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Invited Review

The lymphocyte-dendritic cell system

Y. Imai[1], M. Yamakawa[2] and T. Kasajima[2]

[1]Division of Pathology, Yamagata Medical Center, Yamagata, Japan and

[2]Second Department of Pathology, Tokyo Women's Medical College, Shinjuku-ku, Japan

Summary. Antigens provoke immune responses. The group of immunocompetent cells related directly to this response includes T and B cells, macrophages (Mø) and dendritic cells (DCs). DCs acting as antigen-presenting cells have been recently recognized to be important in initiating the immune response.

B cells and follicular dendritic cells (FDCs), the major immunocompetent cells in the B-cell dependent area, play an important role in humoral immunity, while T cells and interdigitating cells (IDCs), which are the major immunocompetent cells in the T-cell dependent (TD)-area, play an important role in cellular immunity. The B cell-IDC interaction in the TD-area is also essential for the B-cell response against TD-antigen. Consequently, the lymphocyte-DC interaction is essential in the response to antigenic stimulation and in inducing the potent effector cells. B cell-DC, T cell-DC and DC-B cell-T cell interactions are regulated in pre-determined sites by complex and varied mechanisms. Much recent evidence demonstrates that DCs modulate lymphocyte biology in its broadest aspects, including generation, differen-tiation, proliferation, and activation.

In this review, we outline recent studies on the generation, structure, and function of lymphatic tissues, propose the concept of the "Lymphocyte-Dendritic Cell System (LDS)", and finally describe the significance and functions of this system in health and disease.

Key words: Lymphocyte-dendritic cell system, Lymphoid follicle, Germinal center, Dendritic cell, Follicular dendritic cell, Langerhans cell, Interdigitating cell

Content

Offprint requests to: Dr. Yutaka Imai, Division of Pathology, Yamagata Medical Center, Fukamachi 1-7-57, Yamagata 990, Japan

I. Introduction

Both intrinsic and extrinsic antigens provoke immune responses. The group of immunocompetent cells related directly to this response includes T and B cells, macrophages (Mø), and dendritic cells (DCs). When these cells are activated, various cytokines are produced and released in their vicinity to induce activation and proliferation of themselves and other cells, finally resulting in humoral and cellular immunities. DCs acting as antigen-presenting cells (APCs) have been recently recognized to be important in initiating the immune response.

Lymphoid tissue contains a lymphoid follicle (LF) in the B cell-dependent area; and the paracortex and interfollicular areas are T cell-dependent (TD) areas (Beckstead, 1983; Imai and Yamakawa, 1996). LFs are subdivided into primary and secondary LFs. Primary LFs contain many small B cells and a few follicular dendritic cells (FDCs) but no germinal center (GC). Secondary LFs comprise a GC containing many large B cells and FDCs, and the mantle zone. LFs also occur in non-lymphatic tissues involved in chronic inflammation, autoimmune diseases, and tumors. Their morphology and function are similar to those in lymphatic tissues such as lymph nodes, spleen, and tonsils.

B cells and FDCs, the major immunocompetent cells in the B cell-dependent area, play an important role in humoral immunity, while T cells and interdigitating cells (IDCs), which are the major immunocompetent cells in the TD-area, play an important role in cellular immunity. The B cell-IDC interaction in the TD-area is also essential for the B cell response against TD-antigen. Consequently, the close cellular interaction between DCs and lymphocytes gives rise to highly specific cellular and humoral immunities against both intrinsic and extrinsic antigens. In this review, we outline recent studies on the generation, structure, and function of lymphatic tissues, propose the concept of the "Lymphocyte-Dendritic Cell System (LDS)", and finally describe the significance and functions of this system in health and disease.

II. Generation, structure and function of lymphatic tissues

A. Cellular composition and generation of lymphoid follicles

1. General concepts of lymphoid follicles

The large LFs seen in chronic tonsillitis, reactive lymphadenitis, and in other conditions are classified into

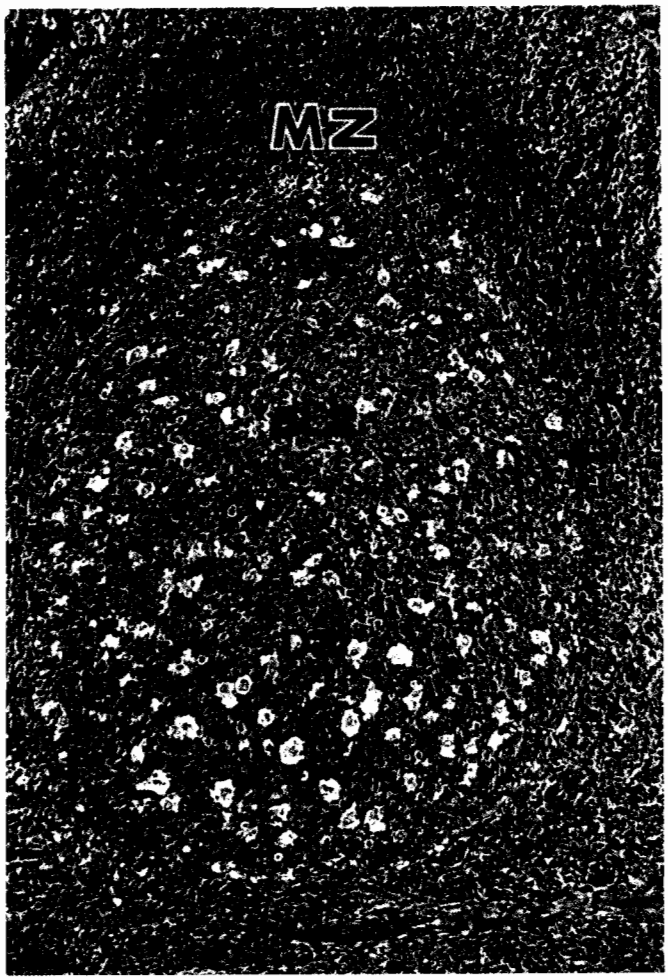

Fig. 1. Hyperplastic lymphoid follicle in chronic tonsillitis. Lymphoid follicle is composed of the mantle zone (MZ) and germinal center. The latter consists of the light zone and dark zone (DZ). Furthermore, the light zone is divided into apical light zone (ALZ) and basal light zone (BLZ). The outer zone cannot be easily identified only using HE stain. HE stain. x 180

five zones as seen under light microscopy (Hardie et al., 1993) (Fig. 1); the mantle zone, the outer layer, consists mainly of membrane (m)IgM$^+$, mIgD$^+$ small lymphocytes; the apical light zone in the uppermost GC, the dark zone in the lowermost GC, the basal light zone situated between the apical light and dark zones, and the narrow ring-shaped outer zone at the junction of the periphery of the light and dark zones and the mantle zone (Figs. 1, 2). However, some differences of zonation of LFs between tonsils and lymph nodes have been recently pointed out (Brachtel et al., 1996).

The GC is the site for the oligoclonal growth and differentiation of memory B cells and plasmablasts against antigens (Kroese et al., 1987). Activated B cells migrate into the GC and undergo somatic mutation in the variable region of the immunoglobulin (IgV-region) gene. B cells with a lower antigen affinity die immediately by apoptosis, while those with higher affinity survive and continue to differentiate. Surviving B cells contact with the antigen retained on the cell surface of FDCs and undergo Ig class-switching to differentiate into memory B cells, expressing mIgG in the spleen and lymph nodes, and mIgA in intestinal Peyer's patches. These memory cells are relatively long-lived and circulate in peripheral blood to enable a rapid response to even small amounts of invading antigens.

2. Cellular composition of lymphoid follicle

At least two other cell types, CD4$^+$ T cells and non-lymphoid IDCs, as well as B cells and antigens, are indispensable for GC formation (Tew and Mandel, 1979; Vonderheide and Hunt, 1990; Kosco et al., 1992).

There is much evidence that T cells are critical for formation of LFs: Thymus-deficient "nude" mice and rats lack GCs, both normally and after antigenic stimulation (Jacobson et al., 1974) (Table 1). Similarly, mice with severe combined immunodeficiency (SCID) generally lack GCs, although if T cells as well as B cells are injected, mature GCs develop (Kapasi et al., 1993).

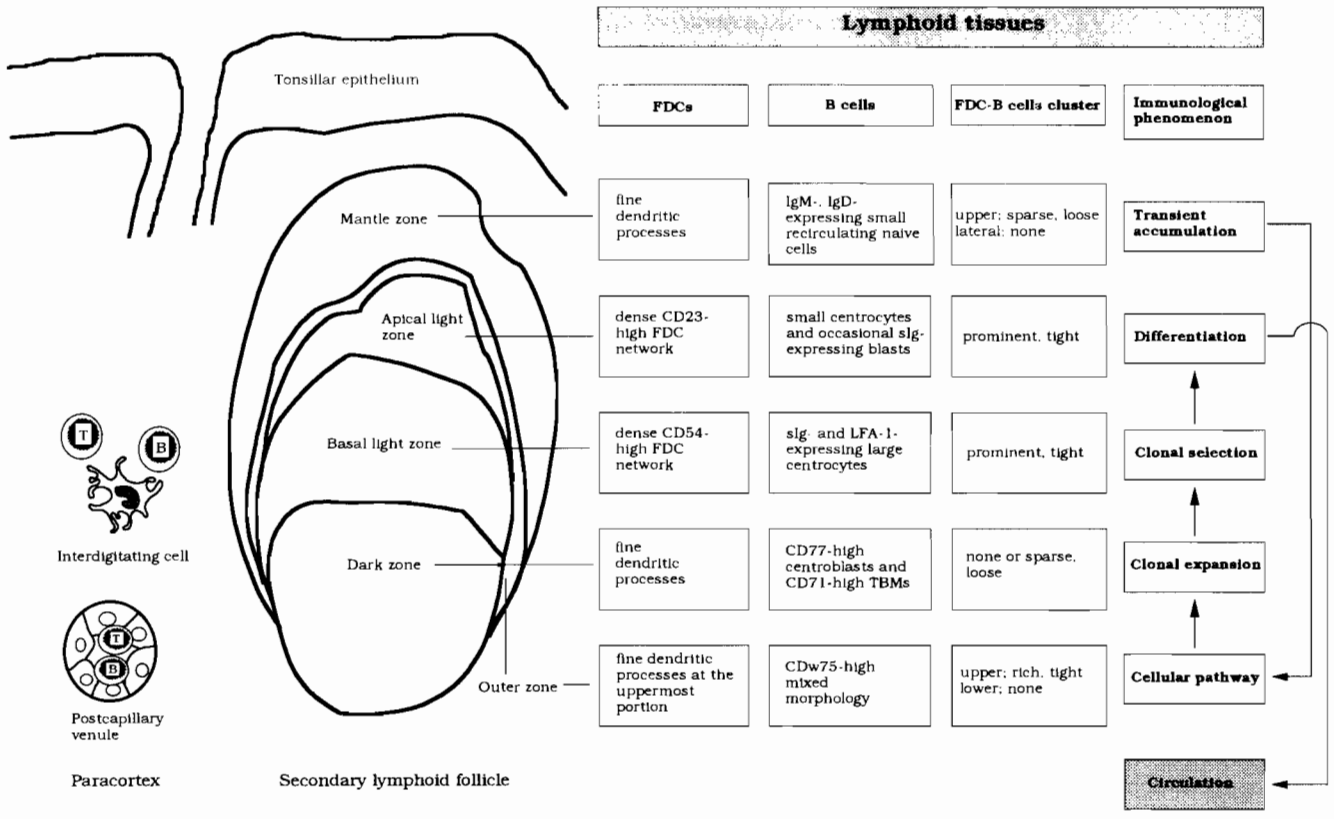

Fig. 2. Characteristics of follicular dendritic cells and B cells and function of tonsillar secondary lymphoid follicle. Lymphocytes migrate from postcapillary venules and contact with dendritic cells in paracortical area (interdigitating cell), and B cells accumulate to the mantle zone and express surface IgD and IgM. A part of the mantle zone lymphocyte builds up a follicular dendritic cell (FDC)-lymphocyte cluster to be stimulated with antigen trapped by FDC and may migrate to the dark zone through the outer zone. Germinoblasts and B lymphocytes in the dark zone actively divide and exhibit clonal expansion. Large lymphocytes in the basal light zone are negatively or positively selected according to affinity to antigen of their surface B cell receptor, and cells with low affinity to corresponding antigen die by apoptosis and those with high affinity survive to migrate to the apical light zone, where they differentiate into memory B cells or plasmablasts. Finally, these differentiated cells may leave the lymphoid follicle to home to the bone marrow, inflammatory sites, Peyer's patches and so on.

Transgenic mice lacking the CD28 molecule on activated T cells are deficient in several processes (GC formation, somatic mutation, and Ig-class switching), and have decreased power of positive cell selection and antibody production (Lane et al., 1994). FDCs which can trap immune complexes (ICs) on their cell surfaces and retain them for long periods are critical in B cell differentiation and maturation in the GC. Furthermore, major histocompatibility complex (MHC) class II molecule-deficient mice lack GCs, and have decreased numbers of B cells but have terminally differentiated plasma cells. As they age, transgenic mice have very few IgM^+, IgD^+ B cells, a low serum level of IgG1, and cannot respond to TD-antigens (Cosgrove et al., 1991), demonstrating the importance of the cellular interaction mediated by MHC class II molecules in GC formation. In conclusion, mature GCs can occur only when antigen-specific cellular interactions between B cells, $CD4^+$ T cells (but not αß T cells) (Dianda et al., 1996) and FDCs are set up. Tingible body Mø (TBMs) are also required for formation of GCs.

3. Generation of lymphoid follicle

Liu et al. (1991c) and Bachmann et al. (1996) have studied the primary and secondary immune responses to TD- and T cell independent (TI)-antigens in the rodent spleen and have studied the localization of antigen-specific B cells. Hapten-specific B-blasts are found in three different sites, namely, around the FDCs in the TD-area, in the IDC network, and in the splenic red pulp. A similar phenomenon has been observed in the para-cortical areas of lymph nodes and mucosa-associated lymphoid tissues (Gray, 1988a; Liu et al., 1992). TD-antigen-specific B-blasts are seen in the extrafollicular TD-area during the first few days of the primary immune response, and depend on cellular interactions with helper T cells and IDCs. In the secondary immune response B-blasts migrate from the splenic marginal zone to the TD-areas. A proportion of the activated B cells differentiate here into plasma cells. Between one and three B-blasts appear in the LF within 36 hours of TD-antigenic stimulation (Kroese et al., 1988). The B-blasts grow exponentially and fill up the LF within 4 days of immunization. Three days after the simultaneous administration of two different haptens, between 6 and 31% of LFs contain B-blasts specific to each one, revealing the oligoclonality of the GC reaction. Similarly, the simultaneous administration of three independent haptens demonstrates the monospecificity (12.5%) of the GCs (Liu et al., 1992). Three days after immunization, the number of intrafollicular B-blasts is 1-1.5 x 10^4 with a cell cycle time of about 6 hours. Ig class switching occurs during the period of exponential proliferation of the intrafollicular B-blasts and before the distinct appearance of centroblasts and centrocytes (Gray et al., 1991; MacLennan et al., 1992; For et al., 1993). Four days after immunization, the typical GC begins to appear, and mIg^+ B-blasts disappear from the GC followed by the accumulation of mIg^- centroblasts at the end of one pole of the FDC network. This phenomenon also indicates the conversion of B-blasts in the primary LF to centroblasts in the dark zone of the GC. Dividing centroblasts do not increase in number because they are themselves the source of centrocytes. Three weeks after immunization the GC reaction is gradually diminishing and both centroblasts and centrocytes have disappeared leaving only a small cluster of proliferating B-blasts in the FDC network. The follicular reaction induced by the TI-1-antigen is much weaker than that induced by the TD-antigen (Liu et al., 1991c).

Precursors of GC B cells may be recirculating virgin B cells derived from bone marrow (Seijen et al., 1988; Kroese et al., 1991; Tsiagbe et al., 1992). The following observations support this hypothesis: in animals treated with anti-IgM antibody at birth the development of B cells is completely blocked and GCs are absent (Bazin et al., 1985); when thoracic duct lymphocytes are injected into animals, they migrate to the primary LF and the mantle zone of the secondary LF in the peripheral lymphoid tissues. In addition to these bone marrow-derived B cells non-bone marrow-derived Ly-1 $(CD5)^+$ B cells as a self-renewing lineage also migrate into the GC (Herzenberg et al., 1986).

