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Dendritic cells: phenotypic and functional heterogeneity

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Abstract

Dendritic cells are specialized to capture antigens, process them and present them to T cells to initiate, regulate and fine tune immune responses towards pathogens and tumours. The story of these cells began more than forty years ago and the interest for them is ever growing because of their central role in immunobiology. Dendritic cells are heterogeneous for origin, anatomical localization, phenotype and function: several subsets of myeloid dendritic cells and plasmacytoid dendritic cells have been recognized until now. Dendritic cells differentiate from haematopoietic stem cells-derived precursors, migrate from sites of antigen uptake to lymphoid organs and during this process mature to antigen presenting cells capable of interacting with lymphocytes and stimulate both immune response and peripheral tolerance to self. Since dendritic cells play crucial roles in infection, cancer, allergy, autoimmunity and graft rejection, thorough knowledge of their subsets and behaviour will open the path to tools allowing better control of many clinical conditions.

Introduction

The immune system grants for both innate and adaptive responses to pathogens, which depend on different cell types and functions. The innate immune system involves granulocytes, mast cells, macrophages and natural killer cells. These cells use non-clonal recognition receptors, including lectins, Toll-like receptors (TLRs), NOD-like receptors (NLRs) and helicases, to provide quick but generic responses to pathogens. The adaptive immune system response depends on B and T cells which use clonal receptors that specifically recognize antigens or their derived peptides presented by antigen presenting cells and grant for immunological memory (Paluka and Banchereau, 2012).

Dendritic cells (DCs), macrophages and B cells may act as antigen presenting cells; DCs, in particular, are specialized in the "capture" and processing of antigens which are then conjugated with molecules of the major histocompatibility complex (MHC) for their presentation to T cells in order to initiate the immune response. They are also known as dendritic leukocytes and are the most efficient cells for antigen presen-

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tation, being able to elicit T cell response even in very low numbers and to stimulate primary as well as secondary response, thus explaining their nickname of "professional antigen presenting cells" (Steinman, 2012).

Dendritic cells stimulate different immune responses towards pathogens and even tumours, and are also responsible for the peripheral tolerance to self. They play crucial roles also in allergy, autoimmunity and transplant rejection. Owing to their properties, DCs are often called "nature adjuvants" and have been proposed for immunotherapy upon antigen loading (von Bubnoff et al., 2001; Paluka and Banchereau, 2012). However, clinical trials have not yet gone beyond preliminary phases and the limited knowledge on the biology of these cells in themselves and in the context of tissues may well be a cause of failure.

Despite their origin from bone marrow CD34+ hematopoietic stem cells, DCs are heterogeneous and many subsets have been identified both in mice and humans (Bancherau and Steinman, 1998; Paluka and Banchereau, 2012; Steinman, 2012). All DC subsets are characterized by the expression of specific membrane molecules, involved in antigen capture and presentation. The most important DC subsets are the myeloid DCs (mDCs) and the plasmacytoid DCs (pDCs) (Dzionek et al., 2000; Shigematsu et al., 2004). Among mDCs, Langerhans cells (LCs) are peculiar for localization, molecular phenotype and morphology. They are localized within epidermis and stratified squamous mucosal epithelia, express E-cadherin, CD1a and langerin/CD20, and contain Birbeck granules, a unique organelle detected at electron microscopy (Birbeck et al., 1961; Valladeau et al., 2000; Romani et al., 2003). Langerin/CD207 is a C-type lectin localized not only at the cell surface, but also in the endosomal recycling compartment, in Birbeck granules and in other tubular and vesicular structures (Valladeau et al., 2000; Romani et al., 2003). Due to their position within epidermis and mucosae, LCs are critical for the induction of immune responses towards pathogens and tumours and are credited to play a pathogenic role in allergic skin diseases (Paluka and Banchereau, 2012, Von Bubnoff et al., 2001).

Dendritic cells history

Dendritic cells are found within lymphoid organs, epithelia, connective tissue and lymph (Pimpinelli et al., 1994). Recognition of these cells as a population specific for differentiation and function has come through three distinct lines of research (Hoefsmit et al., 1982; Fossum, 1989; Metlay et al., 1989).

1800 to 1970

Paul Langerhans described for the first time in 1868 dendritic epidermal cells which were thereafter designated with his name: they have been indeed the first dendritic cell discovered.

In the 1950s LCs were regarded as melanocytes that had lost the capacity to make melanin pigment (Masson, 1948; Breathnach, 1965).

Birbeck et al. (1961) demonstrated the presence of LCs in vitiligo, thus showing that they were not melanocytes, and by electron microscopy identified a characteristic organelle which thence on has been designated Birbeck granule.

The 1970s

In the 1970s a first line of research was represented by microscopic studies that aimed at defining the cell types of lymphoid organs for an accurate classification of proliferative diseases involving these organs. In particular, cells with dendritic shape were identified among the stromal elements of the T-dependent areas of secondary lymphoid organs (Veldman, 1970; Kaiserling and Lennert, 1974). These cells have cytoplasmic extensions that make contact with other similar cells and lymphocytes and therefore have been called interdigitating cells or interdigitating reticulum cells. Veerman (1974) proposed that the interdigitating cells in the thymus-dependent area of the rat spleen form a microenvironment allowing T cells to differentiate and proliferate. These cells are derived from bone marrow precursors and migrate into lymphoid organs via peripheral tissues and lymphatics, eventually becoming interdigitating reticulum cells (Kelly et al., 1978; Hoefsmit et al., 1979). A role has been proposed for these cells also in directing the structural organization of lymphoid tissue in T-cell lymphomas (Ribuffo et al., 1983), including those of the skin (Romagnoli et al., 1986; Pimpinelli et al., 1994).

