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Follicular Dendritic Cells in Non-Hodgkin Lymphomas: Localisation, Characterisation and Pathophysiological Aspects

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INTRODUCTION

IN LYMPHOID TISSUE, lymphocytes and additional cells of the mononuclear phagocytic system and the dendritic cell family can be identified. Follicular dendritic cells (FDC) are restricted to the B-cell regions of secondary lymphoid tissue, i.e. lymph-nodes, spleen and tonsils. Their long cytoplasmic extensions form a dense framework throughout the follicles [1]. FDC trap and retain immune complexes on the surface of their processes for long periods [2]. During the secondary immune response, these antigen-antibody complexes are internalised by B-lymphocytes. Subsequently, they undergo rapid proliferation resulting in the expansion of the virgin-B and memory-B-cell pool and an increased level of immunoglobulins in the serum [3, 4].

FDC are also present in non-Hodgkin lymphomas (NHL) derived from follicular centre cells [1]. As they do in the non-malignant tissue, here FDC form a network which contains accumulating neoplastic B cells. This intimate association appears to be pathognomonic for germinal centre cell-derived neoplasias [5]. Occasionally FDC may be identified in non-follicular centre cell-derived NHL when a pseudonodular growth pattern is observed [6, 7]. In these cases the neoplastic lymphocytes seem to have their normal counterparts in the follicle mantle zone [6].

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In this review we will focus on the neoplasias with FDC involvement. The antigenic phenotype of FDC in normal conditions and neoplastic disorders will be summarised. *In situ*, cell borders between FDC and adjacent lymphocytes are difficult to distinguish by light microscopy. Therefore, accurate analysis of FDC surface antigenic profile has been performed by several scientists subsequent to the preparation of single cell suspensions enriched in FDC [8–12].

In vitro studies with FDC isolated from murine lymph-nodes or human tonsils indicate their importance as an accessory cell in the secondary immune response. Additionally to the presentation of antigen, a major role of FDC appears to be the stimulation of germinal centre B-lymphocytes [13]. Until now, only a very limited number of data are available on *in vitro* experiments with FDC isolated from lymphoma tissues. In the second part of this summary we will unfold the interactions between FDC, germinal centre B-lymphocytes and lymphoma cells, respectively. Finally, FDC resistance to irradiation and chemotherapeutic drugs will be considered.

FDC IN NORMAL LYMPHOID TISSUE

The detection of FDC by conventional light microscopy or histochemical techniques is difficult. The production of monoclonal antibodies (Mab) selective for FDC has enabled scientists to study the distribution pattern of FDC in lymphatic tissue [5, 14, 15]. FDC have been identified in primary follicles and germinal centres of secondary lymphoid tissue. Their branching cytoplasmic extensions form a dense, sharply demarcated dendritic web. In addition, FDC have been observed in the mantle zone that surrounds the germinal centre. In these sites their fusiform processes are more loosely arranged [1, 16].

FDC have not been identified in the extrafollicular regions of the lymphatic tissue [17] nor in sections of normal thymus, liver, skin or kidney [15]. Follicular centre cell lymphomas often imitate the pattern and cellular composition, characteristic of a normal germinal centre reaction. Thus, FDC have been identified above all in lymphomas with follicular growth patterns [1, 6].

LYMPHOMA ENTITIES WITH FDC INVOLVEMENT

Germinal centre cell-derived NHL

In low grade malignant NHL derived from germinal centre cells (i.e. centroblastic–centrocytic lymphoma) nodules resembling the secondary follicules within the non-malignant lymphatic tissue are detected. These nodules contain FDC where they constitute a well defined, dense spherical meshwork. The monoclonal B-cells of the centroblastic and centrocytic type are enwrapped tightly by the cytoplasmic processes of these FDC [6].

Only in some cases of high malignant NHL derived from germinal centre cells (i.e. centroblastic lymphomas) have FDC been identified. In these neoplasias FDC are often less densely packed or are present in irregular clusters or clumps, sometimes showing an asymmetrical layout [6].