Furthermore, recent cytokine researches have demonstrated several significant findings that the generation/differentiation of LFs and FDCs is dependent on lymphotoxin α and αß (Kratz et al., 1996; Matsumoto et al., 1996), tumor necrosis factor (TNF)-ßα/TNF receptor-1 signaling (Hir et al., 1996; Neumann et al., 1996; Pasparakis et al., 1996), B7-2:CD28/CTLA-4 (Han et al., 1995a,b; Ferguson et al., 1996), CD40 and

Table 1. Previous reports on the agenesis of germinal centers and follicular dendritic cells

TARGET MOLECULE	AGENESIS/ NEOGENESIS	REFERENCE
Knockout mice		
TNF-α	Agenesis	Pasparakis et al., 1996 Müller et al., 1996
TNF receptor I	Agenesis	Neumann et al., 1996 Pasparakis et al., 1996 Hir et al., 1996
Lymphotoxin	Agenesis	Matsumoto et al., 1996 Müller et al., 1996
CD40	Agenesis	Kawabe et al., 1994
CD40L	Agenesis	Xu et al., 1994
MHC class II	Agenesis	Cosgrove et al., 1991
CD28/CTLA-4	Agenesis	Ferguson et al., 1996
rel B	Agenesis	Burkly et al., 1995
ß7-integrin	Agenesis	Wagner et al., 1996
Anti-IgM treatment	Agenesis	Cerney et al., 1988
Anti-CD40L treatment	Agenesis	Han et al., 1995a
Anti-CD28 treatment	Agenesis	Han et al., 1995a
Transgenic mice		
Lymphotoxin	Neogenesis	Kratz et al., 1996
TNFα	Neogenesis	Douni et al., 1996
CTLA-4	Ageneis	Lane et al., 1994 Ronchese et al., 1994

CD40L (Kawabe et al., 1994; Xu et al., 1994; Han et al., 1995a,b; Noelle, 1996), MHC class II (Cosgrove et al., 1991), ß7-integrin (Wagner et al., 1996), and CTLA-4 in transgenic mice (Lane et al., 1994; Ronchese et al., 1994; Liu and Banchereau, 1996) (Table 1).

B. Structure and function of lymphoid follicle

The scheme of the structure and function of lymphoid follicle is summarized in Fig. 2.

1. Dark zone

The dark zone contains abundant dividing centroblasts as a source of centrocytes. The zone appears dark as a result of the narrow compact basophilic cytoplasm of the centroblasts. Centroblasts have little or no mIg or cytoplasmic Ig (MacLennan et al., 1991). The tingible bodies consist of condensed chromatin of dead cells which failed to express the antigen-specific mIg on their cell surfaces during somatic mutation. The FDC network is widely but loosely distributed in the dark zone. Centroblasts strongly express CD77 antigen, a marker of activated B cells (Hardie et al., 1993). The cell cycle time of centroblasts is about 7 hours and they generate adequate numbers of centrocytes in under 24 hours (Liu et al., 1991c). The dark zone has some IgD^+ B cells (Billian et al., 1996; Liu et al., 1996a).

At the same time as the TD-antigen stimulates GC formation, high affinity antibody against the proper antigen is produced (Klauss et al., 1980). In this process, active gene rearrangement occurs in the IgV region of centroblasts through somatic mutation (Allen et al., 1987; Berek and Milstein, 1987; Alzari et al., 1990; Apel and Berek, 1990; Jacob et al., 1991a, 1993; Maizels, 1995; Källberg et al., 1996; Liu et al., 1996b; Rajewsky, 1996; Texidó et al., 1996). This somatic mutation occurs only during the first few days of the immune response (Cumano and Rajewsky, 1986; Manser, 1990). Mutation occurs at a very high rate of one per 1,000 base pairs in a cell division, compared with a rate of one per 10,000 base pairs in pre-B cells (Berek, 1992). Most of the mutations are confined to the 5' and 3' flanking region ("hot spot"), adjacent to complementarity determining-1 region of VH and VL genes (Lebecque and Gearhart, 1990), and are mostly point mutations, though occasionally insertions or deletions. One IgV region gene has on average 6 mutations in the later stages of the primary immune response and in the early stage of the secondary response (Manser, 1990). The mutation does not always accompany Ig-class switching; most occur in stages on the IgM gene during clonal expansion. The mutations in a base in the secondary response, that is, during only 2 weeks, increase the antibody affinity 10-fold higher compared with that in the primary response (Berek, 1992). However, it remains unclear whether the mutation occurs only in the GC B cells (Leanderson et al., 1992; Nossal, 1994a). Within GCs, isotype switching of Ig genes occurs after the onset of somatic mutation (Liu et al., 1996b) and IL-10 selectively regulates murine Ig isotype switching (Shparago et al., 1996).

Studies of the molecules and cytokines which stimulate proliferation of the GC cells can be summarized as follows: 1) Neither anti-CD40 antibody nor interleukin (IL)-4 alone stimulates $CD77^+$, peanut aggulutinin $(PNA)^+$ tonsillar cells, but together they have a synergistic effect on cell to proliferation (Mangeney et al., 1991; Tsiagbe et al., 1992; Galibert et al., 1996a; Wheeler and Gordon, 1996). 2) Both $Ly\text{-}1^+$ B cells and GC B cells in mice are stimulated by IL-5, but the proliferation of the former is more easily inhibited by interferon (IFN)-γ than the latter. IL-5 produced by the Epstein-Barr virus-infected human B cells may proliferate themselves in an autocrine model (Tsiagbe et al., 1992). 3) The CD19 molecule complexed with the complement receptor (CR) 2 (CD21) on the surface of GC B cells also induces B cell proliferation and enhances antibody production (Heinen et al., 1991; Carter and Fearon, 1992; van Noessel et al., 1993). The ligation of CD19 to only about 100 antigen receptors (0.03% of the total) per B cell lowers the threshold for antigenic stimulation of B cells and induces cell proliferation. The CD19 molecule, a member of the Ig superfamily, is a 95 kDa glycoprotein which can pass through the cell membrane (van Noesel, 1993). 4) FDCs express nerve growth factor receptor (NGFR) and NGF enhances DNA synthesis in B cells in a dose-dependent manner (Otten et al., 1989).

However, it is still unclear which types of cell secrete these signals to promote B cell proliferation and also which types of B cells in the LF are responsible for generating these signals.

2. Basal light zone

This zone does not contain centroblasts but there are densely-packed large non-dividing pyroninophilic centrocytes. The dark zone contains proliferating centroblasts and the light zone non-proliferating centrocytes (Nieuwenhuis and Opstelten, 1984). A minority of cells in the basal light zone enter the S-phase of the cell cycle. The FDC network expresses and secretes CR2 (CD21) and intercellular adhesion molecule (ICAM)-1 (CD54), but little or no FcεRII (CD23). The FDCs are pyroninophilic and possess one or more well-developed nuclei.

Most centrocytes leave the GC over a period of one or two days to become memory B cells or plasmablasts, or die through apoptosis (Liu et al., 1989; MacLennan et al., 1992; Han et al., 1995b). Apoptotic cells are characterized by cell shrinkage, cell membrane vesiculation, condensed chromatin, and DNA laddering (Wyllie et al., 1984). Apoptotic cells are found more frequently in the basal light zone compared with the other zones in the GC. It may be difficult to distinguish the basal light zone from the dark zone when a markedly expanded dark zone contains frequent apoptotic bodies. It has recently been reported that cell selection has

already started during the cell division stage in the dark zone (Ziegner et al., 1994). However, production of high affinity antibody against antigen, and cell selection are carried out only in the GC (Berek et al., 1991; Jacob et al., 1991b; van Rooijen, 1993). The most important factors for cell selection are the degree of down-regulation of the mIg receptor on centrocytes after somatic mutation (George et al., 1993; Pulendran et al., 1995) and the probability of contacting the antigen retained on the surface of the FDC (Tew and Mandel, 1979; Foote and Milstein, 1991). In general, DNA-damaged proliferating cells stay either in the G1- or G2-phase before mitosis until the damaged DNA has been repaired (Strasser et al., 1994). Both positively and negatively non-selected centrocytes return to the dark zone, mutate again, and may be once more selected (Berek and Ziegner, 1993; Kelper and Perelson, 1993; Nossal, 1994a).

Induction of apoptosis in the centrocytes is a complex process (Nossal, 1994b; von Boechmer, 1994), as follows. 1) Phosphatidylserine on the surface of the B cell is specifically recognized by tingible body macrophages (TBMs) which promote the phagocytosis of damaged B cells (Fadock et al., 1992). 2) Cyclic adenosine monophosphate (cAMP) occurs on the majority of cells in the GC, but cAMP activity is very marked on the centrocytes in the light zone accompanying both apoptosis and rescue from apoptosis, indicating the Ca^{2+} ion-cAMP-dependent regulation of apoptosis (Knox et al., 1993). 3) Conversely, a Ca^{2+}-independent, CD40-mediated process of regulation of apoptosis of $CD38^+$ B cells has been reported (Callard et al., 1993; Knox and Gordon,1993; Han et al., 1995; Nakanishi et al., 1996). Antigen-specific, activated T cells with CD40 ligand modulate the mIg-dependent apoptosis of B cells together with an increasing level of granulocyte-colony stimulating factor (G-CSF) expression in B cells (Tsubata et al.,1993). 4) Tyrosine phosphorylation by protein tyrosine kinase rescues GC B cells from mIg-dependent apoptosis (Knox and Gordon, 1994). 5) The B-cell-FDC interaction through lymphocyte function-associated antigen (LFA)-1 (CD11a/CD18)-ICAM-1 (CD54) adhesion and the very late activation antigen (VLA)-4 (CD49d)-vascular adhesion molecule (VCAM)-1 (CD106) modulates B cell selection (Koopman et al., 1991). 6) CD77 protein is a marker not only of activated B cells but also of GC B cells entering apoptosis (Mangeney et al., 1991). 7) IL-1α recombinant (r)25KDa CD23 enhances the survival of GC B cells (Liu et al., 1991a). 8) Expression of bcl-2 protein is essential for the long-term survival of antibody forming and memory cells, and GC B cells lacking this protein tend to proceed to apoptotic death (Liu et al., 1991b; Núñez et al., 1991; Korsmeyer, 1992; Oltvai et al., 1993; Genaro et al., 1994; Nüñez, 1994; Allman et al., 1996; Pittaluga et al., 1996). Long-lived recirculating IgM^+ and IgD^+ mantle zone B cells express a large amount of bcl-2 protein. In contrast, the proliferating centroblasts in the dark zone and the centrocytes in the basal light zone accompanied by frequent apoptotic bodies, lack *bcl-2* expression. B cells in the apical light zone which have migrated from the basal light zone express this protein. 9) The CD40 molecule, NGFR and TNF-α receptor have structural homology and may regulate apoptosis via *bcl-2* expression (Tsiagbe et al., 1992). 10) Prolonged B cell receptor cross-linking regulates negative selection of GC B cells (Galibert et al., 1996b). 11) APO-1/Fas (CD95) also regulates GC B cell differentiation (Lagresle et al., 1995; Watanabe et al., 1995; Choe et al., 1996). 12) On the other hand, Nakamura, et al. (1996) have recently revealed the death of GC B cells without DNA fragmentation.

3. Apical light zone

Lymphocytes forming the light zone are relatively small, less closely packed and deeply basophilic. Consequently, the light zone appears brighter than the dark zone. FDCs in the apical light zone strongly express FcεRII, CR2, and ICAM-1 and form a dense meshwork through their cytoplasmic projections (MacLennan et al., 1991). Although there are plasma cells in the GC in some diseases such as Castleman's disease (see below), this cell type is generally rare (van Rooijen, 1990; Tsiagbe et al., 1992).

The apical light zone is the site where centrocytes differentiate into memory B cells or plasmablasts, and FDCs play a central role in this B cell differentiation. ICs retained in the cap area rapidly undergo dissociation and re-binding with a dissociation half-life of approximately 1 hour (Hammarback and Valle, 1990). Free antigens induce memory B cell differentiation (van Rooijen, 1990).

The molecules and the cytokines involved in GC B-cell differentiation are as follows: 1) Isolated FDCs express membrane-bound FcεRII and secrete soluble 37 kDa fractions of FcεRII as the signal for the differentiation and selection of the centrocytes (Rieber et al., 1993). FcεRII is also a receptor for CR2 and modulates the antigen-presenting function of FDCs and IgE production (Aubry et al., 1992; Heuchoz et al., 1994; Henchoz-Lecoanet et al., 1996). The synergistic effect of FcεRII soluble fragment and IL-1α rescues centrocytes from apoptosis, and induces the differentiation of IgG-secreting plasmablasts (Liu et al., 1991a). 2) Antibody response to a T-dependent antigen requires B cell exposure of CRs (Croix et al., 1996). 3) IgM secretion is enhanced by the cooperative effect of IL-5 and IL-2 (Tsiagbe et al., 1992). IFN-γ (1500u/ml) strongly inhibits Ig-secretion. Tumor growth factor (TGF)-ß is a more powerful inhibitor of lymph node B-cell proliferation than IFN-γ. 4) B cells cannot differentiate into Ig-secreting cells even though they make contact with helper T cells activated by anti-Ig antibody and lymphokines (Leanderson et al., 1992). 5) Nuclear factor B, which specifically binds to DNA and promotes various immune response genes, has been

described (Sen and Baltimore, 1986; Baeuerle, 1991; Laherty et al., 1993). It belongs to the multigene family related to proto-oncogene c-rel, and is a heterodimer composed of 48 to 55 kDa (p50)- and 65 kDa (p65)-subunits. In the LF, the former is strongly expressed on the nucleus of FDCs and the latter on the nucleus of scattered lymphocytes, indicating the independence of the two subunits in the differentiation and maturation of B cells (Feuillard et al., 1994).

Expression of IL-5 and TGF-ß1-3, but not the other cytokines, including IL-1α, IL-1ß, IL-2, IL-3, IL-4, IL-6, IL-8, IL-10, IL-13, TNF-α, TNF-ß, IFN-γ, granulocyte/macrophage-colony stimulating factor (GM-CSF) and G-CSF, occurs in the GC (Andersson et al., 1994). Recent studies have demonstrated the cytokine expression IL-1ß and IL-7 on FDCs (Toellner et al., 1995; Kröncke et al., 1996). The localization of cytokines in the GC is controversial, and at present the data lack coherence.

Because GC formation and the affinity maturation of antibody occur only in the secondary response, the most reliable means of identifying memory B cells in the GC is by detecting the mutated Ig-gene (Mackay, 1993), which is observed predominantly in μ^-, δ^- B cells and less frequently in μ^+, δ^+ B cells. Memory B cells are derived from the pool of both δ^- and δ^+ B cells. Although a few memory B cells express the phenotype μ^+, δ^+ or μ^+, δ^-, the majority are μ^-, δ^-. Moreover, most naive B cells have a low level of heat-stable antigen (J11D) (Mackay, 1993). Compared to naive B cells, memory B cells respond more easily to small amounts of antigen but less to polyclonal activation by mitogens. While most but not all memory T cells have a short or intermediate life-span (a few weeks or months), naive T cells survive from a few months to years (Mackay, 1993), and memory B cells about 20 weeks. μ^+, δ^+ naive B cells express L-selectin (CD62L) and are thereby able to pass through the high endothelial venule to migrate into lymphatic tissues such as lymph nodes (Diacovo et al., 1996), but details of the process of memory B-cell migration are unclear.

4. Outer zone

The narrow space named "the outer zone" is located in the periphery of the apical light and dark zones, covering the whole GC. The FDC network is somewhat loose and expresses little or no FcεRII. Characteristically, lymphocytes in this zone express CDw75 more strongly than the other GC cells (Nieuwenhuis and Opstelten, 1984; Hardie et al., 1993). The outer zone contains more different cell types than other GC zones, including lymphocytes similar in appearance to the centrocytes of the apical light zone, Ki-67$^+$ blasts and plasma cell-like cells. Centrocyte-like cells again migrate into the dark zone where some are selected. As mentioned below, CD4$^+$ TH2 cells with a powerful capacity to secrete IL-4 also accumulate at the junction between the mantle zone and the GC (Bhan et al., 1981; Kasajima et al., 1987; Butch et al., 1993). The CD4:CD8 ratio of this site is 12:1, while that of the TD-area is 2:1 (Rouse et al., 1982).

5. Mantle zone

The mantle zone covering the light zone, thickens on the top of the light zone, gradually tapers, and finally disappears at the lateral rim of the dark zone. The cells and functional characteristics of this zone are similar to those of the primary LF, that is, both sites contain recirculating, mIgM$^+$ and mIgD$^+$ small resting B cells as the precursors of centroblasts in the dark zone. The mantle zone lymphocytes are in addition CD10$^-$, CD20^{dim}, CD23$^+$, CD38$^-$, CD39$^+$, CD44$^+$, CD71$^-$, and PNA$^-$ (Küppers et al., 1993; Lagresle et al., 1993). Cells isolated from the mantle zone have a variety of polyclonalities with most showing germ line V genes.

The FDC network in the apex of the light zone dips into the mantle zone as a front for IC-trapping. Resting B cells in the mantle zone have bcl-2 protein and its mRNA (Kondo et al., 1992; Rodríguez et al., 1992; Chleq-Deschamps et al., 1993). On the other hand, GC cells have bcl-2 mRNA but not its protein (Kondo et al., 1992), suggesting a discordance between protein and mRNA expressions. Moreover, treatment of resting B cells with anti-Ia antigen antibody or agents which increase intracytoplasmic cAMP, for example dibutyryl cAMP and isopreterenol, induces apoptosis in nearly all B cells (Newell et al., 1993).

C. Interfollicular area

The TD-interfollicular area consists of many T cells and some scattered IDCs and Mø. The three dimensional structure is maintained by fibroblastic reticulum cells (FRCs) together with reticular fibers (Tykocinski et al., 1983; van Vliet et., 1986). T cells with a CD4:CD8 ratio of 2:1 comprise 90% of the cells in this area (Rouse et al., 1982). The area surrounded by postcapillary venules, the portal of entry of lymphocytes into lymphatic tissues, is closely packed predominantly with T cells and is therefore also termed the "T-cell area" (Michie et al., 1993). The remaining area, termed the "mixed area", contains scattered T and B cells with a capacity for vigorous proliferation. In the early stage of TD-antigenic stimulation, IDCs as APC and helper T cells induce proliferation of antigen-specific B cells. Here, some activated B cells also differentiate into plasma cells.

