Biochimica et Biophysica Acta 1862 (2016) 352–367

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Dendritic cells in brain diseases☆

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ARTICLE INFO

Article history:
Received 7 July 2015
Received in revised form 5 November 2015
Accepted 5 November 2015
Available online 10 November 2015

Keywords:
Neuroinflammation
Stroke
Multiple sclerosis
Neurodegenerative diseases
Epilepsy
Brain tumor

ABSTRACT

Dendritic cells (DCs) are professional antigen presenting cells that constantly survey the environment acting as sentinels of the immune system, including in the CNS. DCs are strategically located near the cerebrospinal fluid, but they can potentially migrate to draining cervical lymph nodes either triggering immunogenic T cell responses or displaying tolerogenic functions. Under physiological conditions, the presence of DCs in the brain parenchyma is minimal but their numbers increase in neuroinflammation. Although DCs belong to a distinct immune cell lineage, they show various phenotypes and share certain common markers with monocytes, macrophages, and microglia. All these cells can express major histocompatibility complex class II, and acquire similar morphologies hampering their precise identification. Neuroinflammation is increasingly recognized in many brain disorders; here we review the literature reporting DCs in the inflamed brain in disease conditions and corresponding animal models of multiple sclerosis, stroke, brain tumors, Alzheimer's disease, Parkinson's disease, and epilepsy. This article is part of a Special Issue entitled: Neuro Inflammation edited by Helga E. de Vries and Markus Schwaninger.

1. Introduction

Neuroinflammation is a common denominator in many neurological and even psychiatric diseases. Neuroinflammation is a reaction to a disturbed environment that under physiological conditions can take place at very low levels, designed to restore balance in the central nervous system (CNS). Neuroinflammation in disease conditions can be a strong reaction in response to neuronal cell damage or neuronal death, infection, acute brain damage – as in trauma or stroke – accumulation of toxic products, autoimmune responses, tumors, genetic conditions, vascular dysfunction, altered function of neuronal networks and neurotransmitter systems, stress or imbalance in the autonomic nervous

Abbreviations: Aβ, amyloid-β; ABRA, amyloid-β-related angiitis; AD, Alzheimer's disease; APC, antigen presenting cell; APP, amyloid precursor protein; Arg-1, arginase-1; B7-H1, human B7 homolog 1 (PD-L1); Batf3, basic leucine zipper transcriptional factor ATF-like 3; BBB, blood–brain barrier; BDCA, blood dendritic cell antigen; BDCA-1, CD1c; BDCA-2, CD303; BDCA-3, CD141, thrombomodulin; BDCA-4, CD304, Neuropilin-1; BMDC, bone marrow-derived DC; C1q, 1st C1 complex subcomponent of classical complement activation pathway; CAA, cerebral amyloid angiopathy; CCL, chemokine (C-C Motif) ligand; CCR, chemokine (C-C Motif) receptor; CD, cluster of differentiation; cDC, conventional DC; CNS, central nervous system; COX2, cyclooxygenase-2; CSF, cerebrospinal fluid; CX_3CR1, chemokine (C-X3-C motif) receptor 1; DAP12, DNAX activation protein of 12 kDa; DC, dendritic cell; DEC-205, CD205, Ly75; DNGR1, C-type lectin receptor marker of DC lineage (also known as CLEC9A); EAE, experimental autoimmune encephalomyelitis; ERK, extracellular signal-regulated kinases; EYFP, enhanced yellow fluorescent protein; F4/80, EGF-like module-containing mucin-like hormone receptor-like 1; Fc, immunoglobulin receptors; FCD, focal cortical dysplasia; Flt3, FMS-like tyrosine kinase 3; FPR1, formyl peptide receptor 1; G-CSF, granulocyte-colony stimulating factor; GFP, green fluorescent protein; GM-CSF, granulocyte macrophage colony-stimulating factor; GM1, monosialotetrahexosylganglioside; Gr1, antibody clon RB6-8C5 recognizing Ly6G and Ly6C; HLA, human leukocyte antigen; Iba-1, ionized calcium binding adaptor molecule 1; ICOS-L, inducible costimulator ligand; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IFNAR, type I interferon receptor; IL, interleukin; ILT7, CD85g; infDC, inflammatory DC; iNOS, inducible nitric oxide synthase; Lin^-, lineage-negative; Ly, lymphocyte antigen; MBP, myelin basic protein; MDDC, myeloid-derived dendritic cell; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; mTOR, mammalian target of rapamycin; NLRP3, NACHT, LRR and PYD domains-containing protein 3; PD, Parkinson's disease; PD-L1, programmed cell death-ligand 1; pDC, plasmacytoid DC; PGE2, prostaglandin E2; PI3K, phosphatidylinositol 3 kinase; RAGE, receptor for advanced glycation endproducts; RIG-I, retinoic acid-inducible gene 1; rtPA, recombinant tissue plasminogen activator; SCA1, stem cells antigen-1; SIRP1α, signal regulatory protein α, CD172A; TGF, transforming growth factor; Th, T helper; Tim-1, T cell immunoglobulin and mucin domain; TLR, toll-like receptor; TNF, tumor necrosis factor; Treg, regulatory T cell; TREM2, triggering receptor expressed on myeloid cells 2; VEGF, vascular endothelial growth factor; XCR1, chemokine (C Motif) Receptor 1.