A second line of research was the histopathological analysis of dermatological immune-mediated diseases, where LCs were found in contact with lymphocytes in the inflamed skin (Silberberg-Sinakin, 1973, Silberberg et al., 1976). This led to conceive LCs as implicated in allergic reactions and in other immunologic reactions, so that they were eventually regarded as cells of immune system (Rowden et al., 1977; Stingl et al., 1977) and were recognized to derive from progenitors present in the bone marrow (Katz et al., 1979; Perreault et al., 1984; Goordyal and Isaacson, 1985). Studies in the mouse and humans demonstrated the antigen-presenting function of LCs (Stingl et al., 1978; Braathen and Thorsby 1980; Green et al., 1980; Bjercke et al., 1984).

A third line of research was initiated by Steinman's group (Steinman and Cohn, 1973, 1974) who isolated cells with a peculiar dendritic shape from the mouse spleen, hence their designation as dendritic cells. It was then demonstrated that DCs present exogenous antigen to T cells in an MHC-restricted fashion and can induce specific cytolytic T cell responses by cross-priming lymphocytes (Bevan, 1976). These cells were shown to have a low phagocytic activity and to be potent stimulatory of T-dependent immune responses, in particular the proliferation and maturation to effectors elements of helper T cells. Although they are not the only cells in the body with this property, they seem to be mandatory for the stimulation of primary immune responses (reviewed by Metlay et al., 1989). High expression of major histocompatibility complex class II molecules (MHC-II) is instrumental to that function (Steinman e Witmer, 1978; Steinman et al., 1979) even if it is not enough to explain their differential role in respect to other MHC-II expressing cells.

The 1980s

This decade brought to a deeper knowledge of the origin, differentiation, life cycle and function of DCs. Human DCs in peripheral blood were characterized in detail by Van Voorhis et al. (1982). Witmer et al. (1984) reported that the T cell areas in lymphoid organs are the main location where DCs are found and suggested that they activate T cells which, once activated, leave the lymph node and migrate to the site

of inflammation. Indeed, DCs were discovered to be responsible for the activation of naïve T cells, that subsequently interact with B cells and stimulate them to generate plasma cells and produce antibodies (Inaba and Steinman, 1985).

Langerhans cells were recognized as full fledged members of the DC family and the concept of DC maturation (see below) was developed from studies on murine LCs (Schuler et al., 1985). A comprehensive review on immature and mature DCs appeared at the end of the decade (Romani et al., 1989).

Witmer-Pack et al. (1987) documented the requirement of GM-CSF for DC maturation. Moreover, it was shown that T cell fail to proliferate upon antigen presentation in the absence of co-stimulatory signals and instead become unresponsive to further activation (Jenkins and Schwartz, 1987).

Towards the end of the decade, cells with abundant rough endoplasmic reticulum (like plasma cells) but with irregular cell surface were shown to behave as antigen presenting cells and to be able to secrete huge amounts of type I interferons (IFN; Fitzergerald-Bocarsly, 1988; Facchetti et al., 1989). They were first designated plasmacytoid T cells or plasmacytoid monocytes and later on have been recognized as a peculiar type of dendritic cells, named pDCs (Cella et al., 2000; Colonna et al., 2002; see McKenna et al., 2005, for review), while the other DCs, including LCs, have been designated mDCs (Banchereau and Steinman, 1998).

The 1990s

Towards the end of the century it was observed that DCs are also able to effectively stimulate the activation of CD8$^+$ cytotoxic T lymphocytes (Young and Steinman, 1990; Shen et al., 1997), the differentiation of plasma cells from B lymphocytes (Fayette et al., 1998) and the survival of plasmablasts (De Vinuesa et al., 1999). The B7-1/CD80 and B7-2/CD86 ligands and their receptors on T cells, respectively CD28 and CTLA-4, were identified as crucial regulators of T cell responses; later, additional co-stimulatory molecules were identified on DCs (Springer, 1990; Caux et al., 1994a; Caux et al., 1994b). A method was devised to obtain DCs from monocytes (Sallusto and Lanzavecchia, 1994), allowing to study the basic functions of DCs in humans. Also, studies in apparently different model organisms led to the identification of TLR, first in the fruit fly and then in the mouse (Lemaitre et al., 1996; Poltorak et al., 1998), and DCs were shown to express these receptors, possibly implied in antigen recognition and capture (Medzhitov et al., 1997). It was eventually shown that DCs are involved in tolerance and immune regulation (Banchereau and Steinman, 1998), although the details on when these functions occur, rather than immune activation, and how they are regulated remain still unclear.

Plasmacytoid DCs were recognized as associated with protection from opportunistic infections (Siegal et al., 1999).

The 2000s

The calcium dependent, C-type lectin receptor (CLR) DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin) was found to be expressed by mDCs and to mediate transient adhesion to T cells, necessary for their activation (Geijtenbeek et al., 2000a, 2000b). C-type lectin receptors (CLRs) were iden-

tified as an important family of pattern recognition receptors. They interact with pathogens through the recognition of mannose, fucose and glucan carbohydrate structures and are involved in the induction of specific gene expression profiles in response to specific pathogens, either by modulating TLR signalling or by directly inducing gene expression (Geijtenbeek, 2009).

Plasmacytoid DCs were shown to regulate events during the course of viral infections, atopy, autoimmune disease, and metastatic cancer (Liu, 2005; McKenna et al., 2005).

In most recent years mDCs have started to be used in immunotherapy, although yet with poor results (Figdor et al., 2004; Tacken et al., 2007; Palucka and Banchereau, 2012; Klechevsky and Banchereau, 2013; Tel et al., 2013).

Subsets of dendritic cells

Dendritic cells derive from hematopoietic stem cells (see reviews by Steiman, 1991, and Cella et al., 1997). DC progenitors in the bone marrow give rise to circulating precursors that home to tissues, where they reside as immature cells (Banchereau et al., 2000). DCs are a heterogeneous cell population whose members may acquire diverse maturation states and functions (Schmidt et al., 2012). In both humans and mice two distinct types of dendritic cells have been identified, mDCs and pDCs. The origin of the former is from common myeloid progenitor cells, while that of the latter has yet to be conclusively defined (Bancherau and Steinman, 1998; Dzionek et al., 2000; Shigematsu et al., 2004).