In the rat of about 16 days gestational age, the lymph node rudiment begins to appear and is completed at about 20 days of gestation. In human, the lymph node appears at about 3 months gestational age, though details of the generation of the interfollicular area are not clear.

III. Dendritic cells

A. Classification of dendritic cells

The group of DCs consists of two major subgroups, B cell- and T cell-associated DCs (Tew, 1993; Caux et

al., 1995a) (Table 2). The former are FDCs in the LFs, and the latter consist of epidermal Langerhans cells (LCs), the connective tissue DCs, DCs in blood (dendritic leukocytes) and efferent lymphatic vessels (veiled cells) in the non-lymphoid tissues, and IDCs in the TD-area of lymphoid tissues. DCs isolated from many lymphatic tissues such as the spleen are called "lymphoid DCs", and have recently been considered to be compatible with IDCs. A common characteristic of these DCs is an ability to present antigens to B and T cells and to activate them. Morphologically they have complex dendritic cytoplasmic projections, one or more lobulated nuclei, and a clear cytoplasm with sparse organelles.

Table 2. Classification of dendritic cells

1. B cell-associated dendritic cells
A. Follicular dendritic cells
2. T cell-associated dendritic cells
A. Non-lymphatic tissue dendritic cells
1) Langerhans cells
2) Connective tissue dendritic cells
3) Unknown-origin dendritic cells
a. Indeterminate cells
b. Dermal Langerhans cells
c. Granstein cells (in mice)
B. Dendritic cells in circulatory fluids
1) Veiled cells (dendritic leukocytes)
C. Lymphatic tissue dendritic cells
1) Interdigitating cells
2) Germinal center dendritic cells

B. Follicular dendritic cells (FDCs)

1. Definition

FDCs are defined as cells with dendritic cellular morphology which are found in all reactive secondary LFs and within follicle-like structures in malignant non-Hodgkin's lymphomas. They trap and retain IC on their cell surface, and have FcRs and CRs. FDCs comprise only about 1% of total GC cells. Their immunophenotype is summarized in Table 3. It has been confirmed that Ia-antigen (Ia) on FDCs is delivered to FDCs from surrounding B cells (Gray et al.,1991). Monoclonal antibodies relatively specific to human FDCs, such as R4/23, Ki-M4, and Ki-FDC1p, have been developed. The strictest definition of FDCs is to demonstrate one of their most important roles; the capability to trap and retain ICs (Table 4). In this narrow sense DCs in the dark zone which do not trap or retain ICs are not FDCs. At present, because not only the function of DCs in the dark zone but also the functional differences between FDCs in the five zones are unclear, DCs in the dark zone can be provisionally regarded in a broad sense as FDCs or one of the FDC subtypes (Imai et al., 1991, 1993).

2. Ultrastructure of FDCs

FDCs create and support the three dimensional meshwork of the LF through interconnections between their cytoplasmic extensions (Imai and Yamakawa, 1996). FDCs have an irregular slender shape: between 51 and 68% possess a lobulated nucleus (Schmitz et al., 1993) (Fig. 3a). They have rather condensed chromatin aggregated in the nuclear periphery, and complex cytoplasmic extensions. The cytoplasm has sparse rough endoplasmic reticulum, very few lysosomes, very little or no phagocytotic activity, and very slight proliferative activity (Sato and Dobashi, 1996). We have reported two morphologically different types of FDCs in the GC (Imai et al., 1983). One, located in the light zone, traps ICs and has abundant labyrinth-like structures and desmosome-like junctions between FDCs (Fig. 3b). The other is found throughout the whole LF and has desmosome-like junctions but does not have labyrinth-like structures. Schuurmam et al. (1993) have reported seven subtypes of FDCs; many undifferentiated subtypes predominate in the dark zone and well differentiated subtypes in the light zone.

3. Cellular origin of FDCs

There is no consensus on the cellular origin of FDCs, in spite of many studies.

The ultrastructural observations revealing the similar location and morphology of FRCs and FDCs, and the existence of transitional cell types between the two, suggest that FDCs are derived from fixed FRCs (Heusermann et al., 1980; Müller-Hermelink et al., 1981; Bardadin and Desmet, 1984). FRCs in the periphery of the mantle zone and FDCs in the GC both produce complement component C1q (Maeda et al., 1988) and trap ICs (Imai et al., 1986a; Yamakawa et al., 1991b).

On the other hand, a monocytic cell line (THP-1) expresses Ki-M4, an FDC marker, when stimulated by culture supernatants of T and B cell lineages, suggesting that FDCs originate in the bone marrow (Fliedner et al., 1990). However, experiments on post-irradiation bone marrow chimeras (Humphrey et al., 1984, Humphrey and Sundaram, 1985) and on splenic transplantation (Imazeki et al., 1992) suggest that FDCs are stational cells but not of bone marrow origin. Experiments transferring bone marrow cells from other animals to SCID mice also contradicts the bone marrow origin of FDCs (Imai et al., 1993; Yoshida et al., 1994) (Fig. 4). Injection of B cells into SCID mice induces LF formation with an FDC-like meshwork. Simultaneous injection of T and B cells can induce mature GCs (Kapasi et al., 1993). A study using the polymerase chain reaction demonstrates that FDCs express mRNA of CR2 but not lymphocytic markers (CD4, CD20 and CD45), fibroblastic markers (fibronectin, platelet-derived growth factor), or other cytokines (IFN-γ, TNF-α, IL-3, and IL-6), again suggesting that FDCs are

Table 3. Immunophenotype of human follicular dendritic cell.

ANTIBODY/CLONE	CD	COMMENT	ANTIBODY/CLONE	COMMENT
LFA-2	2	(±)vivo/vitro	**Complenents and their regulatory factors**	vivo/vitro (LZ, MZ)
Leu 1	5	(±) vivo	**Blood coagulation- & fibrinolysis-factors**	vivo
BA-2	9	(±) vivo (Germinal center)	**FDC-associated antibodies**	
Complement receptor 3	11 b	vivo/vitro	2BF11, N3A4, HJ11, 2BD11, N3C3, HJ2	vivo
Leu M3, My 4	14	(±) vuvo (Germinal center)	11CD8, HJ7, N2C1, *ED1, 8AF7, BL13	vivo
Sialyl Lewis^x	15s	vivo	R4/23, Ki-M4, DF-DRC1, Ki-FDC1p	vivo/vitro (MZ, LZ>DZ)
FcγRIIIB (Leu 11b)	16b	(±) vivo/vitro	BU10, Ki-FDCM4p	vivo/vitro (MZ, LZ>DZ)
B4	19	(±) vivo/vitro	**Intermediate filaments**	
Complement receptor 2	21	vivo (MZ, LZ>DZ) (mRNA)	Actin	vivo/vitro (MRNA)
LEU 14	22	(±) vivo/vitro	Tubulin	vivo/vitro
Fc εRII	23	vivo/vitro (LZ)	Vimentin	vivo/vitro
OKB2, VIB-C3	24	(±)vivo/vitro	4-prolyl hydroxylase	vivo
β1-integrin	29	vitro	DAKO fibroblast	vivo
FcγRII	32	(±) vivo/vitro	**Other immunological markers**	
Complement receptor 1	35	vivo/vitro (MZ, LZ>DZ)	MHC class I antigen	vivo/vitro
BL14	37	(±) vivo/vitro	MHC class II antigen	vivo/vitro
OKT 10	38	vivo/vitro	Nerve growth factor receptor	vivo
S2C6, G28-5	40	vivo	Acid cystein-proteinase inhibitor	vivo
Hermes antigen	44	vitro	Desmoplakin 1 & 2	vivo
UCHL1	45RO	(±) vivo/vitro	S-100 protein	(±) vivo
Membrane cofactor protein	46	vivo/vitro	Calbindin-D	vivo (MZ, LZ>DZ)
VLA-α3	49c	vivo/vitro(5~10%, LZ)	Monocyte 1	vivo (MZ, LZ, DZ)
VLA-α4	49d	(±) vivo/vitro	IL-6	vitro
VLA-α5	49e	(±) vivo/vitro	TGF-β1,2,3	vivo
VLA-α6	49f	(±) vivo/vitro	**Histochemical markers**	
ICAM-3	50	(±) vivo/vitro	Non-speifific esterase	(±) vivo/vitro
ICAM-1	54	vivo/vitro	α-naphthyl acetic esterase	vivo/vitro
Decay accelerating factor	55	vitro	Adenosine triphosphatase	(±) vivo/vitro
Protein	59	vivo/vitro	5'-nucleotidase	vivo
FcγR1	64	(±) vivo/vitro	Acid phosphatase	vivo
EMB11	68	vivo/vitro	**Lectin binding activity**	
Transferrin receptor	71	vitro	Concanavalin A	vivo
Ecto-5'-nuleotidase	73	vivo/vitro	*Phaseolus vulgaris* agglutinin	vivo
Ii (Invariant chain)	74	vitro	Peanut agglutnin	vivo
OKB4	w75	vivo/vitro	*Lens culinaris* agglutinin	vivo
B7/BB1	80	(±) vitro	*Pissum sativum* agglutinin	vivo
ICAM-2	102	vivo/vitro	*Banhinia purpurea* agglutinin	vivo
VCAM-1	106	vivo		
TNF receptor(p55) (type I)	120a	vivo/vitro		
Cell membrane immunoglubulins				
$\gamma,\mu,\varepsilon,\kappa,\lambda$, chains		vivo/vitro (LZ, MZ)		
IgA1		vivo (Tonsil in patients with IgA neohropathy)		
J chain		(±) vivo		

(±): negative or weakly positive; MZ: mantle zone; LZ: light zone; DZ: dark zone.

Table 4. Definition of follicular dendritic cells (FDCs)

1. Broad sense
A. Light-microscopic: Cells forming reticular meshwork in the lymphoid follicles positive for anti-FDC antibodies
B. Electron-microscopic: Cells having desmosome-like junctions between the same types of cells in the lymphoid follicles

2. Narrow sense
A. Electron-microscopic: Cells having labyrinth-like structures and desmosome-like junctions between the same types of cells in the lymphoid follicles
B. Functional:
1) Cells in the lymphoid follicles to trap and retain immune complex for a long time
2) Cells to form clusters with B cells
3) Cells positive for anti-FDC antibodies to present antigen to B cells

not typical bone marrow- or fibroblast-derived cells (Schriever et al., 1991). Recent studies have demonstrated the expression of acetyl cholinesterase on FDCs in the light zone but not the dark zone (Lampert and van Noorden, 1996).

4. Functions of FDCs

The function of FDCs in each zone of lymphoid follicle is summarized in Table 5.

a. Supporting function. FDCs are loosely fixed to the axis of vimentin$^+$, laminin$^+$ and/or type IV collagen$^+$ fibers just beneath blood vessels (Gloghini et al., 1990).

FDCs are interconnected through desmosome-like junctions. Consequently, FDCs form a widespread three-dimensional meshwork in the GC. Recently we have demonstrated that FDCs adhere to laminin and fibronectin via their respective receptors on FDCs (Ogata et al., 1996) (Table 6).

b. Immune complex trapping and retaining. There are many reports describing IC trapping in the GC. Many authors support the concept that lymphocytes, probably B cells, transfer ICs to FDCs (Enríquez-Rincón et al., 1984; Heinen et al., 1986a,b; Kroese et al., 1986; Braun et al., 1987). This transfer mechanism is Ig-isotype-dependent, and ICs including IgG2, IgG2b and IgG1 isotypes are more efficiently transferred to isolated FDCs than those including IgG3 or IgM. B cells bind to IC via FcR, move toward the GC, and transfer it to contacting FDCs (Heinen et al., 1991). In the spleen ICs are first trapped in the marginal zone surrounding the LF and later move towards the LF, indicating the importance of marginal zone B cells in the IC-trapping mechanism (van Rooijen, 1991).

On the other hand, labeled ICs are trapped on the surface, not only of FDCs but also of FRCs as well as reticular/collagen fibers in the primary LF, pass through the surface of the latter cell types and the fibers in the juxta LF, and finally reach the surface of FDCs in the GC (Imai et al., 1986b; Maeda et al., 1988; Yamakawa et al., 1991b; Sato et al., 1996) (Fig. 5). FDCs have also been proposed as antigen-transporting cells carrying ICs (Szakal et al., 1988).

Both FcγRII and CRs play an important role in trapping and retaining ICs (Yoshida et al., 1993). If complement is not activated, IC is not trapped and retained in the GC, and the production of memory B cells in response to the TD-antigen is not induced. This activation occurs only in the follicular light zone, corresponding to IC-localization (Yamakawa and Imai,

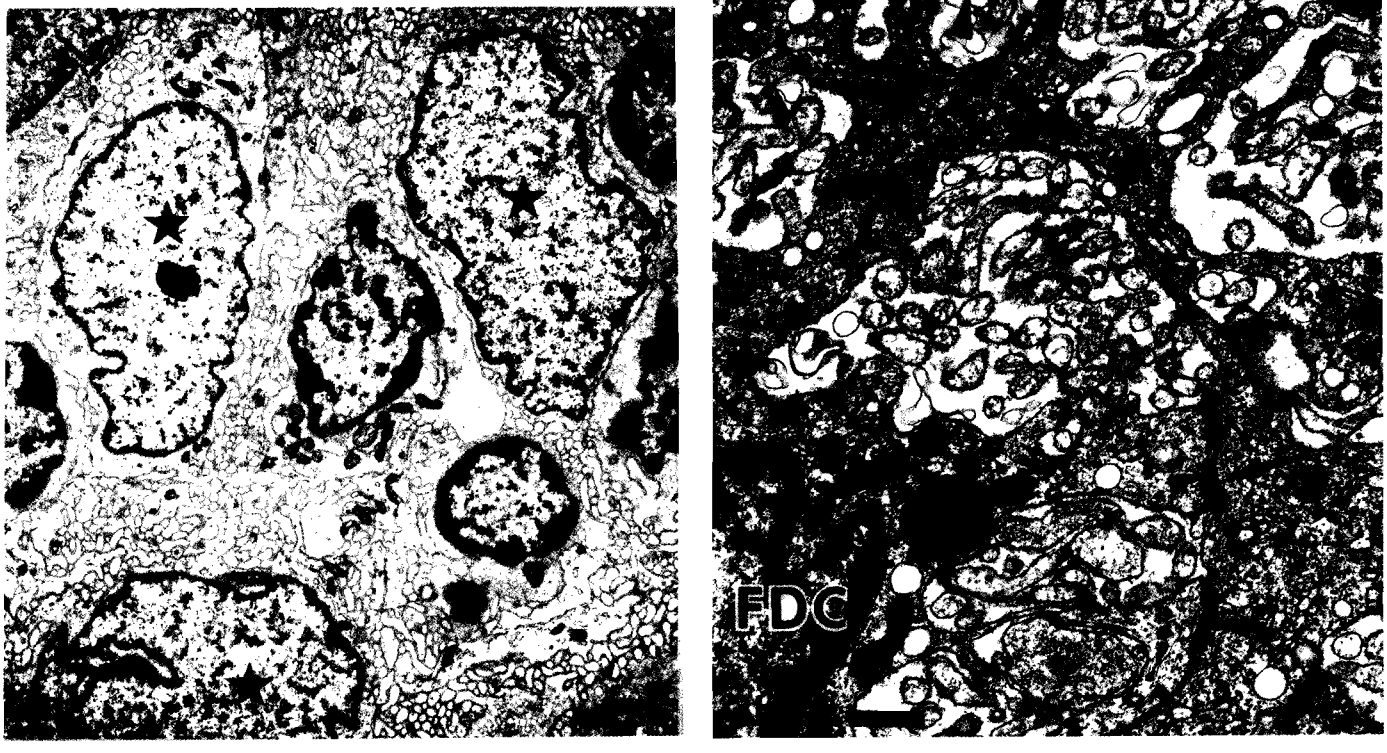

Fig. 3. Transmission electron microscopic figure of follicular dendritic cells (FDCs) in the follicular light zone. **a.** Note the pale nucleus and a large amount of labyrinth-like structure in the cytoplasm of FDCs (asterisks). **b.** Note numerous microvilli, which basically divide into two types (budding type (small arrows)), and dendritic type (arrowheads), and desmosome-like junctions (large arrows) connecting between neighboring FDCs but never B cells and the same FDC. Bar: a, 1 μm; b, 2 μm.

