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INVITED REVIEW

Immune Heterogeneity in Neuroinflammation: Dendritic Cells in the Brain

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Abstract Dendritic cells (DC) are critical to an integrated immune response and serve as the key link between the innate and adaptive arms of the immune system. Under steady state conditions, brain DC's act as sentinels, continually sampling their local environment. They share this function with macrophages derived from the same basic hemopoietic (bone marrow-derived) precursor and with parenchymal microglia that arise from a unique non-hemopoietic origin. While multiple cells may serve as antigen presenting cells (APCs), dendritic cells present both foreign and self-proteins to naïve T cells that, in turn, carry out effector functions that serve to protect or destroy. The resulting activation of the adaptive response is a critical step to resolution of injury or infection and is key to survival. In this review we will explore the critical roles that DCs play in the brain's response to neuroinflammatory disease with emphasis on how the brain's microenvironment impacts these actions.

Keywords Neuroinflammation · Dendritic cells · Immunosuppression · Microglia · T-cells

Introduction

While microglia are clearly the major immune cell of the brain, bone marrow derived perivascular macrophages and other peripheral immune cells preside at the interfaces between the blood and the interstitium of the brain or between the blood and the fluid that bathes the brain, the cerebral spinal fluid (CSF). These myeloid–derived cells represent a cellular component of an immune circuit between the brain immune system and the periphery that includes the hypothalamic/pituitary neuroendocrine pathways and direct neuronal activity. Dendritic cells (DC), a primary subtype of interface cells, serve as a nodal point in the circuit, bridging the signals initiated from the parenchymal microglia to the adaptive arm of immunity in the periphery. The presence of DCs within the brain has been suggested for a number of years, but even now, their derivation and their functions during neuroinflammation remain unclear. Their participation in brain disease, however cannot be ignored. This review begins by describing the characteristics of DCs and the derivation from the bone marrow and continues by discussing brain specific locations, their origin and their importance to neuroinflammatory disease. We end by asking the question if microglia during disease can, themselves, serve as a source of DCs.

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What are dendritic cells?

In the strictest sense mature DCs can be defined as antigen presenting cells (APC) that interact with naïve T cells within lymph tissue to initiate a T-cell response (Geissmann et al. 2010b). Generally, this interaction occurs through the binding of major histocompatibility complex class I (MHCI) or major histocompatibility complex class II (MHCII) to a T-cell receptor (TCR) in the presence of co-stimulatory molecules expressed by the DC. The activation results in the production of inflammatory and/or anti-inflammatory cytokines by the mature DC that feed forward to instruct naïve T cells or memory cells and feedback to further modify the DC's function. The outcome from T cell activation can be tolerogenic, that is a protective immunosuppressive response, or immunogenic, a defensive response that is capable of ridding the tissue of invaders. In order to understand potential functional outcomes during disease processes, it is

critical to understand when and how DCs orchestrate their immune response programs. For the brain, multiple cells have been described as APCs and thus may act as putative DCs. These include astrocytes (Dong and Benveniste 2001; De Keyser et al. 2010), vascular endothelial cells (Razakandrainibe et al. 2012) and microglia within the brain parenchyma and the macrophages located in the perivascular space and meninges (Perry 1998; Fischer and Reichmann 2001; Carson et al. 2006; Ransohoff and Cardona 2010). While neurons have been shown to express MHCI (Redwine et al. 2001), the function of this complex in neurons appears to involve non-immune mechanisms such as modulation of synaptic transmission (Fourgeaud et al. 2010). The large number of potential APCs, thus, complicates the identification of specific cell types involved in an on-going immune process. The expression of surface antigens is one common mechanism that is used to identify DCs. For example, αX integrin receptors, CD11c (also known as complement receptor 4) are expressed on early lineage DCs and have been widely used to identify and to isolate DC cells. However, neither CD11c nor the expression of other integrins such as CD11b (αM integrin; MAC-1) or CD11a (αL integrin; LFA-1) can be used alone to identify DC (Steinman 2012). As discussed later in the review, recent transcription factor screens have provided new information that allow improved discrimination of DCs from other cell types and now allow easier identification of DCs. However, as suggested by Steinman (Steinman 2012) and others (Shortman and Naik 2007; Geissmann et al. 2010b) full understanding of the role of DCs in an on-going immune mechanism will likely require knowledge of the developmental lineage, of the transcription factors expressed, of the migratory status of the cell and of the immune function, in addition to defining the surface antigens.