☆ This article is part of a Special Issue entitled: Neuro Inflammation edited by Helga E. de Vries and Markus Schwaninger.

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http://dx.doi.org/10.1016/j.bbadis.2015.11.003
0925-4439/

system, and possibly alterations in the communication between the brain and the immune system. But to what extent neuroinflammation drives disease onset and progression, or contributes to repair and regeneration is not well understood. Neuroinflammation is a global process that often encompasses the brain and involves peripheral responses with cellular players either resident in the brain or traveling from the periphery, or even acting from the periphery. Many of these cell players interact either locally or from a distance through signaling molecules and nerve wire connections. Therefore, it is likely that studying one cell type will only provide a partial view of the whole process. Keeping this in mind, we set this work to revise some of the current knowledge on the participation of dendritic cells (DCs) in various neuroinflammatory conditions. DCs are the archetypal antigen presenting cells that sense foreign molecules, or access self-proteins abnormally present in the milieu, and present them to T cells to either mount an immune response or induce tolerance. These cells are reported in various brain diseases but their actual role is largely unknown. We aimed to take into account the literature from the immunology and neuroscience fields that provide diverse approaches and sometimes lead to confusing designations of cell types and functions, adding complexity to the difficult task of cell type identification and functional characterization. In the context of neuroinflammatory conditions, we will address the literature about similarities, differences and overlaps between DCs (understood as a unique bone marrow cell lineage), monocyte-derived DCs (MDDCs), inflammatory dendritic cells (infDCs), and reactive microglia. None (or very few) of these cellular phenotypes occur in the brain parenchyma under physiological conditions, where resident microglia display different phenotypes and peripheral immune cells tend to keep away from the brain parenchyma exerting immunosurveillance functions from the choroid plexus, meninges, and perivascular spaces.

1.1. Antigen-presenting cells

The adaptive immune response is based on T lymphocyte recognition of antigens that are presented by specialized cells called antigen-presenting cells (APCs). These cells display small peptides derived from processed antigens bound to major histocompatibility complex (MHC) class I and II molecules. Presentation though MHC I and MHC II depends on the intracellular antigen degradation pathway [1]. Antigens derived from exogenous proteins are processed by lysosomal enzymes of the endocytic pathway and are presented by MHC II. In contrast, presentation through MHC I molecules relies on cytosolic antigen processing in the endoplasmic reticulum which normally involves endogenous molecules, with the exception of a specialized phenomenon called 'cross-presentation' that requires the translocation of exogenous proteins from the lysosomal compartment to the cytosol [2]. Naïve T cells that recognize peptides bound to MHC molecules can become effector T cells. Mechanisms of central [3] and peripheral tolerance [4] ensure the elimination of anti-self-reactive T cells. Immature APCs presenting self-antigen to T cells in the lymph nodes induce T cell anergy, death, or regulatory T cells (Treg) ensuring tolerance to self [5]. However, the repertoire of peptides presented by MHC molecules in non-lymphoid peripheral organs may exceed that in the lymphoid organs [6] and might contribute to the initiation and maintenance of autoimmune conditions [7]. The context of the interaction between T cells and APCs determines priming or tolerization of naïve T cells [8]. Therefore APCs play a crucial role in the mechanisms of tolerance, and the properties of these cells and their local environment are determinant to induce tolerance or immunity.