Table 5. Function of follicular dendritic cells (FDC)

FUNCTION	SITE OF ACTION	OUTLINE
Supporting function	Whole lymphoid	Reticular meshwork of FDC builds up the three dimensional follicle (LF) structure of LFs together with extracellular matrices.
Trapping & retaining of immune complex (IC)	So-called "cap area" (Light zone and a part of outer & mantle zones)	One of the most important roles of FDC. FDC trap and retain antigen as IC via Fc & complement receptors. Long-term retaining of IC requires CR2 (CD21).
Antigen presenting capacity	So-called "cap area" (light zone and a part of outer & mantle zones)	Antigen/iccosome released from FDC surface is presented to surrounding B cells.
Regulation of B-cell proliferation & activation	Dark zone (Outer zone)	FDC promote B cell proliferation and activate resting B cells. Resulting activated B cells act as antigen-presenting cell to T cells. Nerve growth factor is one of the promoting factors. FDC express this receptor.
Cluster formation together with B cells	So-called "cap area" (ight zone and a part many B cells of outer & mantle zones)	FDC-lymphocyte cluster, which composed one or more FDCs and a few T cells, is the most minimal functional unit. Especially, these clusters are rich in basal light zone, which is the site of B cell selection. The mantle zone also contains loosely-packed clusters.
Modulation of B cell apoptosis	Basal light zone and other zones	B cells, which have low affinity to corresponding antigen, die with apoptosis. High affinity B cells further survive to differentiate to memory B cells or plasmablasts.
Inhibition of B cell clonal expansion	Dark & outer zones ?	Selectively, FDC inhibit the B cell clonal expansion.
Replacement of IC	So-called "cap area" (Light zone and a part of outer & mantle zones)	Newly administrated IC replaces the preexisting IC within GC.

Table 6. Localization of adhesion molecules on follicular dendritic cells (FDCs)

ADHESION MOLECULES	CD	MZ	OZ	DZ	BLZ	ALZ
Mac-1	11b	+	+	+	++	++
Sialyl-Le^x	15s	+	+	+	+	++
CD22	22	+	+	+	++	++
Integrin ß1	29	+	+	+	++	++
CD40	40	++	++	++	++	++
VLA-α3	49c	-	-	-	+	+
VLA-α5	49e	-	-	-	+	+
VLA-α6	49f	-	-	-	+	+
ICAM-3	50	-	-	-	+	+
ICAM-1	54	+	+	±	++	++
B7	80	++	++	++	++	++
VCAM-1	106	+	+	+	++	++

MZ: mantle zone; OZ: outer zone; DZ: dark zone; BLZ: basal light zone; ALZ: apical light zone; -: negative; ±: often positive; +: weakly positive; ++: strongly positive.

1992; Yamakawa et al., 1993a) (Fig. 6; Table 7). FDCs are one of the C1q-producing sources in the spleen (Schwaeble et al., 1995).

The complement system is mediated via the actions of CR1 (CD35) and CR2 (CD21) expressed on B cells and FDCs (Ahearn and Fearon, 1989; Kinoshita et al., 1991) (Fig. 7). CR1 on FDCs participates in the trapping of C3b-binding IC. CR1 and CR2 are essential for antibody production against both TD- and TI-antigens in the primary response. CR2 binds tightly to iC3b and C3dg and is a receptor for Epstein-Barr virus (Weiss et al., 1988). CR2 is indispensable for the long-term retention of ICs, one of the most important roles of FDCs.

The binding of the complement component C3d to the coagulation factor kallikrein produces the α-acidic fragment of C3, which inhibits T cell proliferation induced by antigens and mitogens and the production of cytotoxic T cells (Erdei et al., 1991). Insoluble C3b decreases clearance of ICs. Unlike soluble C3d(g) it positively modulates antigen trapping in the LF, B cell and IL-2-dependent T cell proliferations, and the antigen-presenting function of FDCs. Insoluble C3d(g) modulates the movement of activated B cells into the spleen. Insertion of C3b into the IC lattice work inhibits the Fc-Fc interaction important for IC-precipitation. The binding of antigen to C3b destroys the antigen-antibody complex, resulting in induction of solubilization of the ICs.

There are several factors common to the complement system and the blood coagulation and fibrinolysis systems. We have demonstrated that some coagulation and fibrinolytic factors are localized in the GCs (Yamakawa et al., 1991a; Kudo et al., 1992). ICs retained on the FDCs also relate to the production of the idiotype network (Köhler et al., 1989; Berek et al., 1991). The antibody-anti-idiotype antibody complex is itself trapped and retained in the GC.

c. Antigen-presenting function. The antigen-presenting capacity of the FDC to B cells is also mediated by iccosomes which can be isolated from sonicated FDCs (Burton et al., 1991; Wu et al., 1996a). The number of iccosomes decreases markedly in aged mice. IDCs induce activation and proliferation of resting B cells.

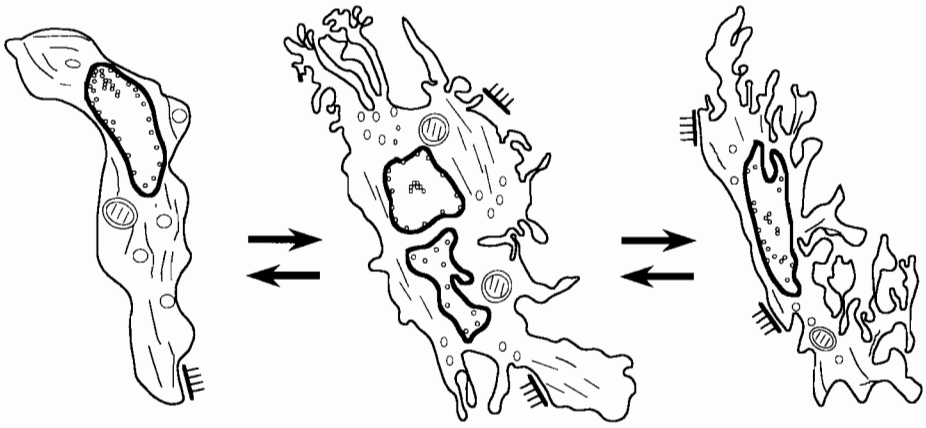

Fig. 4. Hypothesis of origin of follicular dendritic cell. It could be speculated that fibroblastic reticulum cells residing in the juxtafollicular area may transform to fibrohistiocytic cells under some stimulated conditions, and a part of the latter further metamorphose to follicular dendritic cells. (Imai and Yamakawa, 1996).

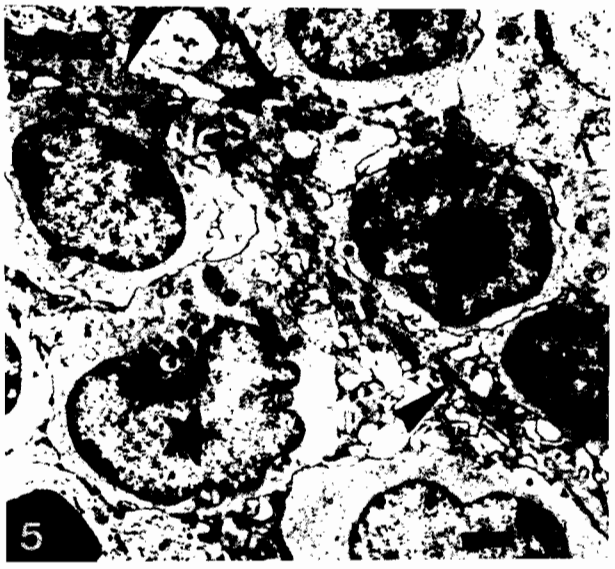

Fig. 5. Electron microphotograph showing the trapping and retaining of immune complex (horseradish peroxidase) by follicular dendritic cell (asterisk) in mouse Peyer's patch. Immune complex also adheres to fibers (arrowheads). Bar: 1 μm.

The activated B cells act as APC to T cells (Burton et al., 1993; Kosco-Vilbois et al., 1993). NGFR expressed on the FDC is a regulator in this mechanism (Thompson et al., 1989b; Strobach et al., 1991; Pezzati et al., 1992). As previously mentioned, NGF increases DNA synthesis of B cells in a dose-dependent manner (Otten et al., 1989), and closely relates to IgM synthesis and secretion in B cells. FDCs also inhibit the clonal expansion of B cells (Freedman et al., 1992).

Long-term immunization of animals with antigen results in periodic waves of antibody titer level. This periodicity results from the long-term retention of the antigen on FDCs. Higher antibody titers result in sequestration of the antigen epitope on FDCs and inhibits further antibody production. Bachmann et al. (1994) recently pointed out that 2-4 months after vesicular stomatitis-viral infection, the level of virus neutralizing IgG correlates with the amount of IC on the FDCs but not with the number of helper T cells or B cells. However, in mice even microgram amounts of IgG antibody specific to red blood cells inhibit more than 95% of the antibody reaction (Wiersma et al., 1989; Heyman, 1990). Lowering the antibody titer exposes the antigen epitopes again and augments antibody production. The inhibition is, however, antigen- but not epitope-specific. If the Fc portion is intact all subclasses of IgG also inhibit the induction of immunological memory. Conversely, IgM antibody enhances humoral immunity against both soluble antigens (ovalbumin and keyhole limpet hemocyanin) and particle antigens (erythrocytes and malarial parasites) in an antigen- but not epitope-specific manner, and affects both IgG- and IgM-levels in the primary response, playing an important role in the induction of memory B cells (Heyman, 1990).

d. Modulation of germinal center B cell apoptosis. Lymphocyte apoptosis can be induced in single cell culture but not in lymphocyte-FDC clusters (Freedman et al., 1990; Lindhout et al., 1993). Lymphocytes in lymphocyte-FDC clusters obtained from human tonsil survive for more than 50 days, and within 6 hrs of separation some lymphocytes emperipolesed in the FDCs are capable of cell division (Tsunoda et al., 1992, 1994). Blocking of the contact between ICs on the FDCs and B cells with anti-κ antibody inhibits B-cell proliferation. The simultaneous cooperation of anti-κ, ICAM-1, and LFA-1 antibodies completely blocks thymidine uptake into GC B cells. These data indicate that FDCs and their cell surface molecules provide

signals that up-regulate several processes including cellular adhesion between B cells and FDCs, and B cell stimulation via antigen receptors. They also stimulate B cell proliferation and rescue B cells from apoptosis (Kosco and Gray, 1992). Recently, we have demonstrated that FDC-associated clusters are not the main site of B-cell proliferation and apoptosis (Ohrui et al., 1997).

C. T cell-associated dendritic cells

1. Definition and classification

The common function of these DCs is to present antigens to T cells. Anatomically, they are divided into three groups (Table 2): 1) DCs in the non-lymphoid tissues, for example heart, lung, and Langerhans cell in skin; 2) veiled cells in circulating blood and afferent lymphatic vessels; and 3) IDCs in the TD-area of peripheral lymphoid tissues including lymph nodes, spleen, Peyer's patches, and the thymic medulla. It is well known that these different DCs are cells in different stages of differentiation and migration. DCs, like Mø, are APCs, and have little phagocytotic activity on their own but are the stronger APC in coculture with autologous lymphocytes. Moreover, these DCs have dendritic morphology, are bone marrow-derived, and strongly express Ia-antigen, but have few or no cell markers for other cell types including Møs, and express them at very low levels. 4) Recently the presence of GC DCs in human tonsillar follicles has been reported (Grouard et al. 1996).

2. Cellular morphology and cell markers

a. Langerhans cell. These are located in, for example, epidermis and squamous epithelium. Epidermal LCs with H&E appear as clear cells in the lower epidermis. The nucleus is irregular, lobulated, and often folded. The cytoplasm is relatively clear, and contains various quantities of microfilaments, microtubules, multivesicular bodies, and characteristic granules called Birbeck or LC granules with cup-, rod-, racket-like, and intermediate shapes. These granules are specifically recognized by Lag antibody (Fujita et al., 1990). The Langerhans cell contains a few lysosomes, and a small amount of rough endoplasmic reticulum, but no desmosomes, tono-filaments, melanosomes, or promelanosomes.

The LC in normal epidermis has a mean cell volume of 213 μm^3 and occurs at a cell density of about $1.6x10^5$ cells/mm^2 epidermis. One LC extends 5-9 cytoplasmic processes in one tissue section plane: their processes overlap but do not directly interact. In total their cytoplasmic extensions cover approximately 25% of the skin surface. LCs comprise 3-8% of total epidermal

Table 7. Localization of complement components and their regulatory proteins in secondary lymphoid follicles

COMPLEMENTS AND THEIR REGULATORY PROTEINS	LIGHT ZONE (%)	DARK ZONE (%)	MANTLE ZONE (%)
C1q	100	0	0
C3d	100	0	33.3
Membrane attack complex	100	0	0
C4b binding protein	100	0	0
Properdin	100	0	41.7
CD21	100	100	100
CD35	100	100	100
CD46	100	0	0
CD55	100	0	0
CD59	100	0	0

%: positive secondary lymphoid follicles/examined secondary lymphoid follicles in tonsillar tissues.

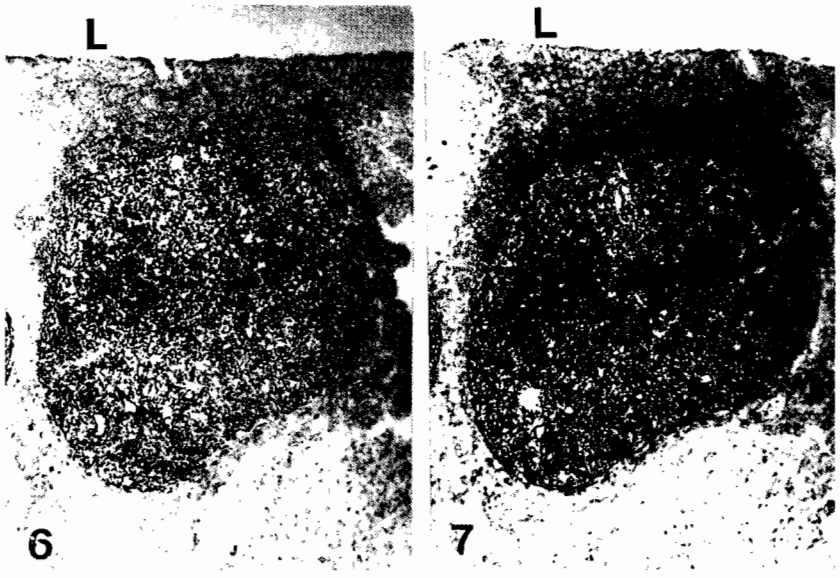

Fig. 6. Immunostain of complement component C3d in secondary lymphoid follicle of appendix. C3d is densely labeled within the whole lymphoid follicle. L: appendical lumen. Counterstained with methylgreen. x 60

Fig. 7. Immunostain of complement receptor 2 (CD21) in secondary lymphoid follicle of appendix. CD 21 is densely labeled within the whole lymphoid follicle. L: appendical lumen. Counterstained with methylgreen. x 60

Table 8. Immunophenotype of human Langerhans cells.

ANTIBODY/CLONE	CD	COMMENT	ANTIBODY/CLONE	CD	COMMENT
Immunophenotypic/ mRMA			ICAM-2	102	vivo (LCs in LN)
O10, Okt6	1a	(down-regulated)	GM-CSF receptor	w116	vitro
NU-T2	1b	(±) vivo (diseased skin)	IL-1α receptor	w121a	vitro
M241	1c	vivo (low)	MHC class I antigen		vivo/vitro
LFA-2	2	vivo (LCH cells)	MHC class II antigen		(up-regulated)
OKT3	3	vivo (LCH cells)	Fc εRI		vivo/vitro, mRNA
Leu 3a	4	(±) vivo	L3B12		vivo
LFA-1 α	11a	(±) vivo/vitro	LA45 antigen		(±) cultured LCs)
Complement receptor 3	11b	(down-regulated)	Neuron specific enolase		vivo
Complement receptor 4	11c	(up-regulated)	S100 protein		vivo
Leu M3	14	vivo	Lysozyme		vivo (a part of LCH cells)
Sialyl Lewis	15s	vivo/vitro	Vimentin		vivo (LCH cells)
FcγRIII	16	vivo/vitro	Neuropeptide Y		vivo
ß2-integrin	18	vivo	Lag		vivo
FcεRII	23	vivo/vitro	MIP-1α		mRNA
OKB 2	24	(cultured LCs)	MIP-2		mRNA
IL-2R α	25	(cultured LCs)	IL-1ß		mRNA
ß1-integrin	29	vivo/vitro	IL-6		vivo/vitro
FcγRII	32	(±) vivo/vitro	TNF-α		vitro (activated LC)
Leu M9	33	vivo/vitro	GM-CSF		vivo
OKM 5	36	(±) vivo/vitro	TGF-ß		vivo
G28-5	40	(cultured LCs)	Peanut agglutinin		(±) vivo
T29/33	44	vivo/vitro	Heat-stable antigen		vivo/vitro (down regulated)
LCA	45	vivo	**Histochemical**		vivo (down-regulated)
VLA-α1	49a	(±) vitro	Adenosine triphosphatase		vivo
VLA-α4	49d	(±) vitro	Adenosine diphosphatase		vivo (down-regulated
ICAM-3	50	vivo	Non-specific esterase		vivo
ICAM-1	54	vivo	Acid phosphatase		(±) (up-regulated)
LFA-3	58	(up-regulated)	Placental alkaline phosphatase		vivo
KP1	68	(up-regulated)	ß-glucuronidase		vivo
Leu-23	69	vivo	α-D-mannosidase		vivo
Ii (Invariant chain)	74	vivo/vitro	Aminopeptidase		vivo
B7/BB1	80	(up-regulated)	Cholinesterase		vivo

(±): negative or weakly positive; LCs: Langerhans cells; LCH: Langerhans cell histiocytosis; LN: Lymph node.

cells. ^{3}H-thymidine uptake of epidermal LCs is 1-2%. They have a mean cell cycle time of 16.12 days, confirming that their proliferation maintains their numbers even though they are slowly growing cells in the S-phase of the cell cycle.