The developmental lineage of DCs has been well described and a summary of the key features of DC development is shown in Fig. 1. DCs arise from a hemopoietic stem cell in the bone marrow from which an early stage precursor, the Common Myeloid precursor (CMP), is formed. The CMP has been shown to give rise to monocytes via the formation of the Granulocyte/Monocyte precursor (G/M) or to the Macrophage and DC precursor (MDP) from which arises the Common DC precursor (CDP). It is generally believed that the formation of the common DC precursor demarcates the commitment to a DC-restricted line. Subsets of DCs, including plasmacytoid DCs (pDC) and conventional DCs (cDC; lymphoid tissue resident and non-lymphoid/migratory DCs) stem from the CDP (Reis e Sousa 2006; Liu et al. 2007; Shortman and Naik 2007; Munn 2010; Satpathy et al. 2011). Very recently, transcriptional network analysis was used to identify specific transcriptional activators whose expression is critical for commitment to the DC pathway (Miller et al. 2012). A subset of genes met these criteria, namely, *Runx2*, *Bcl11a* and *Klf8*. Interestingly; the same genes were identified in the direct lineage pathway for formation of plasmacytoid DC (i.e., CDP to pre-pDC) suggesting that the pDC development is a default pathway for the CDP. Transcription factors involved in the development of cDCs from CDP were also discovered. Miller et al. (Miller et al. 2012) identified a unique set of genes that were shared by both lymphoid (CD8+; CD8-) and migratory cDC (CD103+) but were not shared with tissue macrophages. These genes (*Zbtb-46*. *Flt3*, *Kit* and *Ccr7*) were common to cDCs and were not found on macrophages and thus may be helpful to differentiate monocyte-derived cells from DC populations more clearly.

In addition to better understanding the lineage of DC subsets, careful gene analysis provides clues on how to manipulate DC numbers (Satpathy et al. 2011; Meredith et al. 2012). For example, changes in expression or levels of FMS-like tyrosine kinase 3 ligand (Flt3) and is receptor (Flt3R) have been widely used to alter the available number of DCs in vivo (Kingston et al. 2009; Satpathy et al. 2011; van de Laar et al. 2012). Treatment with Flt3 ligand or knockout of the ligand or its receptor results in dramatic changes in the number of circulating pre-DC as well as in plasmacytoid and conventional DC populations (Maraskovsky et al. 2000; McKenna et al. 2000; Waskow et al. 2008; van de Laar et al. 2012). It is important to realize however, that Flt3 receptor/ligand interactions can be independently regulated. Recent studies by Singh et al. (Singh et al. 2012) have implicated prostaglandin E2 and the EP1 and EP3 receptors in the regulation of Flt3 receptor and of Flt3 ligand's action on the common DC precursor and on pre-DCs. They show that PGE2 is a positive regulator for DC cell development and that reducing PGE2 decreases the effectiveness of Flt3 ligand. This important finding has significant implication for the role of cyclooxygenase (COX1 and COX2) in DC -based immunity in the brain and the potential effects of long-term non-steroidal anti-inflammatory use on DC cell numbers. IL-2 has also been shown to block Flt3 mediated development of pDCs and cDCs as well as altering the functional characteristics of these cells (Lau-Kilby et al. 2011).