Non-germinal centre cell-derived NHL

FDC are consistently present in the centrocytic lymphoma. Congruent with the diffuse growth pattern revealed in the histological examination of centrocytic lymphomas [18] a diffuse, non-nodular distribution of the FDC is visualised in the majority of cases. Still FDC remain closely intermingled with the neoplastic lymphocytes. In this NHL entity, however, the cytoplasmic branches of FDC are not as sharply outlined as they are in the centroblastic–centrocytic subtype. Other authors refer to the centrocytic lymphoma as mantle zone lymphoma [19]. In mantle zone lymphomas, as defined by Weisenburger *et al.* [20], FDC are arranged in a loose and ill-defined mesh with a radiating outline. In the nodules of follicular centre cell lymphomas, however, FDC show a dense, well developed and sharply defined framework [19]. These immunohistochemical findings resemble the FDC distribution in the follicular mantle and the germinal centre, respectively, of normal lymphoid tissues.

Prominent FDC clusters have been detected only in a minority of lymph-nodes from patients with B-cell chronic lymphatic leukaemia (B-CLL) [5, 19]. Lymphoma-associated FDC involvement has furthermore been described in some patients with Burkitt type lymphoblastic lymphoma [6] and Hodgkin's disease [21]. No association has been found with FDC in prolymphocytic leukaemia, hairy cell leukaemia or multiple myeloma [6].

Follicular dendritic cell sarcoma

To our knowledge, only one case of a immunohistochemically confirmed sarcoma derived from the antigen-presenting FDC has been published [22]. In this report, the tumour cells were large with ill-defined cytoplasmic borders and irregular nuclei. The neoplastic cells were intermingled throughout the tumour with normal lymphocytes. As in the normal lymphoid tissue, binucleated and polynucleated FDC could be detected frequently in the follicular dendritic cell sarcoma. Histological examination revealed a storiform like growth pattern of the tumour cells. Evidence for a FDC-derived neoplasia was given by demonstration of CD21, CD23 and CD35 on the cell surface, the positive reaction of the sarcoma cells with the FDC selective Mab R4/23, their negative reaction with Mabs against cytokeratin and the detection of desmosomes [22].

FDC in extranodal lymphomas

Malignant lymphomas detected in biopsy samples of liver, skin or bone marrow are denominated extranodal because of their localisation outside the lymphatic tissue. These organs are normally devoid of FDC [15]. The observation of extranodal NHL with FDC involvement suggests that the accessory cells immigrate into, or are newly formed within, the neoplastic microenvironment. Naiem *et al.* [5] described a case of a follicular lymphoma with tumour-associated FDC infiltrating the kidney.

As already indicated, only in a minority of patients with B-CLL has FDC involvement been observed. However, in as many as 50% of the patients with nodular bone marrow infiltration by B-CLL lymphocytes, FDC have been identified [23]. Since FDC are absent in the normal bone marrow, it may be hypothesised that lymphoma cells elicit the differentiation of FDC precursors already present in the bone marrow.

Mori *et al.* [24] suggest that different lymphoma entities induce different states of FDC maturation. They observed the transition of a mantle zone lymphoma into a follicular lymphoma; this progression was accompanied by an increase in density of FDC associated with this area. The loosely arranged FDC of the mantle zone lymphoma differentiated to form a complete dendritic web characteristic of germinal centre cell-derived neoplastic.

IMMUNOPHENOTYPE OF HUMAN FDC

Non-malignant tissue

Because of the close association betwen FDC and the surrounding lymphocytes, expression of surface molecules on FDC cannot be easily assessed when cryostat sections of tonsils or lymph-nodes are examined. Immunophenotyping of FDC in single cell suspensions has also rendered controversial observations. The inconsistent results obtained by different scientists may be an indication for the heterogeneity of FDC.