LCs express CD1a, Ia-antigen, FcεRII, CR3, and ICAM-1 (Aqel, 1987; Krenàcs et al., 1993) (Table 8). About 60% of total CD1a^{+} LCs, however, are Ia^{-}, and, furthermore, not only LCs but also keratinocytes are positive for Ia-antigen in normal skin. Adenosine triphosphatase (ATPase) is a widely used cell marker for LCs (Miyauchi and Hashimoto, 1989; Carrillo-Farga et al., 1991), but it is less specific than adenosine diphosphatase (Elbe et al., 1989). LCs also express S100 protein, vimentin, and neuron-specific enolase (Fantini et al., 1991).

b. Veiled cells. DCs in circulating blood vessels, afferent lymphatic vessels, and lymphatic sinuses have slender, irregular-shaped lamellipodia and veiled cytoplasmic extensions. Although they enter lymph nodes, they cannot migrate further into efferent lymphatic vessels or the thoracic duct. Veiled cells comprise approximately 1.5% of total mononuclear cells in afferent lymphatics (Spry et al., 1980). The characteristics of this cell are similar to those of IDCs, and both DCs show little or no phagocytotic activity, Ia^{+}, IL-2R^{+}, and CD4^{+}. Some are positive for ATPase and non-specific esterase. The heterogeneity of immunophenotypes and functions of circulating blood dendritic cells (dendritic leukocytes) have been described (Egner et al., 1993; Howard et al., 1996).

c. Connective tissue dendritic cells. These are located in non-lymphoid tissues such as heart, lung, liver and digestive tract, though not in Peyer's patches. Their morphology, immunophenotypes and other characteristics are similar to those of IDCs (Kabel et al., 1988; Knight et al., 1992; Austyn et al., 1994; Woo et al., 1994). However, they show considerable heterogeneity depending on their anatomic sites (Pollard and Lipscomb, 1990; Schon-Hegrad et al., 1991). For example, in lung tissue, interstitial DCs in the alveolar septa are ICAM-1^{+}, Ia^{high}, and FcRs^{-}, unlike DCs in surrounding airway tissues, demonstrating the functional diversities between both types of DCs (Gong et al.,

Table 9. Immunophenotypes of human interdigitating cells.

ANTIBODY/CLONE	CD	COMMENT	ANTIBODY/CLONE	CD	COMMENT
Immunophenotypic			Ii (invariant chain)	74	vivo/vitro
IOT1B	1b	vivo	B7/BB1	80	vivo
M241	1c	vivo/vitro	GM-CSF receptor	w116	vivo/vitro
LFA-2	2	vivo/vitro	ICAM-2	102	vitro
Leu3a	4	(±) vitro	VCAM-1	106	vivo/vitro
OKT 1	5	vivo	TNFR (p75) (type II)	120b	vivo/vitro
Leu 2a	8	(±)vitro	IL-1R	121	VIVO
LFA-1 α	11a	(±) vitro	IL-1α R	121a	vivo/vitro
Complement receptor 3	11b	vivo/vitro	IL-2Rß	122	vivo/vitro
Complement receptor 4	11c	(±) vivo/vitro	MHC class I antigen		vivo/vitro
ß2-integrin	18	(±) vivo/vitro	MHC class II antigen		vivo
Fc εRII	23	vivo/vitro	Fc ε RI		vivo/vitro
OKB2	24	vivo/vitro	Neuron specific enolase		vivo/vitro
IL-2R α	25	(±) vivo/vitro	S100 protein		vivo/vitro
ß1-integrin	29	(±) vivo/vitro	RFD1		vivo
PECAM-1	31	vivo/vitro	IL-1α		vivo (in Castleman's disease)
FcγRII	32	(±) vivo/vitro	TNF-α		vivo
S2C6	40	vivo/vitro	TGF-ß1		vivo
α^{IIbi}-integrin	41a	vivo	Galactose receptor		vivo
Hermes antigen	44	vivo/vitro	**Histochemical**		
4KB5	45RA	vivo/vitro	5'-nucleotidase		vivo
UCHL1	45RO	vivo	Adenosine triphosphatase		vivo
Membrane cofactor protein	46	vivo	Acid phosphatase		vivo
ICAM-1	54	vivo (DCs in blood)	ß-glucuronidase		vivo
LFA-3	58	vitro/vitro	α-napthyl acetate esterase		vivo
Protectin	59	vivo/vitro	α-napthyl butyrate esterase		vivo
KP-1	68	vivo/vitro			

(±): negative or weakley positive, DCs: Dendritic cells

1992; Holt et al., 1992). The former are similar to IDCs, the latter to LCs.

d. Indeterminate cells and dermal Langerhans cells. The indeterminate cell resides in the dermis and lacks Birbeck granules (Harrist et al., 1983). It has an irregular nucleus, abundant mitochondria and intermediate cytoplasmic filaments.

There are two current theories about the significance of indeterminate cells: one considers them to be precursor or immature LCs; the other suggests that they are LCs lacking Birbeck granules, suggesting that the dermal microenvironment induces disappearance of the granules and decreases the level of CD1a expression. Indeterminate cells increase in a variety of inflammatory skin conditions.

The dermis of non-inflamed skin contains sparse DCs which express CD1a and CD1c, but not CD36 and CD11, and lack Birbeck granules. These DCs have antigen-presenting capacity and are termed dermal LCs (Murphy et al., 1985; Cooper et al., 1992). They react with antigens (for example drugs, infectious agents, and autoantigens) transported into the skin by circulating blood and also with extrinsic antigens that invade the dermis directly from the epidermis. They increase prominently in atopic dermatitis. Tumor cells of systemic eruptive histiocytoma have been suggested to be derived from dermal LCs (Saijo et al., 1991).

e. Granstein cells. These are one class of I-J restricted APCs, which reside in mouse epidermis, and are thought to be a subtype of LCs (Granstein et al., 1984). In general, LCs promote the immune response while Granstein cells and Thy-1^+ epidermal DCs suppress it. However, whether this cell is truly an independent entity is open to question.

f. Interdigitating cells (IDCs). IDCs reside in the TD-area of all lymphoid tissues and thymic medulla, and are FcR^- or low, $CR3^-$ or low, and Ia^{high}. Like epidermal LCs they are positive for S100 protein but not CD1a (Table 9). Their long cytoplasmic processes expand into surrounding lymphocytes. IDCs have an irregular nucleus and clear cytoplasm. Their morphology is very similar to that of LCs though they lack Birbeck granules.

g. Germinal center dendritic cells (GC DCs). Grouard et al. (1996) have recently discovered a new type of DCs in the human tonsillar GCs. Unlike FDCs, GC DCs are $CD4^+$ $CD11c^+$ CD3- APC, may stimulate GC T cells and consequently relate to the memory B cell production.

3. Cellular origin

The supportive scheme of the cellular origin of Dcs is shown in Fig. 8. Human peripheral blood contains at least 4 cell types expressing CD33 antigen and with

various degrees of antigen-presenting capacity (Thomas and Lipsky, 1994): 1) The $CD33^{dim}$, $CD14^{dim}$, $CD16^{-}$, Ia^{-} precursor cells of DCs which comprise 2-3% of total peripheral white blood cells; 2) a few $CD33^{bright}$, $CD14^{dim}$, $CD16^{-}$ mature DCs derived from lymphatic tissues which have some antigen-presenting capacity; 3) the $CD33^{dim}$, $CD14^{dim}$, $CD16^{+}$ cells (one subtype of monocytes) lacking antigen-presenting capacity; and 4) the typical $CD33^{dim}$, $CD14^{bright}$ monocytes lacking antigen-presenting capacity. The $CD33^{bright}$ DCs have stronger antigen-presenting capacity and more strongly express Ia-antigen and adhesion molecules including ICAM-1 and ICAM-2 than $CD33^{dim}$ DC precursors.

When $CD34^{+}$ precursor cells prepared from human bone marrow and umbilical or peripheral blood are cultivated with GM-CSF and TNF-α or IL-3, they differentiate into LCs (Pelletier et al., 1984; Reid et al., 1990, 1992; Caux et al., 1992; Santiago-Schwartz et al., 1992; Misery et al., 1993; O'Doherty et al., 1994; Young et al., 1995) and when these precursor cells are cultured with seven cytokines (IL-1ß, IL-3, IL-4, IL-6, stem cell factor, erythropoietin, and GM-CSF), Birbeck's granule-containing LCs and further IDCs are born (Mackensen et al., 1995; Herbst et al., 1996; Peters et al., 1996). $CD34^{+}$ hematopoietic progenitors from human cord blood differentiate in response to GM-CSF plus TNF-α or IL-4 along two independent DC pathways, of which one is $CD1a^{+}$ precursor containing Birbeck's granule and is positive for Lag antigen and E-cadherin, and the other is $CD14^{+}$ DC precursor negative for Birbeck's granule, Lag antigen and E-cadherin but positive for CD2, CD9, CD68, and factor XIIIa (Caux et al., 1995b, 1996; Pickl et al., 1996). Furthermore, human T, B, natural killer, and dendritic cells arise from a common bone marrow progenitor cell subset (Galy et al., 1995). Cultured human monocytes with GM-CSF become $CD1a^{+}$, $CD1b^{+}$, $CD1c^{+}$, PNA^{+}, $CD11^{+}$, and $CD14^{+}$ LCs lacking Birbeck granules (Kasinrerk et al., 1993). CD1a-expression in cultured monocytes progressively up-regulates during 3 days of culture. Lipopolysaccharide, rG-CSF, rIFN-α and -γ, and rIL-1α, -1ß and -6, do not induce differentiation into LCs. Granulocytes, peripheral

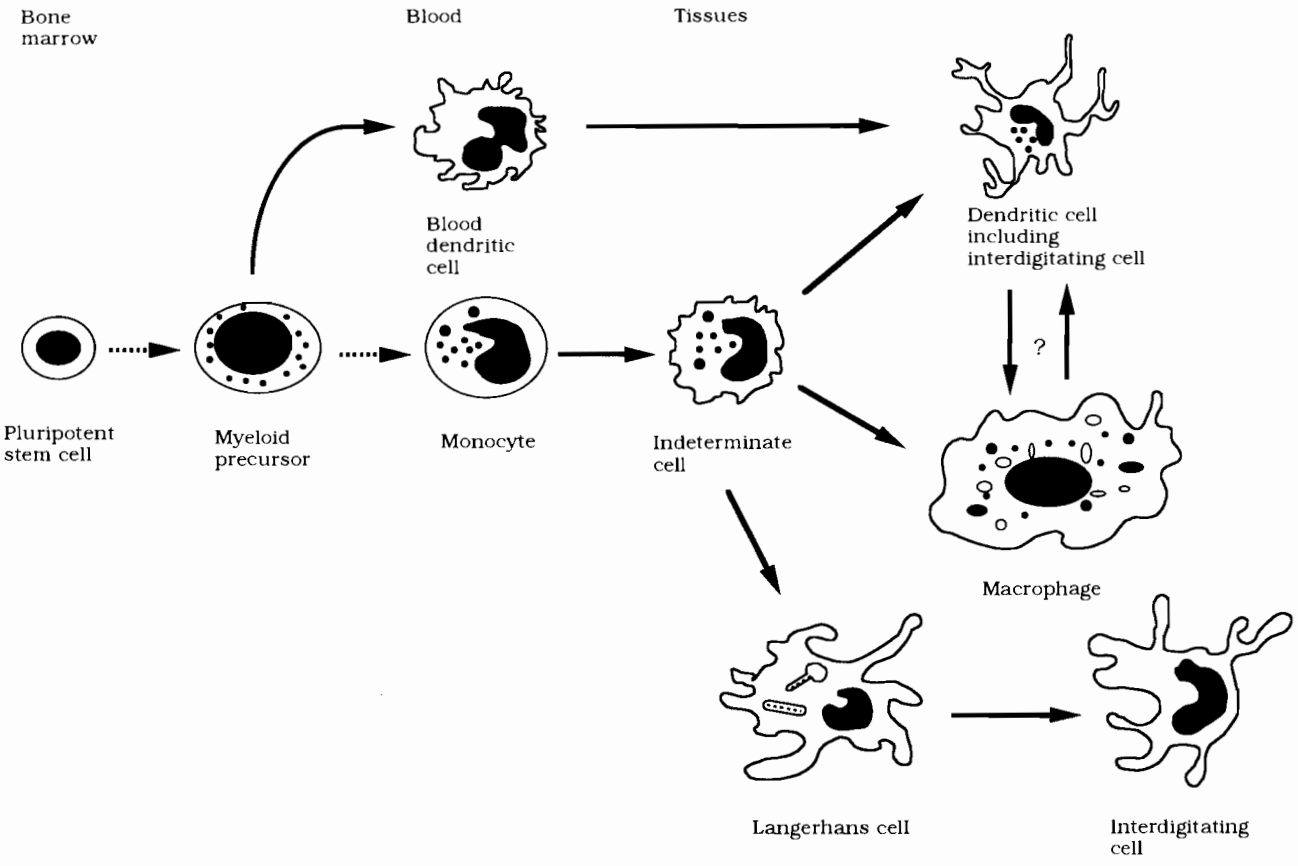

Fig. 8. Origin of dendritic cells. Dendritic cells (DC) have common precursor cells to monocyte/macrophage in the bone marrow. In the early phase, common precursor cells divide into DC- and monocyte/macrophage-lineages. In peripheral blood, DC exhibit as immature DC and after migrating into tissues they fully differentiate (upper pathway in the figure). In turn the late monocytes divide into DC- and monocyte/macrophage-lineages (lower pathway in the figure). The latter lineage and indeterminate cells in tissues. They have weak cell adhesion, phagocytosis, nonspecific esterase activity, and Fc receptor. Cells on the differentiation route, such as CFU-DC, CFU-DC/monocytes, monoblasts, and promonocytes are omitted by dotted arrows. It is a mystery whether DC and macrophages are capable of transforming mutually (modified from a report by Peters J.H., Gieseler R., Thiele B. and Steinbach F. (1996) Dendritic cells: they form ontogenic orphans to myelomonocytic descendants. Immunology Today 17, 273-278).

lymphocytes, and myeloid cell lines cannot differentiate into LCs. GM-CSF, TNF-α and IL-6, and the thyroid hormones T3 and T4 stimulate human peripheral blood monocytes to differentiate not only cytologically but also functionally into mature veiled/DCs (Mooij et al., 1994). Freshly isolated DCs from human thymus do not express CD1a, but express it after a few days of culture (Lafontaine et al., 1992; Wu et al., 1996b; Res et al., 1996). As mentioned below, $CD1a^+$ or $CD5^+$ DCs circulate in normal peripheral blood but comprise less than 1% of the total mononuclear cell fraction (Wood and Freudenthal, 1992). $CD1a^+$ DCs in peripheral blood increase markedly in patients with trauma or extensive burns (Gothelf et al., 1988) and simultaneously, $CD1a^+$ indeterminate cells lacking Birbeck granules appear in the dermis (Murphy et al., 1985). The expression of CD1 molecule on the LC precursor cells derived from bone marrow has been recently demonstrated to be temperature-dependent; that is, stimulation by TNF-α, IL-3 and GM-CSF induces stronger expression at 34 °C, the skin surface temperature, than at 37 °C, the core body temperature (Ueki et al., 1993). These observations suggest that in humans the DC-precursor cells exist both in bone marrow and peripheral blood. Some gradually differentiate into DCs in peripheral blood and enter the epidermis to become mature LCs. Interaction with T cells and expression of CD45RA, CD45RO and B7/BB1 molecules may all be essential for maturation of peripheral blood precursors. After co-culture with the DC-differentiation factor eluted from the supernatant of cultured helper T cells, a cell line derived from human monocytic leukemia has been shown to differentiate directly into IDCs (Takahashi et al., 1992b).

The process of generation of DCs in the mouse has been elucidated in detail (Katz et al., 1979; Breel et al., 1987; Elbe et al., 1989; Inaba et al., 1992; Lu et al., 1994). However, in contrast with humans, mouse DCs are not found in the bone marrow or peripheral blood. In the mouse immature precursors may leave the bone marrow, arrive in peripheral tissues, and differentiate into mature DCs in loco. Although op/op mice lack normal monocytes/Mø due to M-CSF deficiency, they still have epidermal LCs, suggesting that LCs are not derived from blood monocytes independent of M-CSF (Takahashi et al., 1992a).

4. Cell migration

As mentioned above, T-associated DCs are widely distributed in various tissues and are constantly supplied through the blood pool although their turnover in tissues is rapid. Epidermal LCs migrate from skin to draining lymph nodes (Cumberbatch and Kimber, 1990; Kripke et al., 1990), by descending into the dermis dermal LCs. They enter afferent lymphatics as veiled cells, and eventually become IDCs in the paracortical area of draining lymph nodes. These DCs with antigens on their cell surface migrate not only into ipsilateral draining lymph nodes but also into contralateral and distant ones (Hill et al., 1990). IDCs do not migrate further than the lymph nodes. In inflammatory skin conditions these migrating cells increase and LCs with persisting Birbeck granules are found in the epidermis and afferent lymphatics and also in the paracortex of superficial lymph nodes (Shamoto et al., 1992, 1996). Migration of epidermal LCs into draining nodes is augmented in a dose-dependent manner by ultraviolet (UV)-B irradiation (van Praag et al., 1994), urocanic acid ointment (Moodycliffe et al., 1992), and by rTNF-α (Kimber and Cumberbatch, 1992; Cumberbatch et al., 1994). TNFR II (p75) signalling is required for the migration of LCs (Wang et al., 1996).

