B cells into μMT mice, the conduit network around aggregating donor B cells in the paracortex is progressively remodelled. Although the mechanism for this remodelling is not well understood, it is thought that the induction of FDC maturation by incoming B cells that are forming primary follicles has a central role. Indeed, close interaction between FRC conduits and FDCs is observed within mature B cell follicles. Additionally, the FDC population is absent in irradiated wild-type mice that have been reconstituted with LTβ-deficient bone marrow and this allows FRCs to return to the follicles. This suggests that FRCs are displaced from B cell follicles by developing FDCs. Alternatively, FDCs might differentiate from a local population of stromal cells that can also differentiate into FRC-like cells. Although the method of communication has not yet been identified, these studies demonstrate that FDCs interact with other stromal cells during development for the proper localization of each population within the lymph node environment.

Antigen acquisition and processing by FDCs In mice, FDCs are the only cells that are known to be capable of retaining intact opsonized antigen for long periods of time. It is generally accepted that FDCs can retain antigen for up to 12 months, although experimental confirmation is lacking. However, on the basis of extrapolation from decay rates, FDCs are estimated to retain antigen for years after its introduction. Nevertheless, it is not yet clear how antigen is transported to FDCs and by what mechanisms it is retained by these cells.

Trafficking of antigen. Lymph entering the node through the afferent lymphatics is channelled through the SCS into the medulla. FRG conduits access afferent lymph and traverse B cell follicles, where they intersect FDCs. Alternatively, FRC conduits continue into the cortex, where they terminate at high endothelial vessels or the medulla. In the lymph node, the delivery of lymph-borne antigens to FDCs occurs via multiple pathways and the exact route that is taken is determined by the size of antigen and whether it is opsonized with complement. Lymph-borne antigens that are smaller than 70 kDa (approximately 5.5 nm) flow directly to the FDCs via the conduit network. By contrast, large complexes are captured and transported across the SCS by SCS macrophages, which have been referred to as the ‘guardians of the lymph node’. Complexes that are opsonized with complement are shuttled to naive B cells in the underlying follicles, where they are then delivered to the FDCs. Alternatively, intact bacteria, viruses and other large antigens are captured and processed in the medulla by SCS macrophages or CD11c+ lymph node-resident DCs. Whether antigen is transferred to naive B cells...
by resident DCs or by medullary macrophages is not clear. However, it is probable that DCs are capable of directly transporting antigen to the FDCs [FIG. 4c]. This suggests that the conduit network functions as a safety filter for FDCs by protecting them from unprocessed pathogens but also enabling the sampling of small antigens in the lymph.

Immune complexes that arrive in the afferent lymph are taken up by SCS macrophages via Fc receptors and CR3. Strikingly, the C3d-coated immune complexes are transferred from the apical to the basolateral surface of the SCS macrophages, and these complexes are subsequently transferred to CR2-expressing naive B cells in the underlying follicle43. This CR2-dependent transfer of immune complexes raises the question of how C3d can simultaneously bind two different receptors — that is, CR3 on SCS macrophages and CR2 on naive B cells. Recent crystallography studies have solved the crystal structures of C3d bound to CR2 and of C3d bound to CR3 (REFS 47–49). It was noted that CR3 and CR2 bind to distinct sites on C3d and, in combination with the stable in vitro formation of CR3–C3d–CR2 complexes, this suggests a molecular mechanism for antigen transfer. Alignment of the crystal structures of the CR2–C3d complex with the CR3–C3d complex identifies the distinct molecular sites at which C3d contacts these receptors (FIG. 4b).

The ‘hand off’ of antigen (which is present in C3d-coated immune complexes) from B cells to FDCs is unidirectional, although the underlying mechanism is unclear47. Treatment of FDCs with the actin inhibitor cytochalasin D blocks the uptake of immune complexes47, which shows that the FDC mechanism that is involved in antigen transfer is actin dependent. C3d-coated immune complexes form an aggregate or ‘patch’ on the B cell surface47,48, which suggests a spontaneous aggregation of the receptor–ligand complexes. Live-cell imaging of the transfer process in vitro identifies a rapid dispersal of the C3d-coated immune complexes on the FDC surface upon contact with the naive B cell47. The unidirectionality of transfer may be explained by an active ‘pulling force’ of the CR2 receptor, which is anchored to the actin cytoskeleton, and the higher density of CR2 receptor expression by FDCs relative to naive B cells (B.A.H., unpublished observations). The naive B cells can only bind a small proportion of the C3d molecules that are present in the immune complex but, as FDCs are much larger cells, they will probably bind the majority of the available C3d molecules. By pulling the immune complexes inside and thus rapidly sequestering them, the CR2 receptors on the FDC are able to strip the antigen complexes from the B cell. Thus, the combined effect of C3d-coated immune complex aggregates on B cells, the high density of CR2 on FDCs and the active pulling force of the CR2 receptors on FDCs brings about a unidirectional transfer of C3d-coated immune complexes to the FDC.

