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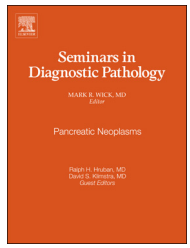

Follicular dendritic cells and related sarcoma

Fabio Facchetti, MD, PhD, Luisa Lorenzi, MD*

Section of Pathology, Department of Molecular and Translational Medicine, University of Brescia, Spedali Civili, Brescia 25123, Italy

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ABSTRACT

Follicular dendritic cells are mesenchymal-derived dendritic cells located in the B follicles, where they capture, retain and present antigens to surrounding B cells, thus playing a pivotal role in triggering and maintaining B-cell adaptive immune response. The term follicular dendritic cells (FDC) was originally introduced by Steinman et al. in 1978. In 1986, Monda and Rosai first reported tumoral proliferations derived from FDC occurring in lymph nodes and the term FDC sarcoma was subsequently coined to identify this neoplasm. FDC sarcoma is nowadays a well recognized entity known to involve both nodal and extranodal sites. In this review we summarize data on physiological functions of FDC in the immune response, their involvement in pathological conditions, and the clinical, histopathological and phenotypic features of FDC sarcoma.

Introduction

Follicular dendritic cells (FDC) are mesenchymal-derived dendritic cells located in the B follicles, where they capture, retain and present antigens to surrounding B cells.[1] They have been originally discovered by Maximow[2] in human lymph nodes and defined as "*embryonal non-phagocytic reticulum cells*" occurring in B follicles. Electron microscopic features[3–6] subsequently prompted to define them "*antigen-retaining reticulum of lymph node follicles*[6] or simply "*reticular cells.*"[5] The term *follicular dendritic cells* (FDC) was introduced by Steinman et al. in 1978, who emphasized their highly irregular arrays of cytoplasmic processes embracing follicular lymphoid cells.[7] Based on these limited set of morphological observations, the authors hypothesized that FDC might play an important role in the GC reaction, which was later proved by a series of experimental studies.[1]

In 1986, Monda and Rosai first reported four cases of tumors derived from FDC, all occurring in cervical lymph nodes.[8] The neoplasm, now recognized as FDC sarcoma,[9] has been found to involve nodal and extranodal sites. The morphological, immunohistochemical, and clinical features of FDC sarcoma are rather well established, but little is known about its molecular and genetic properties.

In this article we summarize data on physiological functions of FDC in the immune response, their involvement in pathological conditions, and the clinical, histopathological, and phenotypic features of FDC sarcoma.

Origin and functions of FDC

While other dendritic cells such as myeloid dendritic cells, Langerhans cells, and plasmacytoid dendritic cells are of hematopoietic origin, FDC derive from mesenchymal precursors,[10] similarly to other members of the stromal compartment of secondary lymphoid organs, which include fibroblastic reticular cells and marginal reticular cells.[1] Experiments in mice showed that FDC precursors are located in the perivascular area and are represented by

* *Corresponding author.*
E-mail address: fabio.facchetti@unibs.it (F. Facchetti).

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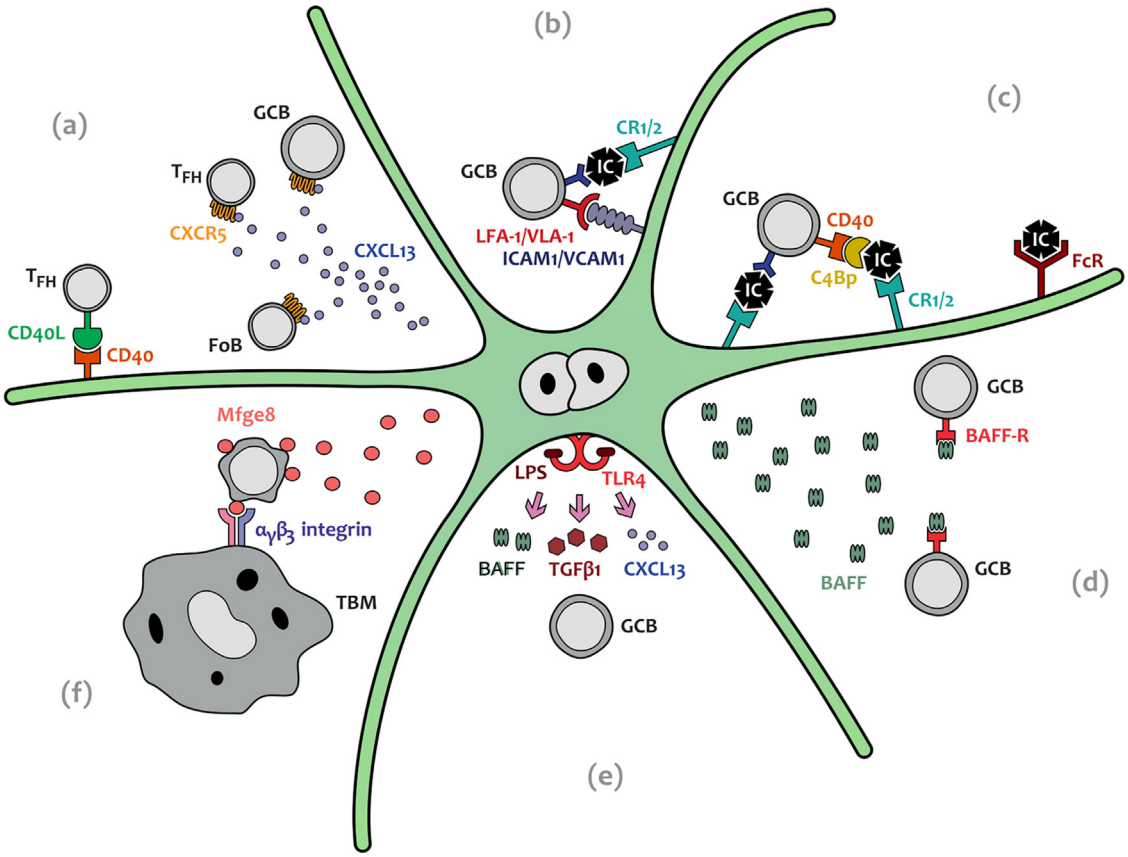