The antigenic profile of human FDC varies according to their topographic localisation within the follicles: CD9 (p24) and CD14 (gp55) have been visualised on FDC in the central portion of the germinal centre but not on FDC localised in the mantle zone [25]. FDC diversity may also relate to different states of activation: CD23 positive FDC (low affinity receptor for IgE) have been described only in the light zone of the germinal centre [26, 27]; the light zone contains mainly centrocytes but few centroblasts.

Furthermore conflicting observations could be explained by the different techniques applied for the isolation of FDC (i.e. proteolytic reagents may cause non-specific alterations of cell surface proteins). In agreement with recently published data [10, 11, 28] FDC isolated from human tonsils express receptors for C3bi (CD11b), C3d (CD21) and C3b (CD35), components of the complement system. The immunoglobulin μ, alpha and gamma heavy chains as well as kappa and lambda light chains were detected on the FDC surface. FDC are intensively labelled for intercellular adhesion molecules, class II antigens and the myelomonocytic antigen CD14.

Lymphoma tissue

As with normal lymphoid tissue, heterogeneous FDC subpopulations have been described in NHL. FDC in mantle zone lymphomas are devoid of CD9 and CD14. However, these

antigens are detected on FDC in follicular centre cell-derived NHL [29]. Obviously the distribution of CD9 and CD14 negative/positive FDC within the normal lymphatic tissue (i.e. negative in follicle mantle, positive in germinal centre) is maintained in neoplasias, related to these localisations.

The antigenic profile of FDC associated with malignant lymphomas generally resembles that of FDC from hyperplastic tonsils but it is not always identical. Imai *et al.* [21] describe a loss of FDC membrane antigens in lymphomas with a diffuse growth pattern, as compared to FDC in follicular lymphomas.

Phenotyping FDC in cryostat sections and cytospin preparations of non-malignant lymph-nodes discloses membrane-bound immunoglobulins. These immunoglobulins are not synthesised by the FDC. Staining with anti-Ig Mab displays trapped immune complexes on the FDC surface. Labelling lymphoma associated FDC for surface immunoglobulins in tissue sections gave negative results [26, 30]. Although the immunological properties of FDC (i.e. immune complex trapping) might not be compromised by the neoplastic conditions, it may be proposed that the lack of antigen–antibody complexes on the FDC surface in some malignant cases is due to the fact that within the malignant environment, the regular processing of antigen, production of antibody and the formation of immune complexes is impeded.

INTERACTIONS BETWEEN GERMINAL CENTRE B-CELLS AND FDC

Presentation of antigen

Within 24 hours of a secondary response to soluble proteins, immune complexes become deposited on FDC [31]. Subsequently, many changes occur within the follicular microenvironment leading to the generation of a germinal centre. The major consequences of the germinal centre reaction are the production of B-memory-cell clones and high titres of specific antibodies. For this response to occur, FDC interact with germinal centre B-cells in the following manner.

Once antigen becomes deposited on FDC, many begin to undergo morphological changes [32]. Their dendritic processes begin to form small spherical structures (0.3–0.5 μm in diameter) which maintain immune complexes on their surface (i.e. immune complex coated bodies, abbreviated iccosomes) [32]. As the iccosomes are formed, the lymph-node experiences an oedematous state which facilitates the dispersion of the iccosomes throughout the germinal centre. B-cells become intimately associated with the iccosomes and eventually internalise the surface-bound antigen. The uptake and processing of antigen within the B-cells has been observed at the ultrastructural level [32]. In addition, the ability of the B-cells to then present the antigenic peptide to T-cells has been shown functionally using an *in vitro* culture system [33]. The observations suggest that *in vivo*, B-cells receive an antigenic signal from the FDC which activates the B-cells making them susceptible to secondary signals.

As the reaction continues, germinal centre B-cells undergo rapid proliferation. Concurrent with this high rate of mitosis is the appearance of cells which are dying via an apoptotic mechanism [34]. In order to obtain higher affinity B-cell clones as well as cells differentiating towards antibody formation, additional factors are required to the antigenic stimulus provided by FDC. These may come from two sources. Firstly, T-cells present within the germinal centre are probably induced to secrete lymphokines necessary for B-cell proliferation and differentiation upon stimulation by the antigen processing B-cell. Secondly, FDC may provide stimuli via molecules they express on their plasma membrane (i.e. CD40, CD54) [10, 12]. The exact molecular nature of the FDC B-cell interaction is currently being examined.