DCs are widely distributed in the epithelium of the uterine cervix, urinary bladder, and airways, and in the parenchyma of the hepatic portal area, the mucosa of the gastrointestinal tract, and the connective tissues of the kidney and skeletal muscle. Epithelia affected by squamous metaplasia also contain DCs. Like LCs these DCs migrate into afferent lymphatics and draining nodes to become functionally mature IDCs. On the other hand, DCs originating from the transplanted heart reach the spleen and aggregate in the splenic red pulp and in the periphery of the white pulp. Finally they migrate into the TD-area. Splenic DCs move via the blood stream rather than via afferent lymphatics as is the case in the skin and lymph nodes (Larsen et al., 1990a, b).

5. Functional maturation of dendritic cells

Epidermal LCs are immature DCs (Schuler and Steinman, 1985; Kitajima et al., 1996a,b), and gradually develop the capacity to present antigens to T cells during their migration to the TD-area of draining lymph nodes. The function of LCs is divided into two sequential phenomena: an antigen-processing function in the epidermis, and an antigen-presenting function in draining lymph nodes and the spleen (Romani et al., 1989a). Only the latter process induces a T-cell response. APCs take up extracellular native protein (antigen) into intracytoplasmic endosomes (Fanger et al., 1996). The endosome is acidic and contains various proteolytic enzymes which disintegrate proteins. Thereafter, processed antigens (peptides) bind to Ia-antigen and are exposed on the cell surface (antigen processing). Cytokines and adhesion molecules produced by DCs play an important role when the Ia-antigen binding proteins (peptides) stimulate T cells (antigen-presenting).

Freshly isolated LCs in culture gradually lose their Mø-like characteristics, including non-specific esterase activity and expression of F4/80 antigen, FcR and CR3, but increase about10-fold their ability to activate heterologous T-cells, and expression of Ia-antigen and B7/BB-1 (CD80) increases 5-10-fold (Cumberbatch et al., 1991b; Symington et al., 1993; Lee et al., 1993). The synthesis of Ia-antigen and invariant chain (CD74) gradually decreases up to the antigen-presenting stage (Puré et al., 1990; Stossel et al., 1990; Kämpgen et al., 1991; Anderson et al., 1993). A decrease in endosome

essential for antigen-processing is also seen. The expression of adhesion molecules including CR4 (CD11c), ICAM-1, LFA-3 (CD58), and sialyl Lewis X (CD15s) increases, accompanied by cell migration, while Birbeck granules and CD1a as well as CR3 (CD11b) decrease or disappear (Romani et al., 1989b; Teunissen et al., 1990; Bruyuzeel et al., 1992; Ross et al., 1994) (Fig. 9). ICAM-1 and LFA-3 molecules on LCs are both important for their interaction with T cells.

Mature DCs do not have prominent phagocytic activity. However, DC precursor cells in the mouse (Inaba et al., 1993), freshly isolated LCs, and splenic DCs (Sousa et al., 1993) can ingest BCG myocobacteria, yeasts and 3.5 μm-diameter latex beads, and grow to become stronger APCs (Coates et al., 1996; Garrigan et al., 1996). Unlike Mø, DCs cannot phagocytose colloidal carbon.

When fluorescent isothiocyanate (FITC) as hapten is applied to skin to induce contact hypersensitivity, epidermal LCs ingest it and in 1-3 days transport it directly to draining lymph nodes (Macatonia et al., 1987; Hill et al., 1990; Kimber et al., 1990). The FITC-holding DCs in lymph nodes are mature and strongly activate T cells (Cumberbatch et al., 1991a). Furthermore, mice injected with T cells obtained from these lymph nodes also demonstrate contact hypersensitivity. On the other hand, the characteristics and function of DCs isolated from mouse heart and kidney only resemble those of immature DCs (Austyn et al., 1994). Human DCs are activated through CD40 cross-linking (Caux et al., 1994b).

These findings indicate that freshly isolated, inactivated LCs and splenic DCs are immature APCs with weak antigen-presenting capacity but excellent antigen-processing capacity, while LCs activated *in vitro* and IDCs in lymphatic tissues are mature APCs with extremely strong antigen-presenting capacity but no antigen-processing capacity (Girolomoni et al., 1990).

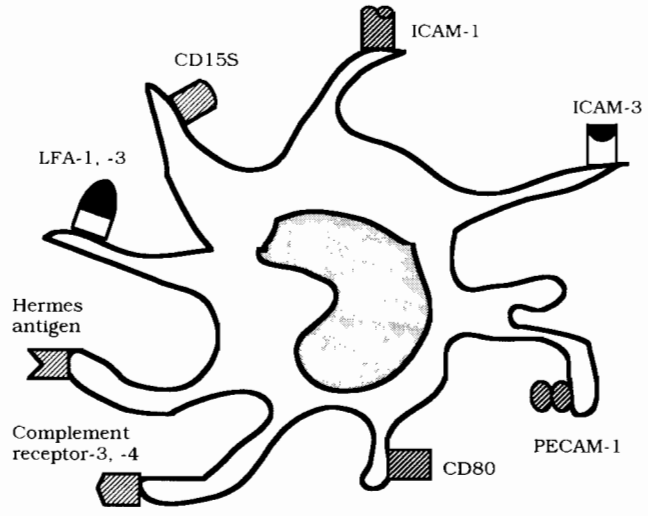

Fig. 9 . Some characteristics of human dendritic cells (DC). They strongly express CD4, CD11a, CD32, CD33, and CD86, and also weakly CD11b, CD40, CD54, and CD64, secrete IL-15, IL-12 (p40), and MIP-1ß and have IL-1 receptor (R) types 1& 2, IL-2Rα and ß (cultured DC), IL-6R, GM-CSFR α and ß, IFN-γR, and TNFR (p75).

6. Dendritic cells and cytokines

Thymic and blood DCs as well as LCs produce IL-1α and IL-1ß (simultaneously IL-1ß converting enzyme in murine LCs) (Barkley et al., 1990; Lafontaine et al., 1991; Ariizumi et al., 1995; Larregina et al., 1996), and even freshly isolated LCs secrete IL-6, macrophage inflammatory protein (MIP)-1a, MIP-2, and prostaglandin D (Matsue et al., 1992; Heufler et al., 1992). Both normal LCs and the cells of human Langerhans cell histiocytosis produce GM-CSF (Emile et al., 1993). DCs produce prostaglandin D (Urade et al., 1989) and $CD4^+$ blood DCs IFN-α (Ferbas et al., 1994). The two DC clones CB1 and D2SC/1 express mRNA for TGF-ß and TNF-α (up-regulated), but not IL-4, TNF-ß, IL-10 or IL-12 (Granucci et al., 1994). Mature human LCs synthesize IL-12 (Kang et al., 1996) and IL-15 (Blauvelt et al., 1996). Consequently, during differentiation and maturation DCs produce various cytokines.

The ability of DCs to activate T cells is affected by cytokines released by other cell types including macrophages. IL-1 augments the binding of DCs to T cells and Ia-antigen expression on DCs, but decreases the number of Ia^+ DCs (Koide et al., 1987; Lundqvist and Bäck, 1990). Both TGF-ß and IL-10 decrease the antigen-presenting ability of LCs while GM-CSF enhances the expression of Ia-antigen on LCs (Enk et al., 1993; Ullrich, 1994). GM-CSF helps maintain the dendritic morphology and survival of LCs and blood DCs for up to 6 weeks, induces the increasing functional activity and maturation of LCs, and suppresses the expression of CD1a on LCs. T-cell proliferation induced by splenic DCs and veiled cells is augmented by GM-CSF (Witmer-Pack et al., 1987; Heufler et al., 1988; Markowicz and Engelman, 1990). The binding of IL-1 to IL-1 receptor up-regulates the GM-CSF receptor and modulates DCs in a similar fashion to GM-CSF (Kämpgen et al., 1994). TNF-α promotes LC survival and migration from skin to draining nodes (Cumberbatch et al., 1994), but not their functional maturation, unlike GM-CSF (Koch et al., 1990; Rambukkana et al., 1995). Recombinant IFN-γ up-regulates Ia-antigen expression on LCs, and prostaglandin synthesis inhibitors increase the number of Ia^+ LCs (Willis et al., 1991). DCs promote the secretion of IL-2, IL-4, and IFN-γ from T cells (Willis et al., 1991). Human rIL-10 inhibits the growth of $CD4^+$, $CD8^+$ T cells induced by allogeneic $CD1a^+$ DCs (Caux et al., 1994a).

7. *In vitro* function of dendritic cells

In culture DCs are essential immune stimulators for activation of resting T cells, leading to a cellular immune

Table 10. Immune responses induced by dendritic cells.

IN VITRO	IN VIVO
T cell proliferation Mixed leukocyte reaction (hetero-, allo-MRL, Mls) Antigen specific proliferation (non-self protein antigen) Non-specific proliferation (Con A, PHA, $NaIO_4$, CD3 Super antigens)	Delayed type hypersensitivity Contact skin reaction (allergy)
Induction of cytotoxic T cell - Heterogeneous MHC class I antigen - Viral-infected host cell - Chemical modified host cell	Graft-versus-host rejection - Kidney, Spleen, Heart, Skin - Blood transfusion - H-Y antigen
Antibody production (Blood cell antigen, protein antigen)	Antibody production Immunological tolerance

response (Croft et al., 1994) (Table 10). Other leukocytes, such as mouse splenic macrophages and resting B cells, do not have this immune stimulatory activity. During presentation of antigens to T cells, DCs release proper activating signals including cytokines, as previously described. DCs have been shown to have the following functions *in vivo*: 1) Mouse DCs have powerful stimulatory activity in allogeneic mixed leukocyte reaction (MLR). The degree of this activity depends on the dose of DCs. Blood and tonsillar DCs as well as splenic DCs also possess this activity. DCs also stimulate B cells in auto- and iso-MLR. *In vivo* this mechanism may account for antigenic stimulation of B cells in the TD-area. 2) MHC class II antigen-restricted helper T cells are essential in the generation of cytotoxic T cells. The presence of DCs is associated with both helper and cytotoxic T-cell immune responses. 3) DCs induce B cells to produce antibodies against the TD-antigen by two different pathways. Generation of antibodies against antigens, such as the epitope of sheep red blood cells depends on cytokines including IL-4 released from T cells. On the other hand, antibody production to antigens such as a hapten-carrier complex requires actual cell contact between activated T-immunoblasts and B cells. Thus, in one pathway of antibody production DCs stimulate T cells to produce lymphokines, while in the other DCs induce T cells to become lymphoblasts and promote antibody synthesis by B cells. 4) Cell division of T cells evoked by mitogens occurs only in the presence of DCs. 5) DCs are also required for restimulation of memory T cells.

IV. Lymphocyte-dendritic cell system (LDS)

A. Cellular composition and significance of LDS

The LDS includes all DCs and lymphocytes in most tissues and organs. DCs consist of B cell-associated FDCs and T cell-associated DCs (Tew, 1993) (Table 2). The density of DCs is different in each tissue and organ. DCs localize not only in lymphatic tissues but also in many other non-lymphatic tissues where a rapid response to antigenic stimulation is required. Lymphocyte-lineage cells develop in the bone marrow and migrate from the peripheral blood into various lymphatic tissues to become mature lymphocytes. Recirculating lymphocytes also migrate in large numbers into inflamed non-lymphatic tissues. DCs are essential for all the pathways of lymphocyte differentiation, maturation, and activation. It has recently been reported that DCs are required for the generation of immature lymphocytes in bone marrow and for maturation of non-bone marrow, peritoneum-derived Ly-1 $(CD5)^+$ B cells.

In conclusion, it is now well recognized that the interaction between DCs and lymphocytes is essential for the generation, growth, differentiation, and functional activation of lymphocytes. It is important to consider the function of both cell types in the systematic concept of the LDS.

B. Follicular dendritic cell-lymphocyte interaction

1. T Cells in germinal centers

Human lymphoid GCs, especially in the outer and light zones, contain $CD4^+$, Leu7 $(CD57)^+$, $CD11^-$ TH2 cells with other immunophenotypes such as $CD16^-$, IL-2R $(CD25)^-$, $CD45RO^+$, $CD69^+$, $CD71^-$, Ia^-, $Mel14^-$ and PNA^-. These T cells do not possess cytotoxic activity but their immunophenotypic characteristics are similar to natural killer cells (Velardi et al., 1986; Yuda et al., 1989; Ikeda et al., 1994). Such T cells comprise about 5% of total GC cells (Heinen et al., 1991; Tsiagbe et al., 1992). Lack of $CD4^+$, $CD57^+$ T cells in the dark zone prevents the generation of harmful B cells which respond to autoantigens (Nossal, 1994a,b). GCs contain only a few $CD8^+$ T cells (Tsiagbe et al., 1992).

$CD4^+$, $CD57^+$ T cells may contact certain GC B cells and secrete cytokines essential for B cell growth and Ig-class switching (Tsiagbe et al., 1992). As mentioned below, the ligation of CD40-CD40 ligand and B7/BB1-CD28 play an important role in adhesion between T cells, B cells, and IDCs. Recent studies have indicated that the LFs are a major site of specific T cell

growth (Gulbranson-Judge and MacLennan, 1996).

2. Follicular dendritic cell-B cell adhesion

The FDC-lymphocyte clusters obtained from human tonsils contain many $CD19^+$, $CD22^+$ B cells and a small number of T cells, but no macrophages (Petrasch et al., 1990; Tsunoda et al., 1992). The co-culture of mouse FDCs and lymphocytes generates the large cell aggregates consisting of 1-3 FDCs to which 30-90 B cells, but only 1-5 T cells adhere (Kosco et al., 1992). Isolated B cells from the GC are LFA-1^+, $CD44^{low}$, VLA-4^{low}, VCAM-1^- and ICAM-1^-. Binding between ICAM-1 and VCAM-1 on FDCs, and LFA-1 and VCAM-1 on B cells are the major ligand-receptor interactions which modulate GC B cell growth and differentiation (Koopman et al., 1991; Kosco et al., 1992; Ree et al., 1993; Tanaka et al., 1994; Leite et al., 1995) (Fig. 10).

3. Follicular dendritic cell-T cell interaction

The adhesion of GC T cells to FDCs has also been described (Gray and Skarvall, 1988; Clark et al., 1992; Butch et al., 1994) (Fig. 10). FDCs are one of the most potent stimulators of proliferation of allogeneic peripheral blood mononuclear cells and T cells in the MLR (Burton et al., 1993). TH2 cells themselves contact FDCs via CD40-CD40 ligand interaction, receive some signals from the antigen bound to Ia-antigen on FDCs, and survive as memory T cells (Gray, 1991; Gray et al., 1991; MacLennan et al., 1991). Activated but not resting T cells bind to cultured FDCs (HK cells), a process partially inhibited by anti-LFA-1, ICAM-1, VCAM-1, and VLA-4 antibodies (Kim et al., 1994). The ligation of LFA-1-ICAM-2, LFA-1-ICAM-3, CD40-CD40, and VLA-4-VCAM-1 are important in FDC-T cell adhesion (Hart and Prickett, 1993; Kim et al., 1994).

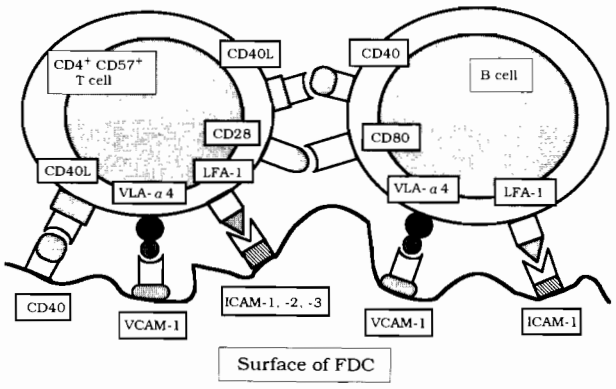

Fig. 10. Adhesion molecules mediating the cellular interaction among follicular dendritic cells, B cells and T cells in the germinal center. FDC: follicular dendritic cell; VLA: very late activation antigen; LFA: lymphocyte-function-associated antigen; VCAM: vascular cell adhesion molecule; ICAM: intercellular adhesion molecule. $CD4^+$ Leu7 (CD57) $^+$ T cells in the outer and light zones of human lymphoid follicles are analogous to natural killer cells, but lack cytotoxicity.