Dendritic cells and the brain

Location of dendritic cells in the brain

The expression of CD11c and MHCII are commonly used to identify the presence and location of DCs in the brain. Matyszak et al. in the early 90's (Matyszak et al. 1992; Matyszak 1998; Matyszak and Perry 1998) and later Bulloch and colleagues (Bulloch et al. 2008) described a

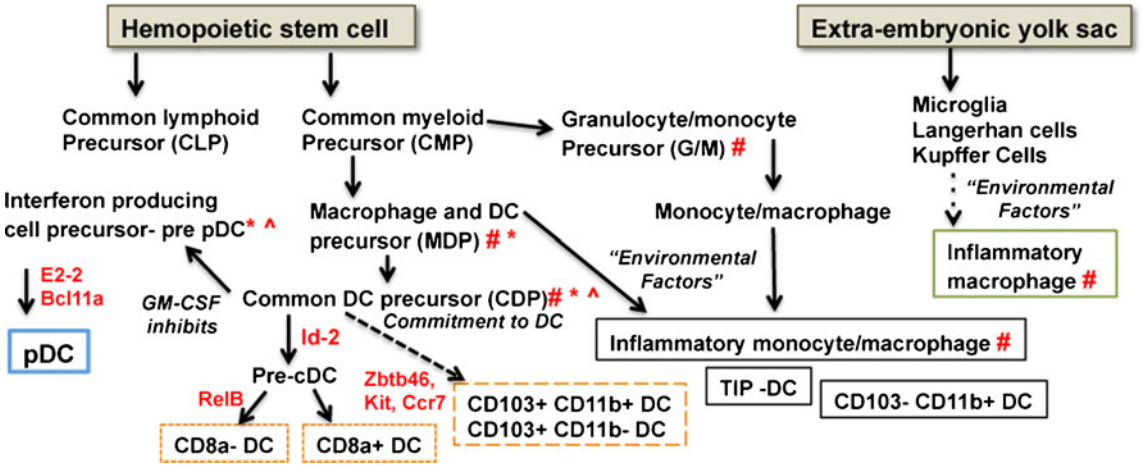

Fig. 1 Generalized diagram dendritic cell subtype lineage. *Red letters*- transcription factors required for that pathway. # - dependence of lineage on GM-CSF; * - dependence of lineage on Flt3, ^- dependence of lineage on M-CSF

population of macrophages that had morphological and antigenic characteristics of dendritic cells (CD11c immunopositive – CD11c+) in the brain. These cells were found, for example, within the interstitium (stroma) of the choroid plexus between the fenestrated capillaries and the basal surface of the choroid epithelium (ependyma) The choroid plexus arises as an invagination of the brain ventricles and is one of the areas where blood is in close proximity to CSF. This area of the brain is highly secretory and produces growth factors, peptides, neurotropins and molecules such as transthyretin (TTR) that binds to and stabilizes other proteins (Johanson et al. 2011). In addition, the choroid plexus produces copious amounts of water plus solutes thus providing the CSF fluid. The CSF-blood interface is well suited to invasion of circulating hemopoietic cells (Fig. 2a). Unlike other areas of the brain, the blood -CSF barrier does not rely on endothelial tight junctions in blood vessels to restrict entry across the endothelium into the stroma (interstitium) and thus entry to the CSF. The endothelial cells in this region lack tight junctions, are fenestrated and lack an astrocyte layer. These anatomical features create a high degree of capillary permeability. Diffusion of large molecular weight molecules such as immune complexes or proteins such as ferritin or horseradish peroxidase that do not ordinarily permeate brain capillaries are minimally restricted. Instead, the primary barrier for passage of material is the epithelial layer and the tight junctions between epithelial cells (Johanson et al. 2011). As a result, the stromal interstitium between the basement membrane of the epithelium and the capillary basement membrane is known to accumulate large macromolecules (Hurley et al. 1981). This region is ideal for antigen trapping by antigen presenting cells such as cDCs or pDCs. Furthermore, the stromal layer is replete with phagocytic macrophages that have the capability of antigen presentation (Graeber and Streit 1990; Matyszak et al. 1992; McMenamin 1999).