During differentiation DCs may go through an immature and a mature phase. The transition of mDCs to maturity is marked by modifications of the immunophenotype and the acquisition of strong immunostimulatory power (Villadangos and Heath 2005; Johnson and Ohashi, 2013). LCs are part of the immature DCs (Shortman and Caux, 1997; Hubert et al., 2005). pDCs appear in blood as already mature (McKenna et al., 2005).

Myeloid dendritic cells

Myeloid CD34+ progenitors differentiate into monocytes (CD11c+ CD14+ DC precursors) that yield immature DCs in response to granulocyte/macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-4 (Sallusto and Lanzavecchia, 1994) and macrophages in response to macrophage colony stimulating factor (M-CSF). Myeloid progenitors also differentiate into CD11c+ CD14- precursors, which yield LCs in response to GM-CSF, IL-4 and transforming growth factor (TGF)-β and macrophages in response to M-CSF (Bancherau et al., 2000). Myeloid progenitors can differentiate into LCs also through CD1a+ CD14- precursors, generated upon five days culture of CD34+ cells with GM-CSF and TNF-α, by continuing culture with the same factors for seven more days (Caux et al., 1996; Cella et al., 1997). Also tissue resident, CD14+ monocytes cultured with GM-CSF, IL-4 and TGF-β can give rise to LCs (Geissmann et al., 1998). Therefore it is actually conceived that DCs may arise from dedicated circulating precursors in steady state ("classical" or "conventional" DCs) and from monocytes in inflammation (Kushwah and Hu, 2011).

Table 1 - Types and characteristics of dendritic cells.

	Myeloid cells		Lymphoid cells
Subtypes	Langerhans cells	Connective tissue (including dermal) myeloid dendritic cells	Plasmacytoid dendritic cells
Differentiation pathway	Bone marrow haematopietic stem cell => common myeloid precursor => circulating monocyte (a subset?) => Langerhans cell and immature myeloid dendritic cells in non-lymphoid tissues => lymph => mature dendritic cells in lymphoid tissue.		Bone marrow haematopietic stem cell => common myeloid precursor (and common lymphoid precursor ?) => circulating mature plasmacytoid dendritic cell => peripheral lymphoid organs via high endothelial venules
Localization	Stratified squamous epithelia of skin and mucosae Upon maturation => lymphoid tissue and thymus	Non-lymphoid connective tissue, lymph	Lymphoid tissue, blood, lymph
Morphology	Oval body with long dendrites Oval, indented nucleus Birbeck granules	Oval body with long dendrites Oval, indented nucleus	Roundish, basophilic body with short projections Well developed rough endoplasmic reticulum and Golgi apparatus
Membrane markers	MHC-II BDCA-1 (CD1c) BDCA-3 (upon maturation) CD1a CD11c DEC205 DCIR/CLEC4A E-cadherin Langerin/CD207 TLR 1, 2, 3, 6, 10	MHC-II BDCA-1 (CD1c) BDCA-3 (upon maturation) CD11c CLEC-6 DCIR/CLEC4A DC-SIGN LOX-1 Factor XIII TLR 2,4, 5, 6, 8, 10	MHC-II BDCA-2 (CD303) BDCA-4 (CD304) CD1d DEC205 CD123 TLR 7, 8, 9
Principal interacting cell types	T cells NK cells	T cells NK cells B cells	T cells NK cells B cells Myeloid DCs

Myeloid DCs typically express CD11c, class II molecules of the MHC (MHC-II) and CD40, moreover upon maturation they express CD83 and the co-stimulato-

ry molecules CD54, CD80 and CD86 (Banchereau et al., 2000). They are specialized for antigen presentation through MHC-II and induction of a CD4^{+} T-cell response (Banchereau et al., 2000; Lewis and Reizis, 2012), but can also present antigens to CD8^{+} T-cells and interact with natural killer (NK) cells (Albert et al., 1998; Moretta et al., 2003).

Mature mDCs reside in T areas of the lymphoid tissue including the spleen white pulp (Banchereau et al., 2000).

Peripheral blood contains mDC precursors (Banchereau et Steinman, 1998), immature (Bancherau et al., 2000) and mature mDCs (Franks et al., 2013), pDCs (Liu, 2005) and so called inflammatory DC (see below; Schäkel et al., 2002). The subsets of DCs in peripheral blood may be distinguished by the differential expression of three cell-surface molecules: CD1c, also know as BDCA-1, CD303 or BDCA-2, CD141 or BDCA-3 and CD304 or BDCA-4. BDCA-1 (CD1c) is expressed by mDCs (Palucka and Banchereau, 2012). The expression of BDCA-2 and BDCA-4 is confined to pDCs, as described below (Bancherau et al., 2000; Dzionek et al., 2000; Palucka and Banchereau, 2012; Franks et al., 2013). BDCA-3 (CD141) is expressed by mDCs with high capacity to capture exogenous antigens for presentation on MHC class I molecules (MHC-I), such as epidermal Langherans cells, also described later.

In stratified squamous epithelia of the skin and mucosae mDCs are represented by LCs, which express CD1a and langerin/CD207, and in connective tissue there are interstitial DCs, which express CD1c and DC-SIGN and, sometimes, also CD1a. There are phenotypic and functional differences between these two cell types, as detailed below (Nestle et al., 1993; Palucka and Banchereau, 2012; Klechevsky and Banchereau, 2013). mDCs are also observed in lymph vessels as veiled cells and in lymphoid tissue as interdigitating cells, as detailed below.