4. Follicular dendritic cell-B cell-T cell interaction

How do FDCs and T cells regulate B-cell maturation? The following suggestions have been made (Koopman and Pals, 1992) (Fig. 11): 1) FDCs trap and retain IC via FcR and CRs and directly present antigen to B cells. The ICs on FDCs are characteristically 440-490Å in periodicity for easy recognition by surface Ig on B cells. 2) FDCs secrete ICs as IC-coated bodies (iccosomes). GC B cells specifically bind to these iccosomes via the mIg receptor, pinocytose them, and then present the processed antigen to GC-T cells dependent on MHC class II molecules. Antigen-specific T cells activated in this way conversely induce B-cell proliferation and antibody production. 3) FDCs produce some factors related to B cell differentiation and maturation. For example, the CD23 strongly expressed on FDCs is released as a soluble protein. Only a few pre-plasmablasts rescued from apoptosis by the synergistic effect of soluble CD23 and IL-1α become target cells for helper T cell-derived IL-2 and differentiate into IgM-producing cells (Holder et al., 1994). 4) Activated B cells express B7/BB1 molecule, a member of the Ig superfamily, as the natural ligand to T-cell antigen CD28 (Linsley et al., 1990; Freedman and Nadler, 1991). After ligation of T cells by CD28, stimulators such as anti-CD3 antibody enhance activated T cells to secrete cytokines, including IL-2, TNF-α GM-CSF, and IFN-γ (Linsley et al., 1990; Thompson et al., 1989a; Turka et al., 1990; Bosseloir et al., 1996). The B7/$BB1^+$-activated B cells act as APC to the $CD4^+$, $CD28^+$ T cells in the GC. The ligation of B7/BB1-CD28 promotes lymphokine secretion from T cells and regulates B cells to proliferate and differentiate into plasmablasts or memory B cells. 5) FDC-like cells (HK cells) do not make T cells proliferate, but activated T cells can bind to HK cells and promote proliferation of HK cells, depending on cell contact and soluble factors such as IL-4 (Kim et al., 1994). 6) CD40 is expressed on B cells, DCs, and normal and malignant epithelial cells (Armitage et al., 1993; Renshaw et al., 1994), and enhances the expression of mIg, FcεRII, and CD25 on pre-B cells and

Table 11. Correlation of dendritic cells to T cells (antigen presentation and activation of T cells).

DENDRITIC CELLS	T CELLS
Antigen presentation MHC class I or II and antigen peptide	Antigen recognition TCR and CD4 or CD8
Cell adhesion and costimulatory factors ICAM-1 (CD54) LFA-3 (CD58) B7/BB-1 (CD80)	 LFA-1 (CD11a + CD18) CD2 CD28
Production of cytokines IL-1ß, TNF-α, MIP-1, IL-6, GM-CSF	

B cells (Liu et al., 1991b). Under the synergistic effect of CD40 molecule and anti-Ig antibody, IL-4 derived from TH2 cells promotes DNA synthesis in resting B cells and enhances expression of Ia-antigen and FcεRII to induce production of IgG1 and IgE (Callard et al., 1993; Secrist et al., 1994). Centro-cytes rapidly adopt a memory B cell phenotype on co-culture with autologous GC T cell-enriched preparations (Casamayor-Palleja et al., 1996).

Consequently, proliferation of FDCs and B cells, GC formation, and the final stage of B cell maturation and activation are regulated by several important bi-directional interactions. These include the interactions between T and B cells, T cells and FDCs via ligation of B7/BB1-CD28 and/or CD40-CD40 ligand, and between B cells and FDCs via adhesion molecules, soluble factors, and cytokines such as IL-4 secreted from TH2 cells (Foy et al., 1993; Kasajima et al., 1993; Knox et al., 1993; Kasajima and Audoh, 1994). Production of highly specific B cells to antigen therefore requires complex FDC-B cell-T cell interactions.

C. Dendritic/Interdigitating cell-T cell adhesion

Adhesion molecules relating to the DC/IDC-T cell interaction have been gradually analyzed (Table 11). Human DCs express various adhesion molecules, including LFA-1, LFA-3, ICAM-1, ICAM-3, sialyl

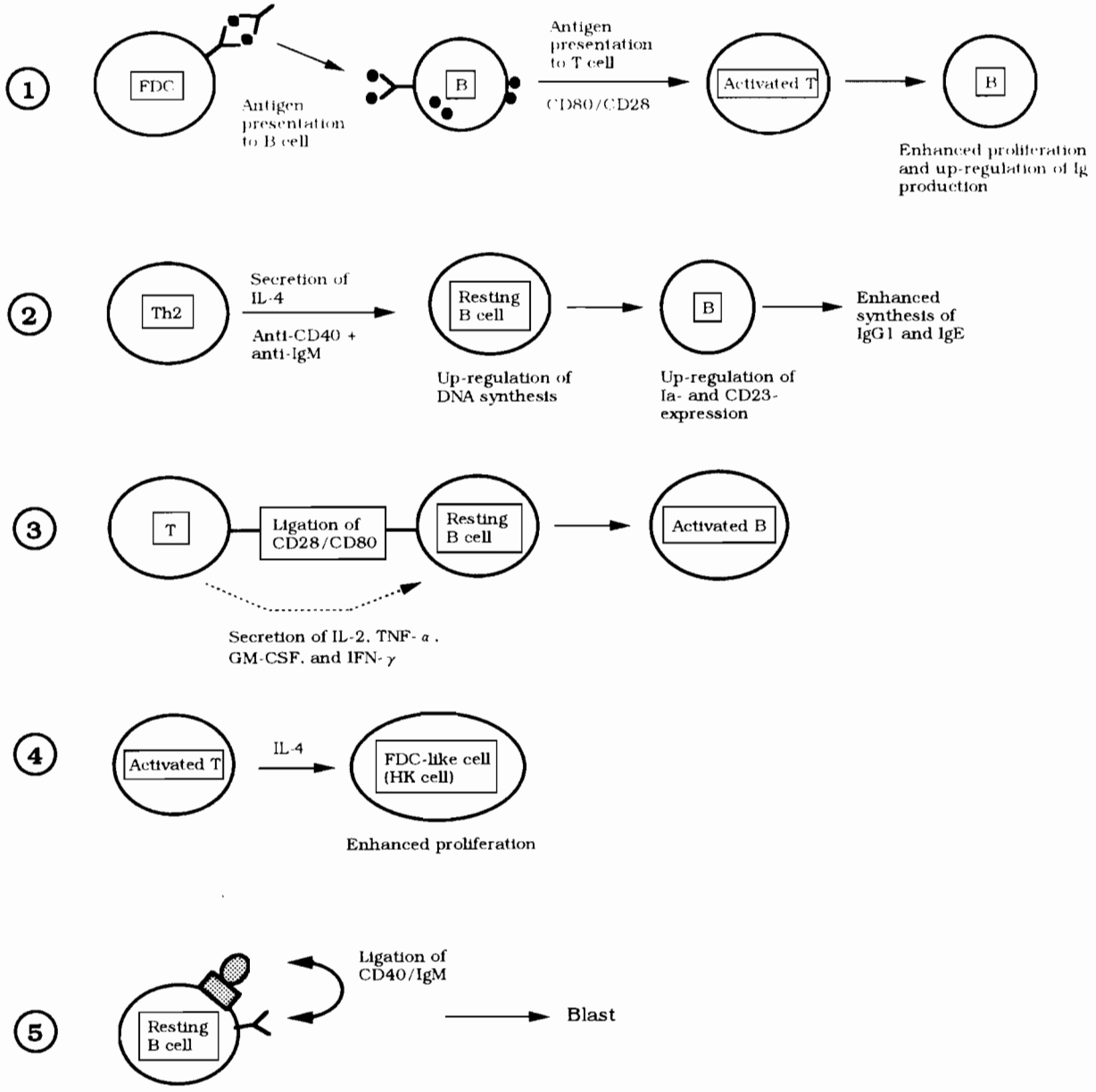

Fig. 11. Cellular interaction among follicular dendritic cells, B cells and T cells in the germinal center. Refer to the text for details.

Lewis X, CR3, CR4, PECAM-1, B7/BB1, CD40 (Thomas et al., 1993; Péguet-Navarro et al., 1995), and Hermes antigen, but not the integrins ß1 and ß3, nor the Ig superfamily (CD2 and CD56) (Landry et al., 1990; Bruynzeel et al., 1992; Prickett et al., 1992; Ross et al., 1994) (Table 7). Like blood monocytes, freshly isolated immature DCs from human peripheral blood are LFA-3$^+$, ICAM-1$^+$ and B7/BB1$^+$ (Thomas et al., 1993). After 36 hrs in culture the expression of ICAM-1, B7/BB1, and Ia-antigen is up-regulated. These results indicate that immature DCs in peripheral blood act as mature DCs after the abundant expression of Ia-antigen and other supplementary factors such as ICAM-1, LFA-1, and B7/BB1. ICAM-3 on human LCs, which plays an important role in antigenic stimulation of T cells, may be a major adhesion molecule for LFA-1 (Aceredo et al., 1993).

Mouse DCs are also positive for Mac-1, ICAM-1, LFA-1, heat-stable antigen and CD44 (Ardavin and Shortman, 1992; Enk and Katz, 1994). Heat-stable antigen expressed on immature CD4-, CD8-double negative or CD4-, CD8-double positive thymocytes, activated B cells and LCs, provide CD4$^+$ cells with the costimulatory signal for the TH1 cell-dependent skin immune response (Enk and Katz, 1994).

Fig. 12. Immunoelectron microscopy of one of the complement regulatory factors, decay accelerating factor, in secondary lymphoid follicle in a patient with Hashimoto's thyroiditis. Positive reaction is found on the surface of follicular dendritic cells and B cells. Bar: 1 μm.

The binding of fibronectin to its receptor (Klingemann et al., 1991) and the effect of CR3 and FcR on DCs (Inaba et al., 1989) may be important for the clustering of DCs and T cells and T-cell proliferation. However, the details of the interactions between IDCs and T cells and between IDCs and B cells in the TD-areas, are still unknown.

V. Dendritic cells in normal and diseased conditions

A. Follicular dendritic cells in diseases

1. Autoimmune diseases

LFs are found in large numbers in tissues affected by Hashimoto's disease and rheumatoid arthritis, both representative organ-specific autoimmune diseases. The light zone contains thyroglobulin- or rheumatoid factor-IC accompanied by activated complement components (Imai et al., 1986b, 1989; Kasajima et al., 1987) (Fig. 12; Table 12). At the same time FDCs and GC cells express complement regulatory factors on their cell surfaces and thereby escape cell lysis via complement activation (Yamakawa and Imai, 1992; Lampert et al., 1993). GCs in Kimura's disease contain IgE and mouse IDC retains IgE-IC via FcεRII (CD23) (Maeda et al., 1992).

In general, autoantibodies in human autoimmune diseases are IgGs, probably formed after the secondary response (Mackay, 1993). The cell selection of memory B cells responsive to the autoantibody may occur through retention of autoantigens in the GC and the spleen as well as in the affected organs and their regional lymph nodes. Memory B cells injected into antigen-free rats irradiated with a sublethal dose disappear 10-12 weeks later (Gray and Skarvall, 1988). Persistent localization of autoantigens in the GC is therefore necessary to sustain the clones of memory B cells. The significance of the affinity-dependent, antigen-driven B

Table 12.. Localization of immune complexes in the germinal centers in autoimmune diseases.

ANTIGEN	HASHIMOTO'S DISEASE	RHEUMATOID ARTHRITIS
Immunoglobulin		
IgG	+	+
IgM	++	++
IgA	+	+
IgE	-	-
Complement		
C1q	++	++
C3d	++	++
C9	+	+
Properdin	+	+
CD21	++	++
CD35	++	++
Specific antigen		
Thyroglubulin	+	-
Rheumatoid factor	-	+

-: negative, +: weakly positive, ++: strongly positive

cell apoptosis in GCs as a mechanism for maintaining self-tolerance has been pointed out (Han et al., 1995a,b; Shokat and Goodnow 1995; Wen et al., 1996).

2. Viral infection

One virus which has been verified as an infectious pathogen in human FDCs is the human immunodeficiency virus (HIV)-1 the causative agents of the acquired immunodeficiency syndrome (AIDS). The persistent generalized lymphadenopathy (PGL) of AIDS, comprises easily palpable nodes more than 1cm in diameter in more than two lymph nodes other than inguinal nodes, persisting for more than 3 months (Ioachim, 1989). It is characteristic that the absolute number of helper T cells decreases simultaneously with the ratio of helper:suppressor T cells (0.52-0.81; mean 0.64). Histologically, PGL is classified into three types: Type I (Type A) showing acute lymphadenitis in the early stages; Type III (Type C) showing chronic lymphadenitis in the later stages; and Type II (Type B) showing subacute lymphadenitis in the intermediate stages. Type I is characterized by prominent follicular hyperplasia with augmented cell turnover of the GC cells indicated by cell death, increasing phagocytotic activity of TBMs ingesting dying cells, and prominent cell division. At the same time as the FDC meshwork is destroyed, the layer of mantle zone lymphocytes invaginates into the GC. In Type II (subacute lymphadenitis) the progressive destruction of the LFs and GCs is replaced by neovascularization and plasma cell infiltration. In Type III there is severe atrophy or complete disappearance of the LFs including the GC. These histological appearances demonstrate a sequence of events from hyperplasia of the GC and FDC meshwork in the earlier stages to follicle lysis in the later stages, and are closely related to the prognosis of affected patients (Racq et al., 1989; Parmentier et al., 1990).

In AIDS the FDC is one of the major reservoirs and producers of HIV-1, supports the transfer of HIV-1 infection to $CD4^+$ GC-T cells, and causes degeneration of the IDCs themselves (Tenner-Racq et al., 1985; Le Tourneau et al., 1986; Stahmer et al., 1991; Spiegel et al., 1992). It is, thought however that although HIV-1 particles are located on the surface of FDCs, FDC lysis is not evoked by intracytoplasmic HIV-1 viral proliferation (Schmitz et al., 1994). When the FDC clusters containing large amounts of HIV-1 particles appear in the lymphatic vessels and move downstream, HIV-1 particles are translocated to the regional lymph nodes (Mori, 1994). Other cell types in lymphoid tissues, including Mø, IDCs, vascular endothelial cells and $CD45RO^+$ T cells are seldom affected by HIV-1. Ultrastructural examination of HIV-1 infected lymphoid hyperplasia reveals a high proportion of less differentiated FDCs similar in appearance to the cells of follicular lymphoma (Rademakers,1992). In experimental murine AIDS infection with the LP-BM5 retrovirus antigen trapping by FDCs decreases, but costimulation of B cells by FDCs together with anti-κ antibody and IL-4 remains constant. These findings account for the pathogenesis of lymphadenopathy and splenomegaly in Type I PGL (Prevot et al., 1989; Masuda et al., 1994, 1995).

Kitamoto et al. (1991) demonstrated that the prion protein which causes Creutzfelt-Jacob's disease (PrPCJD) in mice accumulates on the FDCs in the GC.

3. Bacterial infection

Helicobacter pylori infection in the stomach commonly induces lymphoid hyperplasia, suggesting that this may be a pathogenetic factor in the development of malignant lymphoma (Genta et al., 1993; Isaacson and Spencer, 1993; Sarsfield et al., 1996). 91% of patients with malignant gastric lymphomas harbour this bacterium compared with 64% of control subjects (Parsonnet et al., 1991; Genta and Hammer, 1994). The histological appearance of lymphoid cell aggregation in gastric biopsies is similar to that of chronic active gastritis and is one of the most useful diagnostic markers for *Helicobacter pylori* infection (Genta and Hammer, 1994).

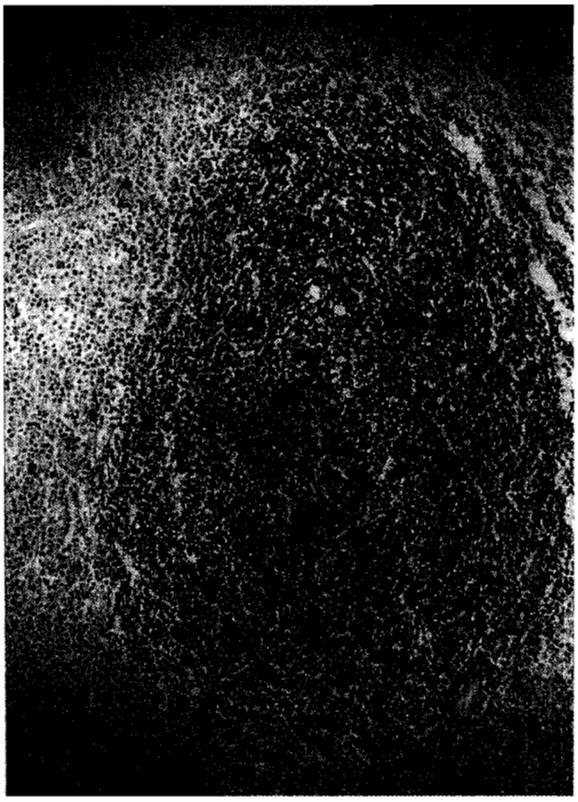

Fig. 13. Immunostain of Ki-M4p, a marker of follicular dendritic cells, in hyaline-vascular type of Castleman's disease. Note the reticular pattern in hyperplastic lymphoid follicle. x 100

4. Hodgkin's disease

The close cellular relationship between FDCs and Reed-Sternberg cells in Hodgkin's disease has recently been noted (Alavaikko et al., 1991; Delsol et al., 1993). Furthermore, in some types, for example the nodular lymphocytic-predominant, nodular sclerosis, and mixed cellularity forms of Hodgkin's disease, the number and the distribution pattern of FDCs correlate well with the clinical prognosis, that is, cases with more numerous FDCs have a better prognosis than those with sparse FDCs (Alavaikko et al., 1994).