The epithelial surface of the choroid layer facing the CSF and CSF, itself, also contain DCs (Serot et al. 1998; McMenamin 1999; Serot et al. 2000). Using conventional confocal microscopy and environmental scanning electron microscopy (ESEM)- that allows imaging of wet tissue with low or no vacuum (McMenamin et al. 2003; Mestres et al. 2011), McMenamin (McMenamin et al. 2003) showed numerous MHCII+/CD11c+DCs lining the outermost aspect of the villi and within the intervillar spaces in rat. Newer studies using fluorescently tagged cells have now confirmed the presence of DCs in the choroid plexus, particularly in the lateral ventricles. Prodinger et al. (Prodinger et al. 2011) used mice that expressed GFP under control of the CD11c *itgax* gene promoter to show GFP-CD11c+cells within white matter, most notably, the fimbria, fornix, corpus callosum and spinal tracts. Preferential location of injected DCs to white matter tracts was previously shown by Carson et al. (Carson et al. 2006). The close proximity to the choroid plexus epithelial surface and to newly-forming CSF suggests that DC in this location are likely to function as sentinels for foreign and self antigens. In addition, DCs in this location have been shown to respond to immune signals, show differences in activation state with disease and migrate to cervical lymph nodes (Pashenkov and Link 2002; Carson et al. 2006). For example, treatment of DCs derived from human blood (monocyte-derived DCs) with CSF taken from patients with neurological diseases such as Multiple Sclerosis (MS) altered their functional phenotype (Pashenkov et al. 2002a, b).

CD11c+cells are also found in the perivascular spaces of the brain. The perivascular space is the interstitial space located between the basement membrane of the glia limitans (astrocyte endfeet) and the basement membrane of the capillary endothelial layer (Fig. 2b). Both basement membranes contain substantial amounts of collagen IV which can be used to identify these layers (Prodinger et al. 2011). Unlike

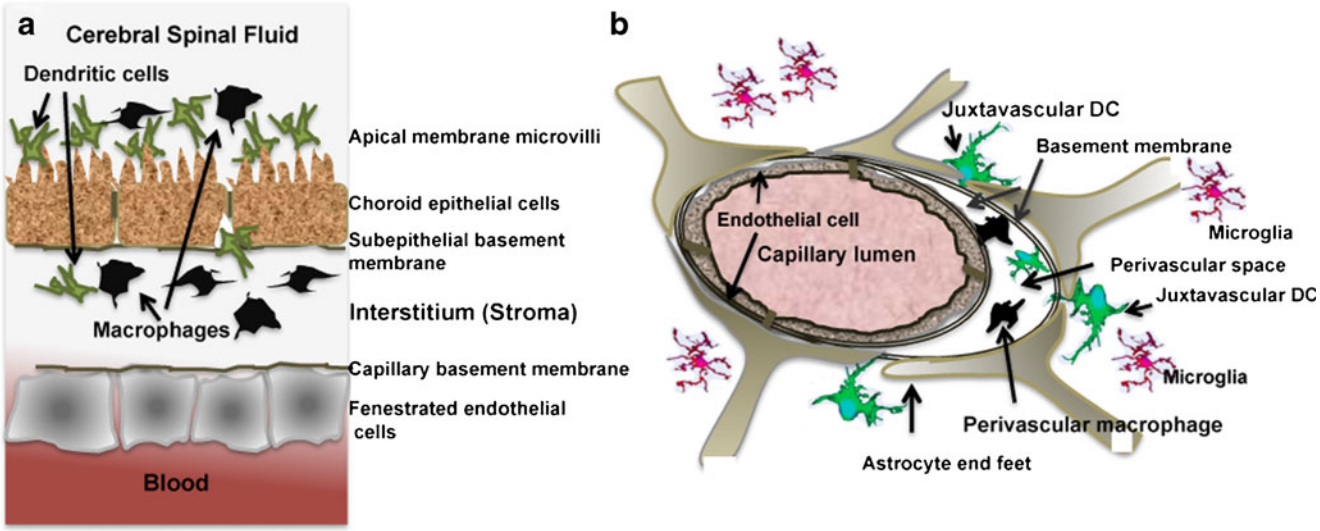

Fig. 2 Location of DCs in steady state brain. a diagram of the location of DCs around blood vessels in the brain. Diagram of the location of DCs at the choroid plexus-CSF interface