Langerhans cells

Langerhans cells are located in stratified squamous epithelia of the epidermis and mucosae. The bone marrow precursors of the LCs pass into the circulation, migrate into tissues through the wall of blood vessels and enter into epithelia crossing the basal membrane (reviewed by Romagnoli et al., 1991). The influence of the epithelial microenvironment induces the maturation of precursor cells into LCs; it cannot be excluded that CD1 antigen may be acquired by these cells even before they enter the epithelium, while Birbeck granules appear after this entry (Bani et al., 1988). The turn over in the epidermis is not high: LCs in the epidermis are long-living. This may in part be attributed to the longevity of individual LC within the epidermal environment, in part to a low level of cell division in the periphery (Romani et al., 2003). Blood-borne precursors are recruited to the epidermis in large numbers only in inflammatory states of the skin: two cytokines are critical for immigration of LC precursors into the inflamed skin, TGF-β and MIP-3α/CCL20 (Borkowski et al., 1996; Merad et al., 2002; Schmuth et al., 2002). MIP-3α is produced by keratinocytes and Langerhans cell precursors express the appropriate receptor, CCR6 (Dieu et al., 1998). LCs have an oval body and some long branches. The nucleus is indented, with pale chromatin except for a thin peripheral rim. The cytoplasm contains cytoskeletal filaments (but no fibrils), mitochondria, few cisternae of rough endoplasmic reticulum, many smooth vesi-

cles and tubules, a large Golgi apparatus and BGs (Montagna and Parrakkal, 1974). The latter are disc shaped with a dilated rim along part of their margin, so in transverse section they appear rod or racket-shaped (Wolff, 1967; Rodriguez and Carosi, 1978). Another marker for these cells is langerin/CD207, a mannose-specific C-type lectin (Romani et al., 2003); an intracellular epitope of this molecule is Lag antigen (Valladeau et al., 2000). Langerin/CD207 recognizes mannose, *n*-acetylglucosamine, fucose and sulfated sugars, and binds pathogens such as HIV and Candida albicans (Idoyagaet al., 2008). BGs are involved in the endocitic pathway and due to their acid environment they are implicated in antigen processing (Valladeau et al., 2000). Some authors consider BGs also trafficking between the endosomal compartment and the plasma membrane along the recycling route (McDermott, 2002). LCs express other molecules such as DEC205/CD205, DCIR (dendritic cell immunoreceptor)/CLEC4A (C-type lectin domain family 1 member-4A), TLRs including TLR 1, 2, 3, 6 and 10, the receptor for the crystallizable fragment of immunoglobulins G, that for the third component of the complement system, interleukin-2 receptor, MHC-I and MHC-II, the lymphocyte common antigen CD45, ICAM-1/CD54, the integrin molecules of the CD11/CD18 family - *i.e.* CD11a, CD11b, CD11c and CD18 - (see for review: Romagnoli et al., 1991; Klechevsky and Banchereau, 2013) and E-cadherin, which mediates the binding of LCs to keratinocytes in epidermis (Jakob et al., 1999). LCs behave as immature DCs, able to capture antigens but expressing low levels of co-stimulatory molecules and with a limited capacity to secrete cytokines (Paluka and Banchereau, 2012). These cells acquire co-stimulatory molecules and secrete abundant cytokines upon maturation, a process that occurs during migration of these cells from the epidermis to lymph nodes and is accompanied by down-regulation of E-cadherin and langerin and by loss of BGs (Tang et al., 1993; Romani et al., 2001; Van den Bossche et al., 2012), not always complete (Schuler, 1991).

Langerhans cells are also capable of transferring endocytosed antigens into the cytoplasm, process them and eventually present them on the cell membrane within MHC-I molecules, to stimulate CD8^{+} T lymphocytes (Paluka and Banchereau, 2012). LCs stimulate CD8^{+} T responses also through IL-15, that is critical for promoting differentiation of naive CD8^{+} T cells into granzyme B^{+} cytotoxic lymphocytes (Klechevsky and Banchereau, 2013).

Dendritic cells of non-lymphoid connective tissue

The normal human dermis hosts highly dendritic cells (Headington, 1986). Some of them express factor XIIIa in normal and diseased skin (Cerio et al., 1989; Nestle et al., 1993; Muszbek et al., 2011; Gondak et al., 2014). The normal skin contains three separate populations of dermal DCs, which have distinctive phenotypic markers. Nestle et colleagues (1993) showed that factor XIIIa positive dermal DCs may be negative for CD1a and CD14, positive for CD1a only or positive for CD14 only and that the expression of CD1a is anyway weaker than that of LCs. CD14^{+} dermal DCs express C-type lectins, including DC-SIGN, LOX-1 (lectin-like oxidized LDL receptor-1), CLEC-6 (C-type lectin domain family 1 member-6), dectin-1, DCIR/CLEC4A; they also express TLRs, such as TLR2, 4, 5, 6, 8, 10 (Klechevsky et al., 2009). The DC-SIGN expression is not restricted to DCs in normal dermis but is expressed also by

macrophages together with other monocyte/macrophage markers, as CD14, CD68, CD163, and CD206 (Ochoa et al., 2008; Töröcsik et al., 2014). The cytotoxic lymphocyte response induced by CD14+ dermal DCs is less potent than that induced by LCs. In addition, CD4+ T cells primed by CD14+ dermal DCs are unique in their ability to promote antibody response, either directly or by priming T follicular helper (T$_{FH}$)-like CD4+ T cells (Klechevsky and Banchereau, 2013). CD14+ dermal DCs secrete IL-10, that limits cytotoxic lymphocyte responses and induces regulatory T cells (Treg or Tr), and express Ig-like transcript (ILT) 2 and ILT 4, known inhibitors of CD8 binding to MHC-I because of sterical hindrance. Conversely, CD1a+ dermal DCs, like LCs, secrete IL-15 in immunological synapses, inducing a cytotoxic response (Klechevsky and Banchereau, 2013). Moreover, even if both LCs and dermal DCs are effective in stimulating immune responses, LCs seem to be particularly effective in stimulating responses to low concentrations of antigens (which may be found in the early stages of viral infection and carcinogenesis; Romagnoli, 2001), while dermal DCs are primarily responsible for the response to high dose haptens (Bacci et al., 1997).