Fig. 1 – Follicular dendritic cell (FDC) functions and interactions in the germinal center. FDC are fundamental for the recruitment of B and T cells in B follicles, especially by secreting CXCL13 (a) and directly interact with B cells by integrins/integrin receptors (b). FDC express on their surface immunocomplexes (IC) that are repeatedly presented to surrounding B-cells (b and c), and sustain their survival and maturation by secretion of different B-cell growth factors (d). FDC can also sense environmental innate stimuli binding microbial lipopolysaccharide via TLR4 (e). The germinal center reaction generates inefficient B cells that undergo apoptosis and FDC mediate apoptotic bodies phagocytosis by tingible body macrophages (f). For details see text ("*Origin and function of FDC*"). BAFF, B activating factor; BAFF-R, BAFF receptor; C4Bp, complement component 4 binding protein; CR, complement receptor; FoB, follicular B-cells; GCB, germinal center B cells; ICAM, intercellular adhesion molecule; IC, immunocomplex; LPS, lipopolysaccharide; Mfge, milk fat globule-EGF factor; TBM, tingible body macrophage; TGF, tumor growth factor; T_{FH}, T follicular helper cells; TLR, toll-like receptor; VCAM, vascular cell adhesion molecule.

platelet-derived growth factor receptor β-positive cells.[11] These studies suggested a two-steps FDC differentiation process, with the initial development of pre-FDC, triggered by lymphotoxin (LT) αβ and leading to expression of milk fat globule-EGF factor 8 (Mfge8) and chemokine (C-X-C motif) ligand (CXCL)13, and a final maturation into complement receptor-positive FDC, mediated by both LTαβ and tumor necrosis factor (TNF) receptor 1.

The discovery of mechanisms underlying FDC origin and functions in animal models may give an input to experiments on human FDC, which are markedly hampered by difficulties in cell isolation and *in vitro* maintenance.[12–14]

FDC immune functions are mediated by their numerous interactions with other components of the B-cell follicle especially in the microenvironment of germinal centers (GC) (Fig. 1).[1] In particular, via CXCL13 FDC attract C-X-C chemokine receptor (CXCR)4 and CXCR5-positive B and T lymphocytes within the follicles (Fig. 1A). A direct interaction of FDC with B cells is primarily based on the expression of integrins (vascular cell adhesion molecule 1/VCAM1 and intercellular adhesion molecule 1/ICAM1) that bind their ligands (VLA-1/α4β1 and LFA-1/αLβ, respectively) on lymphocytes (Fig. 1B). The proper modulation of these immunological synapses establishes the effectiveness of the adaptive immune response following antigen capture and presentation by FDC as immunocomplexes (IC) (Fig. 1C).[15] IC are shuttled to FDC from the marginal sinus by marginal zone or non-cognate follicular B cells[16] and are bound to FDC by either complement or Fc receptors (e.g., CD21, CD35, CD23, and CD32) (Fig. 1C). FDC retain IC in non-degradative endosomal vesicles for long time, periodically recycling them on the cell surface to enhance B-cell activation.[17,18] B cells that bind the antigen on FDC surface receive pro-survival signals, including the B-cell activating factor (BAFF) secreted by FDC (Fig. 1D). Interestingly, FDC can modulate the adaptive response by sensing the environmental innate stimuli, since they express the toll-like receptor (TLR)4 able to interact with microbial lipopolysaccharide. Moreover, activation of the TLR signaling