1.2. Types of APCs

Cells capable of upregulating MHC II expression and antigen presentation include DCs [9], macrophages, monocytes, and in the brain, also microglia [10]. Furthermore, it is now becoming apparent that under certain circumstances some non-APC cells can acquire antigen-MHC I or MHC II complexes from neighboring cells through either a process of cell–cell contact-dependent membrane transfer called trogocytosis, or by transfer of these complexes after secretion of membrane vesicles such as exosomes [11]. Here we will address the main types of APCs focusing on the DCs due to their superior ability, compared to other APCs, to sense, process and present antigen, migrate to lymph nodes, and prime naïve T cells [12]. A summary of the main DC types and DC-related cells is shown in Table 1 and schematically represented in Fig. 1.

1.2.1. Classical dendritic cells

DCs are bone marrow derived cells playing a major role in immunosurveillance for their ability to sample the environment, detect the presence of antigens and induce T cell responses. Most DCs belong to the 'conventional or classical' type and are called cDCs. To accomplish the role of sampling the environment, cDCs are strategically located in the different peripheral organs where they reside and acquire tissue-specific characteristics. Key features of tissue cDCs are migration from peripheral tissues to regional lymph nodes [13], maturation and T cell stimulation [14]. The typical example is the Langerhans cells located in the interstitial spaces of the epidermis, bronchi and mucosae that traffic from the tissue to the draining lymph nodes to present antigen to T cells [15]. Peripheral cDCs enter the lymphatic endothelium and migrate to the draining lymph nodes via afferent lymphatics [16], with the aid of chemokine/chemokine receptor signaling, involving, amongst others, molecules such as CCR7, CCL19 and CCL21 [17]. Consequently, there are two main types of cDCs in the lymph nodes with distinct functions, i.e. the resident cDCs and the migratory tissue-derived cDCs [18]. cDC maturation is required to upregulate MHC II and co-stimulatory molecules. These populations are composed of phenotypically heterogeneous cells and different subsets of resident and migratory cDCs with specific features are defined by the expression of certain markers, e.g. CD8 for lymphoid resident cDCs, CD103 and CD11b for migratory cDCs, which are hallmarks of their functional specialization. A common marker of cDCs is CD11c, but as we will see later, the expression of this molecule is not exclusive of this cell type [19]. The rich assortment of DC phenotypes and functions complicates the study of these cells. For extensive information the reader is referred to specialized reviews addressing this topic in detail [14]. Notably, many cDC markers differ between humans and rodents, confounding the translation of experimental animal studies to the human biology [20,21]. This is particularly relevant for lineage tracing since the current knowledge of DC ontogeny and differentiation from bone marrow precursor cells mostly derives from studies in mice. Although the ontogeny of cDCs is, to some extent, still a matter of debate, developmental precursors that have recently been identified strongly support that DCs are a distinct immune cell lineage [19,22].

1.2.2. Plasmacytoid dendritic cells

A rare subset of DCs called plasmacytoid dendritic cells (pDCs) is found in the blood and the lymph nodes. These cells have crucial functions in the activation of B cells and generation of plasma cells in response to viral infections [23]. pDCs do not express CD11c but express other characteristic markers [24]. Upon stimulation, pDCs can migrate to the lymph nodes [25] and are known for the ability to produce large amounts of IFNs in response to viral infections [26]. However, it has also been shown that maturing pDCs selectively upregulate the expression of inducible costimulator ligand (ICOS-L) and can induce the differentiation of naive CD4 T cells to Treg cells [27]. Therefore, pDCs can either induce immunogenic T cell responses or show tolerogenic functions by inducing $CD8^+$ T cell deletion, $CD4^+$ T cell anergy, and Treg differentiation. For detailed information on pDCs and pDC functions, the reader is referred to specialized reviews on this topic [28,29].

1.2.3. Other non-classical DC-like cells

Blood monocytes can be differentiated in vitro to DC-like cells in the presence of cytokines such as granulocyte–macrophage colony-