the choroid plexus, the tight junctions between capillary endothelial cells serve to restrict movement of solutes from the blood to the brain. This is the site of the blood brain barrier. The perivascular space then lacks the same blood protein access as found in the choroid. However, injection of tracers into the brain's parenchyma clearly demonstrates that the perivascular region is a lymph-like drainage system in the CNS. As recently described by Weller et al. (Weller et al. 2009) interstitial fluid from the brain's parenchyma drains along the basement membranes of capillaries, ultimately reaching cervical lymph nodes in the neck. The perivascular drainage region contains tissue debris and soluble antigens that are available to DC cells for antigen presentation. Expression of MHCII on cells in the perivascular region has been observed for a number of years and is primarily localized to macrophages (also known as perivascular microglia) and an occasional DC (Fig. 2b) (Hickey and Kimura 1988; Sasaki et al. 1996; Perry 1998). In Prodinger's studies they used a combination of thin section electron microscopy and fluorescent microscopy to demarcate the borders between the vascular wall, perivascular space and the juxtavascular brain parenchyma. The results of these experiments clearly show ramified CD11c+cells predominantly located around blood vessels in the brain parenchyma near the vessel (juxtavascular), with sparse GFP expressing CD11c+cells in the perivascular space. Juxtavascular CD11c+DC were found in slice cultures as early as 3 days postnatal. Interestingly, ramified CD11c +DCs in the juxtavascular parenchyma extended processes to the outer layer of the perivascular space (the glial limitans). These processes were found between adjacent astrocyte end feet and abuted the glial limitans basement membrane directly. The presence of CD11c+DC cells situated between the brain parenchyma and the perivascular space allows these cells to potentially sample antigens from two compartments and to present antigen from the parenchyma to T-cells within the perivascular space. The location and action of these brain CD11c+DCs is reminiscent of subsets of CD103+CD11b+DC located at the mucosa/epithelial cell layers in the gastrointestinal tract. Interestingly, DC cells in the GI have been show to extend processes between adjacent epithelial cells in the mucosal lining without compromising the tight junction nature of the cellular barrier (Lelouard et al. 2012). These extensions sample the gut lumen and signal appropriate adaptive immune responses (Chieppa et al. 2006; Rescigno et al. 2008). In this case, the response is immunosuppressive (Denning et al. 2007; Hume 2011). However, the controversy over the specific cell type still looms large in the lamina propria of the gut as is does for the CNS. New data on CX3CR1 expression suggests that there are 2 populations of cells, one a true migrating DC that is CX3CR1-negative and the second, a macrophage that is CX3CR1-positive. Niess et al. (Niess and Reinecker 2005) have shown that CX3CR1 expression is critical for the formation of the transepithelial processes. These data are reviewed by Hume (Hume 2011) and Pabst and Bernhardt (Pabst and Bernhardt 2010) and indicate that the cells in the lamina propria of the GI are macrophages.

Origin of brain DCs

Dendritic cells are best described as a heterogeneous population of cells that differ in tissue location, migratory ability