FDC and proliferation of germinal centre B-cells

Subsequent to the interaction with FDC, germinal centre B-lymphocytes undergo rapid proliferation, resulting in an expansion of the B-memory cell pool. As compared to the extrafollicular region, an increase in ^{3}H-thymidine uptake within germinal centres has been confirmed by several *in vivo* experiments [35, 36]. This indicates that the germinal centre is a site of high mitotic activity. According to Zhang *et al.* [37] the rapidly dividing germinal centre cells have a cell cycle time of 6–7 hours.

Several investigators have presented data concerning the effect FDC have on lymphocyte proliferation. Schnizlein *et al.* [13] showed that the response of murine B-cells to lipopolysaccharides was enhanced when FDC were added to the B-cell preparations. In suspensions of human tonsillar B-lymphocytes enriched for FDC, tritiated thymidine uptake was enhanced as compared to B-cells cultured without FDC [38]. Although the percentage of FDC in both studies was very low and the number of T-cells as high as 25%, these results lead to the hypothesis that FDC may influence B-cell proliferation.

Due to the affinity of FDC towards lymphocytes, FDC tend to coalesce during the isolation procedure, forming small cellular clusters [39]. Approximately 50% of the lymphocytes within the isolated FDC clusters express Ki-67, a G_1 to M phase-associated nuclear antigen [40]. Autoradiography revealed that after prolonged periods of mitogen-free cell culture many of these lymphocytes incorporate tritiated thymidine; on the other hand, isolated germinal centre lymphocytes not involved in FDC cluster formation rarely incorporate the radioactive agent [41]. This suggests that FDC provide a microenvironment adequate to maintain the activation and proliferation of germinal centre B-cells *in vitro*. Whether FDC merely subministrate the antigenic stimulus or actually produce necessary cytokines is still undetermined. Assays for the detection of interferon gamma, tumour necrosis factor alpha, interleukin-3 or interleukin-6 mRNA in FDC have rendered negative results [42].

The rapid proliferative phase of lymphocytes during the germinal centre reaction implies the risk of many neoplastic events [37]. There are indications that the dense FDC mesh constitutes a microenvironment also favourable for the proliferation of cells in the malignant tissue. Staining cryostat sections of follicular lymphoma, Mori *et al.* [24] detected Ki67 positive lymphoma cells localised mainly in the proximity of the FDC. Our group isolated FDC from lymph-nodes of patients with germinal centre cell-derived NHL. Again these FDC formed small cellular clusters containing 2–5 lymphoma cells (Fig. 1). Subsequent to culturing for 68 hours, a large proportion of the lymphoma cells enwrapped by the FDC processes incorporated tritiated thymidine. In contrast, only few lymphoma cells scattered outside of the FDC dependent clusters were ^{3}H-thymidine positive [43]. These observations suggest that the FDC cell surface is a necessary component for B-cell proliferation and may provide a costimulary signal for neoplastic lymphocytes.

FDC RESISTANCE TO RADIATION AND CHEMOTHERAPEUTICAL DRUGS

During the postnatal development of the lymphatic tissue in rodents, lymphoid follicles are formed at 7–9 days after birth