**Cycling of antigen.** Early electron microscopy studies identified immune complexes on the FDC surface, which helped to explain how the antigen gains access to GC B cells. However, this did not explain how antigen could be retained by FDCs for extended periods of time. A solution to this apparent paradox was recently proposed, with the finding that FDCs cycle CR2-bound C3d-coated immune complexes in non-degradative endosomal compartments47. This pathway enables the FDC to protect the antigen from degradation and keep it available for B cells in its native form [FIG. 4a]. How long antigen can cycle and be retained is unknown, however we have found that stable immune complexes containing intact opsonized antigen can still be observed 3 months after antigen injection (B.A.H., unpublished observations).

**Lymph flow through conduits alters stromal cell function.** Under homeostatic conditions, there is a constant flow of lymph fluid through the lymph nodes. However, studies in sheep have suggested that a substantial increase in the rate of lymph flow occurs as an early response to injury or infection49–52. As stromal cells are in close proximity to the sinuses and conduits...
of the lymph node, they may be affected by the increase in fluid pressure and shear stress that occurs in association with increased lymph flow. For example, exposure to low fluid flow rates in vitro enhanced the production of CC-chemokine ligand 21 (CCL21) by FRCs. By contrast, increased flow rates in this model substantially decreased CCL21 production by FDCs. Interestingly, this suggests that the rate of lymph flow may regulate stromal cell function and have an immunosuppressive effect under inflammatory conditions. In addition to FRCs, FDCs directly interact with the conduit network in B cell follicles (Fig. 4a), which suggests that they may also be sensitive to changes in the rate of lymph fluid flow.

If a high rate of lymph fluid flow regulates stromal cell functions, why would this be advantageous under inflammatory conditions? One possibility is that fluid flow may help to 'tune down' immunity to secondary infections. For example, Mueller et al. observed in mice that following initial splenic infection with lymphocytic choriomeningitis virus (LCMV), the immune response to a secondary infection was suppressed. Importantly, the Armstrong strain of LCMV that was used for these studies does not infect stromal cells, unlike the LCMV strain clone 13. A similar observation was made following the infection of mice with other pathogens or the administration of virus-like particles, which confirmed that the effect was not specific to LCMV infection. Intriguingly, the local production of the homeostatic chemokines CCL21 and CXCL13 was dramatically reduced by day 3 following infection, which correlated with the impaired migration of circulating lymphocytes and DCs into the appropriate splenic compartments. The interpretation of these findings was that a local reduction in the levels of homeostatic chemokines might bias the immune response towards responding to the primary infection and limit competition from incoming lymphocytes and DCs for space and resources in the lymph node. Based on these observations, we propose that an increase in lymph pressure and shear stress during inflammation may alter antigen cycling by FDCs, favouring the presentation of pre-existing antigens and limiting the uptake of antigen from a secondary infection. In this model, as well as regulating FDC function, the increased lymph fluid flow could also enhance B cell responses to the primary infecting agent.

Figure 3 The germinal centre reaction. Simplified schematic of affinity maturation in the germinal centre (GC). At the T cell–B cell border of the lymph node, B cells present antigen to T helper cells and receive co-stimulatory signals. The selected cells enter the dark zone of the GC and undergo somatic hypermutation (SHM) by upregulating components of the SHM machinery, including activation-induced deaminase (AID). After one cycle (or possibly more cycles) of proliferation and SHM, the B cells migrate to the light zone. In the light zone, the mutated BCRs that are the product of SHM are now exposed to antigens that are incorporated into immune complexes on the follicular dendritic cells (FDCs). If the affinity of the BCR is very low, the B cell will not receive survival signals and will undergo apoptosis. The remaining B cells need to compete for limited T cell help, which favours the higher affinity B cells and forces the others to undergo apoptosis. Surviving B cells can then undergo one of three fates: they can re-enter the dark zone and undergo further proliferation and SHM, they can exit the GC as plasma cells or they can exit as memory B cells. Re-entry will allow for further affinity maturation. It is thought that FDCs might influence affinity maturation by regulating the amount of antigen on their surface, however, due to technical limitations this has not been shown experimentally. T<sub>H</sub> cell, T follicular helper cell.
FDC antigen cycling could also be affected by the content of the lymph, as the dendritic processes that are extended by FDCs are in intimate contact with the FRC conduits and these cells are therefore likely to be affected by factors other than the shear flow of lymph. This would provide a rapid response to the breakdown products of infectious agents or cytokines and chemokines that are released in response to infection. It is known that the availability of antigen regulates GC persistence and promotes SHM, which is crucial for the generation of broadly neutralizing antibodies. Therefore, by regulating the availability of antigen, FDCs could affect the extent of SHM and, potentially, the generation of broadly neutralizing antibodies. Various pathogens, such as HIV, require multiple rounds of SHM (as many as 200) to elicit an effective broadly neutralizing antibody response. As selection for antigen is necessary and as GC B cells are not thought to migrate among follicles but to remain within a specific site to promote clonal expansion, the longer retention of native antigen by FDCs is important in the successful generation of broadly neutralizing antibodies.