and functional outcome. As discussed above, DCs are known to arise from a common myeloid, FMS-related tyrosine kinase-3 (Flt3) receptor –positive, hematopoietic progenitor. During subsequent stages of development these newly forming DCs enter lymphoid and/or non-lymphoid tissue via the circulation to take up residence in that tissue. (The readers are referred to several excellent reviews for more detailed information on the development of DCs from bone marrow precursors (Reis e Sousa 2006; Liu et al. 2007; Shortman and Naik 2007; Sathe and Shortman 2008; Steinman 2012). For the adult brain, circulating DC precursors (pre-DCs) are a likely source of DCs under normal (steady state) conditions. Their juxtavascular location further supports the idea that brain DCs come from a vascular source and are not derived from within the brain. This was elegantly shown to be true by Anandasabapathy et al. (Anandasabapathy et al. 2011) using Flt3 ligand –treatment to expand the DC population. In their study Anandasabapathy identified an Ftl3 ligand-sensitive population of fluorescently labeled CDllc+(EYFP-CD11c+) cells using two-photon microscopy. Increased numbers of EYFP cells were found in the meninges and the choroid plexus after Flt3 treatment while no change was found in EFYP cells in brain parenchyma. Flow cytometry on brain lysates and on isolated meninges further demonstrated that the sparse EFYP positive cells in the parenchyma were microglia, expressing a CD45Int, CD11c Lo, MHCII negative antigen profile. In contrast, EFYP cells in the meninges were CD11cHi, CD45Hi and MHCII positive and were expanded in number by ligand treatment. To further understand the functional differences, meningeal DCs were purified and the ability to present antigen was compared in vitro to microglia and to splenic DCs. As predicted, the DC populations induced proliferation of allogeneic T-cells but microglia were unable to perform this function. Finally, gene analysis of meningeal DC vs splenic DC showed a high degree of similarity while microglial gene expression profiles were not similar. The authors conclude that the endogenous DCs in normal brain are most likely to arise from pre-DCs that enter the brain perivascular regions at an early stage.

Functional DC subsets in the brain

Immature vs mature; pDC vs cDC

The ability for DCs to carry out their dual functions as sentinels and as priming/regulatory agents for an adaptive immune response depends on the migration of preDCs from the bone marrow to strategic surveillance sites in tissues. For the brain, these sites are the primary drainage areas for the brain's interstitial fluid, the perivascular space and the choroid plexus/CSF. Two primary subsets of preDCs, that is, pDC and cDC, seed non-lymphoid tissue from the bone marrow. These newly recruited pDC or cDC are said to be "immature" and achieve a "mature" state in response to environmental signals (Reis e Sousa 2006). Clear differences exist between the immature and mature DC and these characteristics are summarized in Table 1 (Austyn et al. 1988; Larsen et al. 1990; Lin et al. 1998; Cools et al. 2007). "Immature" DCs demonstrate an organized cytoskeleton and reduced motility and at the same time show increased expression of surface receptors such as Fc and mannose receptors (MMR, CD206) (Table 1). Since uptake of cellular debris or other antigens is critical for the antigen presentation process, increased receptor numbers are essential to the enhanced degree of endocytotic activity and increased phagocytosis commonly observed in immature DC (Satthaporn and Eremin 2001; Wong et al. 2004; Shortman and Naik 2007). However, the expression of co-stimulatory molecules that are required for full T-cell activation is low or incomplete. These combined features lead to efficient antigen capture but are not associated with full antigen presentation within the context of MHCI or II-mediated T-cell interaction. Thus it is generally believed that immature DCs are not fully capable of priming naïve T-cells and are unlikely to generate an immune outcome in this maturational stage (Reis e Sousa 2006). They are, however, excellent sentinels. A distinction also has to be made between immature DCs and other antigen presenting cells. Tissue macrophages can show many of the same characteristics in the steady state as immature DCs. In the brain, parenchymal and perivascular microglia are well known to present MHC class II molecules, to express Fc and mannose receptors, and to express co-stimulatory molecules. As pointed out by Carson and others (Carson et al. 2006; Melchior et al. 2006; Ransohoff and Cardona 2010) however, the level of expression of these molecules by parenchymal microglia is low or restricted to intracellular compartments. Furthermore, neurons are liberally equipped with both direct-contact and soluble inhibitory mechanisms that inhibit microglial immune activity (reviewed by (Ransohoff and Cardona 2010). The inherent down-regulation of microglia in the brain parenchyma coupled with the unique derivation of microglia from egg yolk sac, suggests that microglia may be less efficient APCs then a monocyte/macrophage derived APC such as perivascular microglia. Thus while microglia may perform immune surveillance, their actions to link innate and adaptive arms appear different then APCs in other tissues. It is currently believed that the major role of brain APCs is to re-stimulate activated T cells during their entry into the brain (Goverman 2009; Ransohoff and Cardona 2010). Re-stimulation by perivascular APCs is known to be a factor in Multiple Sclerosis (MS) in humans and in experimental allergic