5. Castleman's disease

The morphology of the FDC network in the plasma cell variant of Castleman's disease is very similar to that in reactive GCs, while the hyaline vascular variant shows a destroyed FDC network, confirming the different pathogenesis of the two variants (Nguyen et al., 1994) (Fig. 13). In Castleman's disease with systemic manifestations FDCs express IL-6 associated with the production of plasma cells (Leger-Ravet et al., 1991). It has also been reported that in the plasma cell variant IL-6 expression is seen on nearly all GC B cells and immunoblastic cells in the mantle zone and interfollicular area, but not on FDCs (Hsu et al., 1993), but this is a controversial finding. IL-6 and its mRNA have not been found in tonsillar GCs (Bosseloir et al., 1989; Andersson et al., 1994).

6. Tumor immunity and follicular dendritic cell tumors

The enlarged draining lymph nodes of gastrointestinal carcinomas show reactive follicular hyperplasia and their GCs trap some cancer-related antigens (Mariani-Costantini et al., 1991). Adhesion molecules in malignant lymphomas associate with their pathogenesis. FDCs are $CR3^+$, VLA-5^+, VLA-6^+ and ICAM-1^+, while centroblastic/centrocytic lymphoma cells are LFA-1^+ and ICAM-1^+ (Imai et al., 1990; Petrasch et al., 1992; Maeda et al., 1993; Ree et al., 1994). In the leukemic stage all adhesion molecules on lymphoma cells disappear. A very small number of FDC tumors have been reported (Pallesen and Myhre-Jensen, 1987; Weiss et al., 1990; Dusenbery and Watson, 1996; Perez-Ordonez et al., 1996). Hepatic FDC tumors may exhibit an Epstein-Barr virus-related clonal proliferation of FDCs (Shek et al., 1996) and inflammatory pseudotumor of the liver may also exhibit the FDC proliferation associated with this clonal type of virus (Selves et al., 1996).

Table 13. Clinical significance of T cell responses.

- Graft-versus-host reaction (various organs, blood, bone marrow)
- Speciific anti-tumor immunity
- Anti-microorganism immunity (induction of cytotoxic T cell, antibody production, production of cytokines)
- Contact hypersensitivity, delayed type hypersensitivity, atopic dermatitis
- Autoimmune disease (multiple sclerosis, juvenile diabetes mellitus, rheumatoid arthritis)
- Acquired immunodeficiency syndrome (HIV-1 infection)

B. T Cell-associated dendritic cells in normal and diseased conditions

1. General concepts

The DC is only one initiator of the immune response. As described above, in general, immune responses associated with DCs begin in lymphoid tissues but not at the antigen-entering sites in the early stage of inflammation. Lymphoid cell infiltration in non-lymphatic tissues provides an appropriate environment to respond quickly to antigenic stimulation *in situ*. Recirculating T cells, which are clonally activated and simultaneously expand their clonalities, migrate from lymphatic tissue to the circulating blood through lymphatic vessels, thereby increasing the probability of encountering APCs. Compared to resting lymphocytes, primed lymphocytes bind tightly via adhesion molecules to endothelial cells of postcapillary venules and therefore easily enter inflammatory sites, and interact with DCs to finally give rise to various immune responses. The function and the clinical significance of DCs is summarized in Tables 10 and 13.

2. Supporting function of Langerhans cells

LCs as supporting cells extend their long cytoplasmic processes beyond the basal cell layer to form a serial network in this site. LCs also play a role in the keratinization of epidermal cells. However, a major function of LCs is to act as APCs to T cells.

3. Dendritic cells in ontogeny

Van Rees et al. (1991) and Nelson et al. (1994) have analyzed the ontogeny of intraepithelial Ia^+ DCs in the neonatal rat airway and alveoli. At 16 days fetal gestation age the Ia^- or Ia^{low} precursors begin to infiltrate the airway tissues. In the 3 weeks following birth, the weaning stage, they mature into Ia^{high} DCs *in situ*. In contrast to DCs, Mø appear at 17 days gestation and their distribution is quite different from that of DCs (van Rees et al., 1991). The expression level of Ia-antigen on DCs in the rat alveolar and airway epithelia increases substantially in the neonatal stage, although the level varies according to the region of the airway. Ia^+ epidermal LCs also mature from Ia^- precursors in the growing postnatal mouse (Romani et al., 1986), but this maturation is not synchronous with that of DCs in the respiratory tract epithelium.

4. Immunological tolerance in the thymus

Through the cooperative effect of thymic epithelial cells DCs select T cells according to the degree of their receptor affinity to autologous MHC antigen. T cells with high affinity disappear when they encounter thymic DCs (Hadzija et al., 1991; Zöller, 1991; Carlow et al., 1992; Aiba et al., 1994). The deletion of the antigen-specific immature $CD4^+$, $CD8^+$ thymocytes by DCs requires the interaction of LFA-1/ICAM-1 (Carlow et al., 1992; Bañus et al., 1993). In addition to the negative selection of immature thymocytes, DCs associate with the non-antigen-specific proliferation and maintenance of thymocytes (Salomon et al., 1994). However, it has been reported that specific APCs are not necessary for the clonal selection of $CD4^+$, $CD8^+$ thymocytes (Pircher et al., 1993). DCs also relate to intracytoplasmic B220 expression in pre-pre-B cells, suggesting that they play a role in the early stages of B-cell differentiation (Saleh et al., 1989).

5. Autoimmune diseases

In the generation of B cell-specific autoimmune diabetes mellitus in an animal model, DCs firstly appear in pancreatic islets of Langerhans cells, followed by lymphocytes (Voorbij et al., 1989). DCs obtained from peripancreatic lymph nodes form cellular clusters together with T cells *in vitro* (Clare-Salzler and Mullen, 1992). DCs are found in large numbers in the synovial fluid of patients with rheumatoid arthritis (Bergroth et al., 1989; Knight et al., 1989; Versehure et al., 1989; Stagg et al., 1991a,b; Thomas and Quinin, 1996) and in the inflamed mucosa of Crohn's disease and ulcerative colitis (Seldinrijk et al., 1989). Some of these DCs display stronger T-cell activation than those in normal tissues. It has also been suggested that Graves' disease may be related to infection by the retrovirus p15E and subsequent dysfunction of DCs (Tas et al., 1991).

DCs present soluble (auto)antigens such as complement component C5 in circulating blood to T cells (Farrant et al., 1986; Crowley et al., 1990; Nair et al., 1992; Stockinger, 1992). Superantigens derived from *Staphylococcus aureus* provoke various types of gastroenteritis (Schlievert et al., 1981; Spero et al., 1988), and those derived from mycoplasmas have been involved in the pathogenesis of polyarthritis (Cole et al., 1979; Atkins et al., 1986; Cannon et al., 1988), suggesting a relationship to autoimmune diseases. Superantigens activate T cells bearing the T-cell receptor Vß gene in a specific MHC-restricted manner (Choi et al., 1989; Kappler et al., 1989; Herman et al., 1990). In such cases, in the presence of DCs even minute quantities of superantigens may become antigenic (Bhardwaj et al., 1992). This is partly because DCs provoke a 10-15 times more powerful T cell response to superantigens than monocytes or B cells.

In foliate pemphigus, $CD1a^+$ LCs are dramatically decreased and bone marrow-derived LC-precursors accumulate in the skin; these precursor have a dendritic morphology, lack Birbeck granules, and are $CD1a^+$, $CD11c^+$, $CD18^+$, $CD45^+$, $CD68^+$ and Ia^+ (Petzelbauer et al., 1993). Mori et al. (1994) have speculated that in cutaneous lupus erythematosus epidermal LCs may be dysfunctional. The appearance of abnormal activated T cells in systemic lupus erythematosus relates to over-expression of B7/BB1 on DCs (Sfikakis et al., 1994). Abnormal expression of CD28 on T cells and B7/BB1 on DCs, and their interaction may determine the progression of this disease.

6. Contact hypersensitivity and other skin diseases

The first barrier in the skin is the keratinized layer of the epidermis, but LCs are the first cells to encounter foreign antigens once they have passed this first barrier (Bos and Kapsenberg, 1986; Knight, 1989). For example, hapten applied to the skin is taken up by LCs in the early stages of contact dermatitis (Macatonia et al., 1986; Sullivan et al., 1988; Grabbe et al., 1995). Haptenized LCs migrate to draining lymph nodes and present the hapten as antigen to T cells. Immunized T cells then migrate to inflamed skin where they act as potent effector cells. Allergic contact dermatitis (delayed-type hypersensitivity) is characterized by hyperplasia of LCs, increased numbers of Ia^+ keratinocytes, T-cell accumulation in the epidermis accompanied by an increased CD4:CD8 ratio, and proliferation of IL-2 producing-T cells (Berti et al., 1985; Tapia et al., 1989; Gerberick et al., 1994). These findings suggest that LCs stimulate proliferation of antigen-specific helper T cells, induce cytotoxic T cells, and finally mediate allergic contact dermatitis.

In lichenoid regions of atopic dermatitis LCs are increased. FcεRII is expressed on IgE^+ LCs through the action of IL-4 and IFN-γ (Astier et al., 1994; Jürgens et al., 1995). FcεRI has a higher affinity for IgE than FcεRII, which is also expressed on LCs (Preesman et al., 1991; Bieber et al., 1992; Maurer et al., 1996). Anti-FcεRII can inhibit induction of atopic dermatitis, but anti FcεRI cannot. The appearance of IgE^+ LCs, however, is not specific to this type of dermatitis as they are also found in other chronic skin conditions such as psoriasis vulgaris, lichen planus, discoid lupus erythematosus, and mycosis fungoides. Some reports suggest that other APCs in the dermis and deeper tissues, rather than epidermal LCs, play a major role in the pathogenesis of atopic dermatitis (Streilein, 1989; Taylor et al., 1991).

Psoriasis vulgaris is accompanied by a marked increase in $CD1a^-$, Ia^+ monocytic cells and by a small increase in $CD1a^-$, Ia^+ LCs. DCs, expressing blood coagulation factor XIIIa have been found in dermal perivascular space in this condition (Morganroth et al., 1991).

7. Graft-versus-host reaction

Epidermal infiltration by $CD8^+$ T cells and

diminished or absent CD1$^+$ LCs are diagnostic features of skin graft-versus-host disease (GVHD). DCs in the transplanted organ provoke GVHD as an immune response to MHC antigen (Austyn and Larsen, 1990; Kover and Moore, 1991; Demetris et al., 1991). The DCs enter the circulation and are carried to the splenic TD-area, where they mature (Larsen et al., 1990a,b). The mature DCs infiltrate the implanted organ via the blood stream (Larsen et al., 1990c). UV irradiation eliminates DCs from red blood cell transfusions. GVHD in bone marrow transplantation is initiated by donor DCs. CD1b$^+$ DCs are not found in the normal kidney but are present in large numbers in the interstitial infiltration of glomerulonephritis. Simultaneously, tubular epithelial cells in situ express Ia- and Ii-antigens (Cuzic et al., 1992). The appearance of CD1b$^+$ DCs may correlate with the progression of interstitial inflammation. Atherosclerotic vessels contain vascular DCs (Bobryshev et al., 1996).

8. Infections

Epidermal of herpes simplex virus type1 infection induces a marked increase in LCs. Interestingly, steroid administration decreases LCs while augmenting the virulence of the viral infection. Infection by human papilloma virus causes not only hyperplasia or papillomatosis of the epidermis or mucosal epithelium but also in rare instances squamous cell carcinoma. LCs decrease in papillomatosis of the uterine cervical epithelium partly because this virus infects LCs directly via FcγR and then induces degeneration and necrosis of LCs (Morris et al., 1983; Morelli et al., 1993). There is a good correlation between the degree of epithelial dysplasia and the number of LCs in the uterine cervix (Morris et al., 1983; Caorsi and Figueroa, 1986).

Recent papers have demonstrated dysfunction of DCs in AIDS (Patterson et al., 1991; Ludewig et al., 1995; Girolomoni et al., 1996). HIV-1 targets LCs, because they express CD4 antigen, FcγRI, FcγRII, and galactose receptor on their cell surface (Hussain et al., 1992; Manca, 1992; Henry et al., 1994). LCs decrease cellular degeneration in AIDS; DC function is diminished in all HIV-1-positive patients (Macatonia et al, 1990, 1991). The HIV-1 reservoir in LCs propagate HIV-1 into T cells (Macatonia et al., 1992). HIV-1-genome in DCs in patients affected by HIV-1-associated heart disease can be frequently demonstrated in endocardial biopsies (Rodrigues et al., 1991). DCs in hepatitis virus-infected mice may also be dysfunctional (Akbar et al., 1993).

In general, the group A streptococcus has low motility and does not invade the pharyngeal submucosa. However, if LCs bind the bacteria, they can be transported into the submucosa (Reed et al., 1994). Both epidermal LCs and dermal DCs increase markedly in mycobacterial and parasitic infections, and CD1a$^+$ LCs massively accumulate in the periphery of granulomas in the papillary dermis.

9. Tumor immunity

DCs participate as APCs in the induction of anti-tumor immunity against various tumors of both squamous cell and non-squamous cell-types (Grabbe et al., 1991; Chaux et al., 1993; Cohen et al., 1994; Nakano et al., 1996). A close relationship has been observed between the number of DCs and the prognosis of patients in some forms of cancers (Schröder et al., 1988; Matsuda et al., 1990; Tsujitani et al., 1990; Nakano et al., 1992). DCs appearing in these cancer tissues are of two different types, LC- and IDC-types (Imai and Yamakawa, 1993; Yamakawa et al., 1993b, 1995). The appearance of DCs correlates with GM-CSF released from carcinoma cells (Tazi et al., 1993; Karube et al., 1994; Colasante et al., 1995), the expression level of Ia-antigen on carcinoma cells (Furihata et al., 1992; Inoue et al., 1993), and the degree of lymphocytic infiltration in the tumor stroma (Papadimitriou et al., 1992). Mouse epidermal LCs and splenic DCs present the tumor-associated antigen to the tumor-primed T cells (Cohen et al., 1994). S100 protein$^+$ IDCs in human lymph nodes express the P-glycoprotein important for inducing drug resistance of tumor cells (Nishii et al., 1994). Many benign and malignant tumors of LCs and IDCs have also been reported (Nakamura et al., 1988, 1994; Yamakawa et al., 1992; Tani et al., 1992; Ben-Ezra and Koo, 1993; Schaumburg-Lever et al., 1994; de Graaf et al., 1994). Peptide-pulsed DCs induce antigen-specific CTL-mediated protective tumor immunity (Celluzzi et al., 1996; Condon et al., 1996; Paglia et al., 1996; Zitvogel et al., 1996) and DCs pulsed with RNA are potent APCs in vivo and in vitro (Boczkowski et al., 1996). Macrophage chemoattractant protein-1 derived from keratinocytes can recruit dendritic/Langerhans cells to skin (Nakamura et al., 1995).

10. Intramucosal dendritic cells

Generally, DCs, one of the major APCs in the mucosa of the gastrointestinal tract, up-regulate immune responses, while Mø down-regulate them (Pavli et al., 1993; Kelsall and Strober, 1996; Maric et al., 1996; Ruedl et al., 1996). It has recently been reported that human LCs secrete a soluble counterpart of Fc(RII which can be detected in peripheral blood (Astier et al., 1994). This soluble receptor inhibits the uptake and phagocytosis of IgG-IC by FcγR-expressing cells such as Mø, which may partly explain the mechamism by which Mø inhibit the immune response.

One of the useful potent ways of preventing T cell-associated immunological disorders is to induce selective immunological tolerance by oral or intragastric administration of antigen (van Wilsem et al., 1994). The LC network is present not only in the epidermis but also in the oral mucosal epithelium. DCs isolated from oral mucosa act as APCs but do not induce immunological tolerance (Silberg et al., 1975).

11. Ultraviolet irradiation

Ultraviolet-B (UV-B) irradiation of the skin results in disintegration of the LC-dendritic morphology by converting them to a spheroidal shape. Furthermore, irradiation dramatically decreases levels of Ia-antigen expression and activity of LC ATPase, and also inhibits the subsequent antigen-presenting capability of LCs and the formation of clusters consisting of antigen-specific DCs and T cells in lymph nodes (Müller et al., 1994). These findings suggest that although UV-B skin irradiation reduces immunosuppression, the decreased numbers of epidermal LCs are not causal in this suppression (van Praag, 1994). In aged mice a decrease in LC precursors reduces the density of epidermal LCs (Sprecher et al., 1990). UV-B irradiation of the corneal epithelium decreases the number of $ATPase^+$ LCs (Hill et al., 1994).

12. Immunosuppressants

Steroids decrease the number of LCs in a dose- and time-dependent manner. However, not all LCs are sensitive. Cyclosporin does not change the level of Ia-antigen on LCs but decreases the antigen-presenting ability of LCs.

VI. Conclusion

The lymphocyte-DC interaction is essential in the response to antigenic stimulation and in inducing the potent effector cells. B cell-DC, T cell-DC and DC-B cell-T cell interactions are regulated in pre-determined sites by complex and varied mechanisms. Much recent evidence demonstrates that the lymphocyte-dendritic cell system (LDS) modulates lymphocyte biology in its broadest aspects, including generation, differentiation, proliferation, and activation. Further analyses of the unresolved problems in the LDS may uncover the mechanisms of many immunological phenomena and eventually lead to specific therapies for immunological disorders.

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