**FDCs in pathogenesis**

*Function of Toll-like receptors on FDCs.* FDCs express an array of Toll-like receptors (TLRs) but the role of these receptors on FDCs is not clear. One possibility is that FDCs may use TLRs to respond to the products of viral and bacterial degradation in the periphery that flow into lymph node conduits. Bone marrow chimeric mice that lack TLR4 expression on stromal cells (including FDCs) have lower levels of SHM and high-affinity antibody production, which suggests that TLR4 signalling in FDCs is crucial for robust antibody response.
responses. Additionally, TLR2 and TLR4 stimulation of FDCs in the gut induces the production of transforming growth factor-β (TGFβ) and BAFF, which leads to IgA class switching in B cells\(^63\). In these two studies, TLR signalling in FDCs induced the upregulation of chemokine and adhesion molecule expression, which indicates that TLR ligands may regulate FDC function. In an elegant study, Pulendran and colleagues\(^64\) showed that the immunization of mice with nanoparticles that contained antigen and ligands of TLR4 and TLR7 induced sustained GCs that persisted for more than 1.5 years. They also showed that the presence of these TLR ligands enhanced B cell affinity maturation. As FDCs are crucial for GC B cell survival and SHM, it is possible that TLR ligands enhance these responses not only through their effects on DCs and B cells but also by directly affecting FDC function. Thus, following infection, TLR ligands in the lymph may rapidly activate FDCs and this could markedly affect the early events in GC formation.

**Prions and HIV.** Although the primary contribution of FDCs to host defence against infection is promoting humoral immunity to protein antigens, pathogens may interact with FDCs directly. For example, prions are taken up by FDCs (as reviewed recently by Aguzzi and colleagues\(^65\)). Prions are proteinaceous infectious particles that, when converted from their physiological form (PrP\(^C\)) to a pathological configuration (PrP\(^Sc\)), cause transmissible spongiform encephalopathy (TSE) in mammals\(^66,67\). FDCs express high levels of PrP\(^C\) and they are thought to be an important site for PrP\(^C\) to PrP\(^Sc\) conversion\(^68\). Experiments using reciprocal bone marrow chimaeras have suggested that PrP\(^C\) expression in stromal cells, but not in haematopoietic cells, is required for PrP\(^Sc\) replication in the spleen\(^69,70\). Following intraperitoneal inoculation, infectious prions accumulate in FDCs before infiltrating the central nervous system (CNS). Furthermore, the ablation of FDCs — through the depletion of B cells or the treatment of mice with LTβR–Ig — prevents the accumulation of prions in the spleen and slows the neuroinvasion process\(^71–74\). Although these studies suggest a crucial role for FDCs during the subclinical stages of TSE, the mechanism by which prions travel from FDCs to the CNS is not well understood. The distances between FDCs and splenic nerves are reduced in mice that are deficient in CXCR5, and this correlates with accelerated neuroinvasion of prions and with clinical manifestations of scrapie\(^75\). However, the mechanism by which prions travel through the splenic nerves into the spinal cord is not known.

In a similar manner to prions, HIV is thought to directly interact with FDCs (FIG. 5). HIV evades host immunity by exploiting the very mechanisms that the immune system uses for host defence. Although few studies have directly examined FDC function during HIV infection, indirect evidence suggests that FDCs actively support viral survival and dissemination\(^76\). HIV is capable of independently fixing complement through complement factor I and, paradoxically, this enhances HIV infectivity \(^77–79\). Fragments of C3 bound to gp160 allow HIV to adhere to the complement receptors CR1 and CR2, which are expressed at high levels.
by FDCs. Additionally, non-neutralizing antibodies specific for HIV — which are found in most patients with HIV — may contribute to the trafficking of virions to FDCs through FcR-mediated binding, whereby the virus maintains the ability to infect surrounding cells for many months (Box 1).

**Perspective**

The long-term retention of antigens by FDCs is required for the maintenance of GCs and for the efficient production of high-affinity antibodies. Indeed, FDCs can be considered as the ‘catalysts’ of the GC reaction and, as with every catalyst-driven reaction, the lower the concentration of the substrate (in this case, the antigen), the more important the catalyst is for ensuring the successful generation of the product (that is, high-affinity antibodies). Concentrating antigen on FDCs becomes more important when antigen availability is limiting, which is often the case under physiological conditions. The discovery that FDCs continuously cycle the antigens that they have taken up within non-degradative endosomal compartments explains not only how antigen is retained for extensive periods but also how it is made available to cognate B cells. Future experiments should help to further define how FDCs participate in actively shaping humoral immunity by regulating antigen availability.

As FDCs express an array of TLRs, it will be of interest to determine whether TLR signalling in FDCs affects the cycling of antigen and, in turn, the process of affinity maturation and the production of broadly neutralizing antibodies. As pathogens such as HIV may be protected within endosomal compartments, reducing the internalization of virions by FDCs may be an important step in generating protective immunity to these infections. Finally, a better understanding of the mechanisms that regulate antigen availability on FDCs could be useful for developing therapies for antibody-mediated autoimmune diseases (Box 2).

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