Table 1 Characteristics of immature and mature dentritic cells

Immature DC	Mature DC
Highly organized cytoskeleton, rounded morphology	Large number of processes
High endocytosis, active phagocytosis	Low CD68, low to no phagocytosis
Expresses mannose receptor Efficient antigen captured	Decreased antigen uptake
Low or Incomplete expression of co-stimulatory molecules	Express co-stimulatory molecules-CD80 (B7,1); CD86 (B7,2)
Intracellular MHC rather than surface expression; non peptide loaded	High surface expression of MHCII, peptide loaded for presentation
High CCR5: Low CCR7 chemokine Pattern, non-migratory	Low CCR5; High CCR7 chemokine pattern, migratory
Not capable of T-cell priming	Provided signals for T-cell priming
High levels of intracellular cystatin C	Decreased intracellular levels of cystatin C but high levels of secreted cystatin C

encephalitis (EAE), a demyelinating disease in rodents that resembles multiple sclerosis (MS) (Greter et al. 2005; Bailey et al. 2007; Cassan and Liblau 2007; Goverman 2009).

The plasmacytoid DC (pDC) is a classic example of an immature DC and is observed in the human and rodent brain (Bailey-Bucktrout et al. 2008; Lande et al. 2008). PDC are highly secretory cells and their principal product is interferon type 1 (IFNα/β) which is rapidly secreted in response to TLR7 or TLR9 activation (Swiecki et al. 2011; Wang et al. 2012). TLR7 (responds to single stranded RNA) and TLR9 (responds to DNA with un-methylated CpG) are intracellular pathogen receptors that sense RNA or DNA, particularly from viruses. Consequently, the rapid production of IFNα/β is a critical step in establishing the brain's immune response to viral infections such as vesicular stomata virus (VSV) or HIV, or to induction of experimental autoimmune encephalomyelitis (EAE) or to sterile injury (Fiette et al. 1995; van den Broek et al. 1995a, b; Honda et al. 2005; Benveniste and Qin 2007; Schmidt et al. 2009; Wang et al. 2010; Salem et al. 2011; Wang et al. 2012). The close relationship between IFNα and IFNβ results in multiple overlapping functions (hence the frequently used abbreviation IFNα/β). IFNα has at least 23 subtypes and is critical to the reduction of viral load, in part by up regulating antigen presentation and increasing T cell responses and natural killer cells (Gibbert et al. 2012). IFNβ has actions more directed at quelling the inflammatory response, including decreasing macrophage/microglia mediated phagocytosis, TNFα production and MMP9 activity (Benveniste and Qin 2007). Both, however, act via the same receptors. The response to interferon, then, depends on the expression levels of the IFNα/β receptor (IFNAR), and on the expression of IFR3, IFR7 or IFR9 (IFN regulatory factor (IFR) transcription factors) (Suh et al. 2009). Increased IFR7 and IFR9 expression levels are frequently used as surrogate markers for the presence of type 1 interferons. In the case of VSV, Detje et al. (Detje et al. 2009) used IFNAR knock out mice to show the dependence of the disease process on IFNα/β signaling. Since an influx of pDC or macrophages that produce type 1 interferon was not observed under these conditions, a local, unknown cellular source (possibly astrocytes) for type 1 interferon was proposed (Detje et al. 2009). Wang et al. (Wang et al. 2011) have shown increased INFβ in astrocytes surrounding motor neurons in amyotrophic lateral sclerosis (ALS). For HIV and for EAE, however, type 1 interferon - secreting cells from outside of the brain (possibly invading pDC) are thought to be involved.

