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

Adriano Aguzzi[1], Jan Kranich[2], and Nike Julia Krautler[3]

[1] Institute of Neuropathology, University of Zurich, Zurich, Switzerland
[2] Institute for Immunology, Ludwig Maximilians University, Munich, Germany
[3] Garvan Institute of Medical Research, Darlinghurst, New South Wales, Sydney, Australia

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

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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.

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