Dendritic cells in the thymus

Dendritic cells are present also in the thymus, where they are key players during thymocyte development because they present self antigens and induce negative selection of potential auto-reactive T-cell clones (Vandenabeel et al., 2001). Those cells are localized almost exclusively in the medulla (Brocker, 1999; Steinman et al., 2003), which seems to be a major site of deletion of auto-reactive selected thymocytes (Hengartner et al., 1988; Sprent and Webb, 1995). Thymic DCs are presumably comparable to those of other tissues for antigen capture and processing. This would lead to the production of MHC-peptide complexes, needed to delete self-reactive T cells; indeed, the cells that express a T-cell receptor (TCR) with specificity for self antigens are removed (Spits, 2001; Steinman et al., 2003). The human thymus contains two populations of mature DCs, expressing different lineage markers and displaying different capacities for IL-12 secretion; the latter is necessary for the negative selection of thymocytes (Lúdvíksson et al., 1999). The major thymic DC population is distinguished by being CD11b- and expresses markers of fully mature DCs. The minor thymic DC population is CD11b+. Both populations are CD4+ (Vandenabeel et al., 2001). After CD40 ligation only CD11b- thymic DCs release substantial amounts of bioactive IL-12, while CD11b+ DCs release scarce amounts of this cytokine (Lúdvíksson et al., 1999; Vandenabeel et al., 2001).

Dendritic cells in lymph and lymphoid organs

During maturation DCs come to express CCR7 that allows their localization to lymphoid tissue, upon migration through lymph vessels and lymphoid tissue in order to efficiently launch immune responses (Paluka and Banchereau, 2012). While in transit through lymph vessels, DCs acquire a peculiar morphology with wide lamellipodia, for which they have been called veiled cells (Hoefsmit et al., 1982; Banchereau et al., 2000). During maturation DCs process the captured antigen into

small fragments which are then conjugated with MHC-II and MHC-I molecules for the presentation to CD4^{+} and respectively CD8^{+} T cells in order to initiate the immune response (Paluka and Banchereau, 2012; Bancherau and Steinman, 1998).

In the spleen there are marginal DCs and in the T-cell rich areas of lymph nodes there are interdigitating reticulum cells (Bancherau et al., 2000; Palucka and Banchereau, 2012). The name evokes the cell shape, indeed they have long branches running among lymphocytes. The nucleus is large, convoluted and lined by a thin band of chromatin (Veldman and Kaiserling, 1980; Steinman et al., 1997). LCs, peripheral connective tissue DCs, veiled cells and interdigitating reticulum cells are all closely related. The latter two types may contain a few Birbeck granules when they come from the epidermis and mucosal squamous stratified epithelia (Schuler et al., 1991).

Inflammatory dendritic cells

Inflammatory DCs can be found in peripheral blood and in tissues upon inflammation (Hespel and Moser, 2012). They have been designated as 6-sulfo acetyl-N-lactosamine (LacNAc)[+] DCs ('slanDCs') based on the expression of that residue on the P-selectin glycoprotein ligand 1 membrane molecule, also known as M-DC8 (Schäkel et al., 2002). They express transcription factors involved in DC differentiation, including DC specific ZBTB46 (Satpathy et al., 2012), and their differentiation does not depend on GM-CSF, at variance with conventional DCs (Greter et al., 2012). Inflammatory DCs are able to induce the differentiation of Th17 lymphocytes (Segura et al., 2013) and take part in adaptive and innate immunity (Hespel and Moser, 2012; Segura and Amigorena, 2013).

Plasmacytoid dendritic cells

The CD11c- CD14- DCs, or pDCs, express high levels of DEC-205 and CD1d, but these molecules may be upregulated also on mDCs upon in vitro culture or LPS treatment (Vremec and Shortman, 1997). Moreover, pDCs regularly express CD11b, CD32 (FcRγ), CD123 (IL-3R) and - in mice - DC specific 33D1 antigen (Nussenzweig et al., 1982; Dudziak et al., 2007; Benitez-Ribas et al., 2008). Initially pDCs were considered to derive from lymphoid CD34+ progenitor cells (Bancherau et al., 2000; Shigematsu et al., 2004), but it has been shown that they are produced in the bone marrow and, in steady-state conditions, circulate in the blood and migrate to lymphoid tissues. At variance with mDCs, they exit the bone marrow already fully differentiated (Sawai et al., 2013). They represent 0.2%–0.8% of peripheral blood mononuclear cells (Liu, 2005) and can migrate to and accumulate in inflammatory sites where they may contribute to the inflammatory response by releasing cytokines and chemokines and activating lymphocytes (Zhang and Wang, 2005). In physiological conditions pDCs are localized in the spleen white pulp and in lymph nodes but not in peripheral tissues (Liu et al., 2005). Circulating pDCs express BDCA-2 (CD303) and BDCA-4 (CD304), which are expressed also on pDCs in the bone marrow. BDCA-2 is a novel type II C-type lectin that can internalize antigen for presentation to T cells (Dzionek et al., 2001), BDCA-4 is identical to neuropilin-1, a neuronal receptor recognizing both the axon guidance fac-

tors belonging to the class-3 semaphorin subfamily and vascular endothelial growth factor and expressed also on endothelial and tumour cells (Dzionek et al., 2002). Its role in pDCs is still obscure. Moreover pDCs express TLR7, 8 and 9 (Zhang and Wang, 2005). These cells represent a front line of anti-viral immunity owing to their ability to secrete large amounts of IFNα in response to viruses (Siegal et al., 1999). At an early stage of viral infection, pDCs produce large amount of interferon (IFN)-α and -β (type I IFN; Dzionek et al., 2000) and can then differentiate into antigen presenting cells (Siegal et al., 1999; Zhang and Wang, 2005). The pDC-derived IFNα may also promote the activation of NK cells and the maturation of other subsets of DCs, thus helping to activate novel T and B cell clones (Zhang and Wang, 2005; Palucka and Banchereau, 2012). pDCs appear highly efficient at cross-presenting antigens to CD8^{+} T lymphocytes, using pre-synthesized stores of MHC-I molecules to stimulate a rapid cytotoxic response to viral infections; moreover they upregulate the expression of MHC-II molecules and induce the maturation of mDCs and their differentiation to antigen presenting cells thanks to the secretion of IFN-α (which also has an autocrine effect) and TNF-α. pDCs can also be tolerogenic by stimulating CD4^{+} CD25^{+} Treg cells (Banchereau and Steinman, 1998; Liu, 2005; Zhang and Wang, 2005; Dudziak et al., 2007; Palucka and Banchereau, 2012), which may be particularly important in case of intracellular infections and tumours (McKenna et al., 2005).