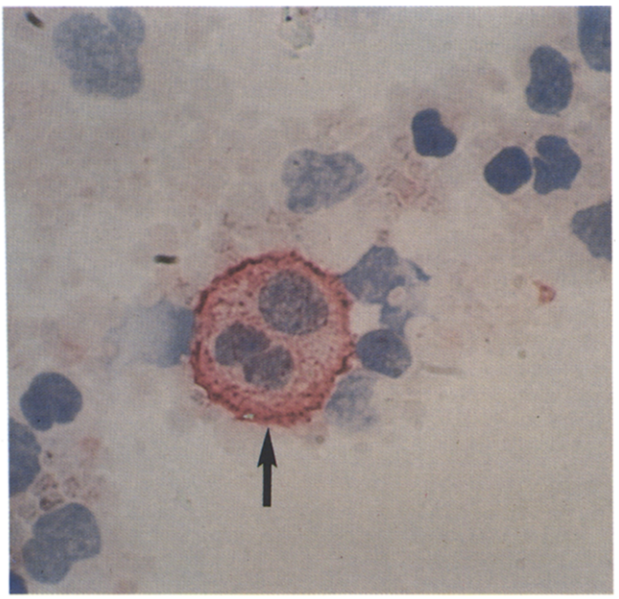

Fig. 1. A follicular dendritic cell isolated from a patient with centroblastic–centrocytic lymphoma identified by the monoclonal antibody DRC1(arrow). Within their cytoplasmic extensions, FDC envelop one to several lymphoma cells forming small cellular clusters.

[44, 45]. Within these primary follicles, lymphocytes are closely packed between non-lymphoid cells. The delicate membrane processes of these non-lymphoid cells constitute a fibroreticular stroma. However, the characteristic ultrastructural features of FDC cannot be identified prior to the appearance of secondary follicles 25–30 days after birth [46]. In the white pulp of human spleens, DRC1 positive FDC can be visualised around the 26th week of gestation [47].

Dijkstra and Döpp [44] hypothesise that FDC or precursor FDC are able to trap lymphocytes and thus induce the formation of follicles. Indeed FDC and the molecules they express may play a role in the ability of B-cells to home to the follicle. Recently, Freedman *et al.* [48, 49] were able to show that binding of B-lymphocytes to germinal centres of the non-malignant lymphatic tissue as well as FDC containing nodular structures in lymphomas is a result of a direct interaction between the very late activation antigen VLA-4 on lymphoid cells and the adhesion molecule INCAM-110 expressed by FDC.

Phipps *et al.* [50] observed that treatment with cyclophosphamide depletes mouse lymph-nodes of T-cells and B-cells while FDC are resistant. When primed spleen cells are injected into these animals, the FDC-containing B-cell compartments of the lymph-nodes are restored.

FDC are very resistant to immunosuppressive agents and the effects of irradiation. In the spleen of irradiated rats FDC were present when given 9 Gy of radiation while lymphocytes were destroyed [51]. In bone marrow chimeras established by irradiating mice with 950 rads, FDC retained the host MHC class I phenotype for over 1 year postreconstitution [52]. The ability of FDC to trap immune complexes can be inhibited by treatment of the animal first with cortisone, then cyclophosphamide, azathioprine and irradiation with 200 rads [53]. Interestingly, FDC in murine lymph-nodes are more resistant to immunosuppressants than FDC in murine spleen [53], a further indication for FDC heterogeneity. Unfortunately no data are available on the effect chemotherapeutical treatments have on FDC from the human system.

SYNOPSIS

FDC are restricted to the B-cell regions of secondary lymphoid tissue such as lymph-nodes, tonsils and spleen. Their major function is to trap and retain antigen–antibody complexes for the induction of a germinal centre reaction. Furthermore, FDC may play a role in the homing of B-lymphocytes. FDC display a unique antigenic phenotype. But inconsistencies on their surface properties still exist in the literature. These differences might be due to FDC heterogeneity. This state could be related to activation and localisation of FDC within the various lymphoid organs.

FDC are also present in NHL derived from germinal centre lymphocytes, i.e. the centrocytic–centroblastic lymphoma and the centroblastic lymphoma and in lymphomas derived from cells of the follicular mantel, i.e. centrocytic lymphoma. The involvement of FDC in extranodal lymphomas suggests that FDC newly immigrate to the neoplastic sites. There are indications that the FDC cell surface may provide a costimulary signal for the activation and proliferation of germinal centre lymphocytes in the non-malignant and the malignant tissue. Cytokines secreted by FDC have not been identified so far. FDC are more resistant to chemotherapeutical agents and irradiation than lymphocytes.

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