Maturation of dendritic cells

As anticipated, DCs differentiate to an immature, antigen absorbing phenotype and then proceed to a mature, lymphocyte stimulating phenotype. The precursors of mDCs enter tissues and quickly differentiate to immature mDCs. Immature DCs are characterized by a high capacity for antigen capture and processing, but low T cell stimulatory ability, because they express low levels of co-stimulatory molecules and have a limited capacity to secrete cytokines (Engering et al., 1997; Palucka and Banchereau, 2012). Circulating DC precursors may also directly encounter pathogens, which induces secretion of cytokines that in turn can activate eosinophils, macrophages and NK cells. After antigen capture, DCs migrate to lymphoid organs and acquire the phenotype of mature cells: they display complexes of antigenic peptides and MHC molecules on the cell surface together with co-stimulatory molecules, leading to the selection of circulating antigen-specific lymphocytes. During this process DCs lose the ability to absorb antigens and come to express the co-stimulatory molecules CD54, CD80 and CD86 together with increased amounts of MHC-II, as well as a peculiar chemokine receptor (CCR7) that allows them to localize to lymphoid tissues. Maturation requires the ligation of CD40 and is associated with the expression of the maturation marker CD83 and the acquisition of the ability to secrete cytokines (Cella et al., 1997; Steiman, 2012). Once arrived in lymphoid tissue, DCs localize in the parafollicular zone and differentiate into interdigitating cells to activate naive T-cells. DCs are able to polarize the immune response to either Th1 o Th2 types and to improve T cell memory (Steinman et al., 2003) by the production of different cytokines that determine the classes of immune response (Bancherau et al., 2000). Furthermore a few DCs move to the germinal centers where they collaborate with T lymphocytes to initiate B cell mediated immune responses. DCs can activate naïve and memory B cells

Table 2 - Dendritic cells adhesion receptors to lymphocytes.

Intercellular adhesion receptors on dendritic cells	Ligands on lymphocytes
MHC-I	TCR, CD8
MHC-II	TCR, CD4
CD40	CD40 ligand
CD54 (ICAM-1)	CD11a/CD18 (LFA-1)
CD58 (LFA-3)	CD2 (LFA-2)
CD80 (B7-1)	CD28 (induces T cell proliferation and differentiation)
	CTLA-4 (CD152) (down-regulates T cell activation)
CD86 (B7-2)	CD28 (induces T cell proliferation and differentiation)
	CTLA-4 (CD152) (down-regulates T cell activation)
CD209 (DC-SIGN)	CD50 (ICAM-3)

(Bancherau et al., 2000) and induce the differentiation of activated-naïve B cells to plasma cells, with the secretion of IL-12 and IL-6 (Dubois et al., 1998).

In turn activated T cells help DCs to achieve terminal maturation, further promoting the expansion and differentiation of lymphocytes themselves. It is believed that, after interaction with lymphocytes, DCs die by apoptosis (Banchereau et al., 2000).

Interaction between DCs and T cells during primary responses occurs within lymphoid tissue, which is reached by naïve T cells from the circulation. During secondary T cell-mediated responses, DCs can interact with lymphocytes also in peripheral and inflamed tissues (Fujita et al., 2011; Eyerich and Novak, 2013; Trucci et al. 2013), also on account of the fact that memory T lymphocytes circulate also through peripheral tissues (Shin et al., 2013).

Antigen capture

Antigen capture may occur in several ways. Immature DCs can internalize large amounts of material through macropinocytosis, through fluid phase and receptor-mediated endocytosis (Engering et al., 1997; Sallusto et al., 1995; Mommas et al., 1999), and through phagocytosis of apoptotic and necrotic cell fragments (Albert et al., 1998), viruses, bacteria and parasites (Inaba et al., 1993; Riscigno et al., 1999; Banchereau et al., 2000).

Receptors that have been identified on dendritic cells include lectins such as the mannose receptor langerin/CD207, DC-SIGN and DEC 205/CD205, Fc receptors such as FcεRI, FcγR type I (CD64) and type II (CD32) (Engering et al., 1997; Banchereau et al., 2000), and TLRs (Erbacher et al., 2009). The mannose receptor, langerin/CD207 (Romani et al., 2003), and DC-SIGN (Geijtenbeek et al., 2000) contain multiple carbohydrate-binding domains; mannose receptor in particular is involved in the internalization of sugar-containing proteins and mediates phagocytosis of various microorganisms which expose mannosylated glycoproteins (Engering et al., 1997). DEC-205

has in its extracellular portion a cysteine-rich domain, a fibronectin type II domain and multiple C-type lectin-like domains and in the cytoplasmic portion an amino acid motif which efficiently targets the endocytosed molecule to late endosomes/class II compartments (Mahnke et al., 2000; Erbacher et al., 2009). TLRs are able to recognize a broad spectrum of different pathogen-associated molecular patterns, including conserved components of protozoa, bacteria, fungi, and viruses (Takeda and Akira, 2005). The recognition of microbial components by DC TLRs results in the expression of inflammatory cytokines and co-stimulatory molecules followed by antigen presentation, linking innate to acquired immunity. FcγRI/CD64 and FcγRII/CD32 are members of a family of cell surface molecules which includes also FcγRIII/CD16 and bind the Fc portion of Ig G (Van de Winkel et al., 1993). Binding to FcγRs leads to endocytose immune complexes or opsonized particles (Fager et al., 1996; Amigorena et al., 1998; Döbel et al., 2013). CD1 proteins are known as non-classical antigen-presenting molecules and bind microbial lipid and glycolipid antigens to present them to T cells (Peiser et al., 2003; Porcelli and Modlin, 1999). Four CD1 proteins (CD1a-d) are expressed by mDCs; LCs express almost exclusively CD1a and CD1c (Elder et al., 1993; Banchereau et al., 2000). The phagocytosis of apoptotic cells is restricted to the immature stage of DC development, and this process is accompanied by the expression of some receptors as CD36, that recognizes apoptotic cells (Savil, 1997; Albert et al., 1998). Upon maturation, these receptors and the phagocytic capacity of DCs are downmodulated (Albert et al., 1998).

Antigen processing and presentation

Antigens captured by immature DCs are degraded in endosomes. The generated polypeptides are trasported into the MHC-II-rich compartments and are loaded on the nascent MHC-II molecules, while DCs mature. Mature DCs reduce their endocytic capacity in favour of high surface levels of MHC and co-stimulatory molecules, making them capable of activating even naïve T lymphocytes. The peptide MHC-II complex is exported to the cell surface, where it remains stable for days and is available for recognition by CD4^{+} T cells (Chow and Mellman, 2005; Cresswell, 2005). DCs can also load MHC-I molecules with antigenic peptides which derive from controlled proteolysis in the proteasome and are transferred into the endoplasmic reticulum. The complex peptide MHC-I is transferred to the cell surface and is recognized by CD8^{+} T cells (Banchereau et al., 2000). The MHC-I molecules can be loaded also with exogenous antigens and this behaviour, termed cross-priming, shows that extracellular antigens can be transferred into the cytoplasm for proteasome-mediated processing (Ackerman and Cresswell, 2004; Whiteside et al., 2004). Recognition of MHC-peptide complexes on DCs by antigen-specific T cell receptor (TCR) constitutes the primary signal in DC-T cell interaction, necessary to stimulate a T-lymphocyte response (Hart, 1997). The activation of T cells is facilitated by the interaction of membrane molecules expressed by these cells, LFA-1 and CD2, with co-receptors expressed by antigen presenting cells, respectively LFA-3 and ICAM-1/CD54 (Wang et al., 2003). These bonds are in synergy with TCR-mediated signals and promote efficient intercellular adhesion, T cell proliferation and differentiation (Zumwalde et al., 2013). Although presentation of antigen to TCR is necessary for the initiation of T cell acti-

vation, co-stimulatory signals delivered by antigen presenting cells are needed for a full-blown immune response (Caux et al., 1994a). Interactions between co-stimulatory molecules expressed by DCs and their ligands expressed by T cells are among those signals (Banchereau et al., 2000). In turn, ligation of CD40 on DCs by CD40-ligand (CD40L) expressed by lymphocytes stimulates the maturation of DCs, with the consequent expression of high levels of MHC-II, CD80 and CD86, the latter two molecules are ligands for CD28 on lymphocytes and stimulate secretion of cytokines by the latter cells (Caux et al., 1994a). Contemporaneous blocking the interactions mediated by CD54 and CD80/CD86 leads to anergy (Caux et al., 1994b; Wang et al., 2003; Palucka and Banchereau, 2012).

Dendritic cells and regulation of tolerance

Besides being immunostimulatory, DCs also induce tolerance in the thymus (central tolerance) and in the periphery (peripheral tolerance). In the thymus this depends on deletion of autoreactive T cells and differentiation of CD4$^+$ T lymphocytes to CD4$^+$ CD25$^+$ Treg cells. DCs present self-antigens to thymocytes in the thymic medulla: if T cells have too high affinity for self-antigens, such as occurs with autoreactive T cells, they are deleted by negative selection (Bancherau and Steinman, 1998; Rathmel and Thompson, 2002).

In peripheral lymphoid organs anergy or active tolerance may be induced (Bancherau and Steinman, 1998; Steinman et al., 2003). If DCs come to present an antigen while remaining immature, e.g. because of antigen load in the absence of inflammatory signals, antigen-specific CD4$^+$ and CD8$^+$ T cells undergo transient activation and proliferation followed by deletion which establishes antigen-specific T cell tolerance (Probst et al., 2014). In these immature, or semi-mature conditions DCs express the Th1-inducing cytokine IL-12, which is part of a tolerogenic phenotype of these cells (Steinman et al., 2003). T cells may go into apoptosis induced via Fas/Fas-ligand pathway (Süss and Shortman, 1996) or through activation of the pro-apoptotic mitochondrial protein Bim (Chen et al., 2007). Another pathway leading to tolerance is activation of CD4$^+$ CD25$^+$ Treg cells, which provide active suppression of response to self and to not-self antigens (Steinman et al., 2003; Fehérvari and Sakaguchi, 2004); also these cells are stimulated by DCs (Probst et al., 2014).

Immune suppression is elicited by Treg cells through secretion of soluble factors, such as immunosuppressive cytokines (IL-10 and TGF-β), and through intimate cell contact (Fehérvari and Sakaguchi, 2004). Among other effects, IL-10 and TGF-β inhibit the maturation of DCs. Treg cells express on their cell surface molecules, such as cytotoxic T-lymphocyte antigen 4 (CTLA4) and lymphocyte activation gene 3 protein (LAG3), that suppress DC activation. CTLA4 mediates the down regulation of its ligands, the co-stimulatory molecules CD80 and CD86 on DCs - that are capable of interacting both with CTLA4 and CD28 (Carreno et al., 2002) - or even the endocytosis of their extracellular domain by lymphocytes (transendocytosis), and triggers the induction of the enzyme indoleamine 2,3-dioxygenase (IDO) (Fallarino et al. 2003; Probst et al., 2014) that catalyzes the conversion of tryptophan to kynurenine and other metabolites which have potent, short-range immunosuppressive effects (Fehérvari and Sakaguchi, 2004). LAG3 is a CD4-related transmembrane protein that binds MHC-

II on DCs and suppresses their maturation and immunostimulatory capacity (Liang et al., 2008). Finally, Treg stimulate an increase in the cytoplasmic levels of cyclic adenosine monophosphate (cAMP) in DCs and thus suppress their activation. This may occur by transfer of cAMP from Treg cells to DCs via gap junctions (Probst et al., 2014) and through the generation of pericellular adenosine from extracellular nucleotides by the ectoenzymes CD39 and CD73 (Probst et al., 2014). The effects of extracellular adenosine are mediated by the four members of the P1 purinergic G-protein coupled receptor (GPCR) family (A1, A2A, A2B and A3), which are expressed on both mDCs and pDCs (Hasko et al., 2008). Binding to A2A and A2B causes stimulation of adenylate cyclase and subsequent increase in intra-cellular cAMP, whereas A1 and A3 have an opposing effect (Challier et al., 2013). A2A receptor activation on mature dendritic cells shifts their cytokine profile from a pro-inflammatory to an anti-inflammatory one, with increased production of IL-10 (Hasko et al., 2008).

An example of physiological immune tolerance occurs in the gut, where Treg cells maintain immune homeostasis and prevent effector cells from causing immunopathology in response to commensal bacteria. Here macrophages secrete IL-1β upon sensing microbial products in the gut; this cytokine triggers a subset of innate lymphoid cells (ILC), precisely ILC3, to produce GM-CSF; and GM-CSF exposed DCs release retinoic acid, which promotes the generation of Treg cells (Aychek and Jung, 2014). ILCs are found in the intestine, lung, skin and liver and are divided into three groups depending on the cytokines secreted; ILC3 secrete mainly IL-17 and IL-22 (Hazenberg at al., 2014).

The mechanisms of tolerance are activated also during pregnancy and allow conception, embryo implantation and foetus development (Hsu and Nanan, 2014; Schumacher and Zenclussen, 2014). The foetus is semiallogenic since it expresses antigens of both maternal and paternal origin and the immune system of pregnant women must defend both the mother and foetus from foreign pathogens while tolerating the semiallogenic foetus. It has been shown that maternal immune T cells specifically recognize paternal alloantigens but pregnancy induces a state of transient T cell tolerance specific for those antigens (Tafuri et al., 1995; La Rocca et al., 2014). The exposure of the female reproductive tract to seminal fluid can promote paternal antigen-specific hyporesponsiveness, inducing a state of transient active immune tolerance in the mother (La Rocca et al., 2014). The seminal fluid contains potent immune-regulatory molecules such as TGF-beta and PGE2-related prostaglandins, which promote the generation of Treg from CD4+ CD25- T cells (Robertson et al., 2009) and the conversion of DCs to a tolerogenic phenotype (Schumacher and Zenclussen, 2014). The continuous release of conceptus-derived paternal antigens into the maternal circulation allows Treg cells to continue emerging and expanding throughout pregnancy, migrate to the uterus and contribute to the generation of a friendly environment for the embryo. In peripheral blood, Treg cells are likely involved in the suppression of maternal effector T cells responsive to foetal antigens (Schumacher and Zenclussen, 2014).

Some tissues are endowed with an immune privilege, so that foreign antigens do not induce a conventional immune response; specifically this happens in the eye and brain (Medewar, 1961). DCs and macrophages come to the eye through blood and are localized in some ocular tissues, predominantly the uvea (iris, ciliary body and choroid); few cells enter the peripheral retina and cornea. When ocular tissues are perturbed, bone marrow-derived cells carrying antigen from the eye are found in

the lymph nodes and the antigens are detected even in the spleen after several hours (Forrester and Xu, 2012). Nonetheless, the local response may be low or absent, in order to preserve the transparency of the eye. Several mechanisms have been proposed to explain ocular immune privilege, including induction of Treg cells, the expression of molecules such as FasL or CTLA4 and the secretion of cytokines that generate an immunosuppressive microenvironment (Stein-Streilein, 2008; Denniston et al., 2011; Wang et al., 2011).

Concluding remarks

Dendritic cells induce, sustain, and regulate immune responses and are essential mediators of immunity and tolerance (Bancherau et al., 2000; Kushwah and Hu, 2011). These cells are a link between innate immunity and adaptive immunity: they identify danger represented either by microbial invasion or cancer or even any tissue damage and initiate immune responses against exogenous and endogenous antigens (Bancherau et al., 2000). DCs are distributed across various organs in the body and are heterogeneous for origin, function and surface marker expression. Depending on the local environment and the presence of extrinsic signals, DCs can behave as immunostimulatory or tolerogenic (Kushwah and Hu, 2011).

Given their central role in controlling immunity, DCs are candidate targets to control many clinical situations that involve T cells: transplantation, allergy, autoimmune diseases, resistance to infection and tumour, immunodeficiency, and vaccines (Bancherau and Steiman, 1998). In autoimmune diseases, DCs are increased in number and activated. In the lung, DC may contribute to allergy and asthma. In transplantation and contact allergy, DCs have been implicated in the induction of immunity as well as tolerance (Banchereau and Steiman, 1998). In mouse models of cancer DCs can capture tumour antigens, cross-present them to T cells in draining lymph nodes and induce the generation of specific CD8^{+} T cells, that contribute to tumour rejection. Attempts are made to prepare DC-based vaccines (Paluka and Bancherau, 2012).

However from the account above one gets the uncomfortable feeling that each DC type, whether mDC or pDC, may behave as stimulatory or tolerogenic, even promoting anergy, and that the mechanisms that lead to one or the other behaviour are still unclear. It is indeed so, and deeper understanding of the mechanisms regulating DC differentiation and the fine tuning of phenotype and function is mandatory to achieve successful exploitation of these cells for medical purposes. The development of methods to generate DC in vitro from precursors found in the bone marrow, spleen or blood has opened pathways to expand knowledge on DC biology (Villadangos and Heath, 2005), in order to eventually gain control on these cells and thereby bend the immune response to health needs.

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