Although pDC represent only about 4 % of the invading CD11c+cells (Melton et al. 2010) their importance to suppressing pathology is clear. Bailey-Bucktrout et al. (Bailey-Bucktrout et al. 2008) have shown that depletion of pDC using a monoclonal anti-PDCA-1 antibody resulted in significant worsening of EAE symptomology. Reconstitution with pDC returned the clinical scores to the control levels. The authors have suggested that Type I Interferon production by the influx of pDC helps to restrict the autoimmune response that is characteristic of the disease process. Studies by Prinz et al. (Prinz et al. 2008) and Guo et al. (Guo et al. 2008) further support the protective nature of myeloid cell-derived type 1 interferon in EAE although through differing mechanisms. For Prinz, type 1 interferons decrease lethality in EAE mice by suppressing chemokine expression, reducing phagocytosis of myelin products and reducing MHCII expression. Guo et al. demonstrated that inhibition of T-helper 17 (IL-17) cell development was a primary factor in type 1 interferon-mediated suppression of EAE. Interestingly, pDC also express the immunoregulatory enzyme, indolamine dioxygenase (IDO) (Munn et al. 2004; Sharma et al. 2007). IDO has been shown to facilitate immunosuppression by activating T-regs and by blocking the production of Th-17 cells (Baban et al. 2009). On the other hand, prolonged or overproduction of IFNα by pDC can be damaging, either directly by killing T-cells that are critical to reducing infection or by secreting chemokines which may further attract T-cells to the brain

(Swiecki and Colonna 2010). Interestingly, pDC lose their ability to produce IFNα on maturation and switch to a state that includes T-cell regulation (Morelli and Thomson 2007). Hadeiba et al. (Hadeiba et al. 2012) have recently shown that pDC expression of the chemokine receptor, CCR9, is characteristic of mature pDCs. Inflammatory signals can block this process and prevent the expression of CCR9.

It is important to note that interferons are now increasingly used as therapies for human disease. Synthetic IFNα, for example, has been developed to treat acute viral diseases such as severe acute respiratory syndrome coronavirus (SARS) (Loutfy et al. 2003; Ward et al. 2005). Interestingly the SARS virus as well as other viruses such as influenza A or Herpes simplex virus attack and block IFN processes including the receptor and IRF3 activity. Perhaps the best known therapeutic effect of IFNβ is it's use in treatment of multiple sclerosis in humans. Here, the anti-inflammatory effects of IFNβ have been harnessed to reduce the pro-inflammatory damage found in either mouse models of MS (experimental allergic encephalomyelitis (EAE) or in humans with MS. However as recently reviewed by Axtel et al. (Axtell et al. 2011) the large number of patients that either does not respond to IFNβ or whose disease is worsened by IFNβ strongly suggests that a great deal remains unknown about MS and IFN's actions in the CNS.

Mature DCs exhibit specific changes in gene expression patterns and in functional outcomes as shown in Table 1 (Satthaporn and Eremin 2001; Re and Strominger 2004; Shortman and Naik 2007). For example, expression of co-stimulatory molecules is a well-described and critical feature of mature cDCs that allows the cells to become fully capable of instructing T-cells. Patterns of chemokine receptors also change. C-C chemokine receptor 5 (CCR5) expression levels are reduced while C-C chemokine receptor 7 (CCR7) levels are increased (Shortman and Naik 2007; Seth et al. 2011). This change facilitates the migration of antigen- carrying DCs from non-lymphoid tissue to lymphoid sites where they interact with either naïve T-cells or re-activate self-reactive T-cells. The movement of sentinel DC's from their home tissue to lymph nodes where T-cells await is critical to the immunostimulatory function of DCs. Thus, the apparent inability of brain DCs to migrate to lymphoid tissue is problematic. Early studies on the brain's lymph system supported the idea that the lack of migration was due to the lack of lymphatic drainage. By injecting labeled myeloid DCs intrathecally into mouse brain, Carson et al. (Carson and Sutcliffe 1999; Carson et al. 2006) however, clearly demonstrated that cultured myeloid DCs were able to migrate to cervical lymph nodes from within the brain. Labeled DCs were found in the meninges and subarachnoid spaces but interestingly, also, in brain parenchyma along myelin tracts such as the corpus callosum, striatum and fimbria. These data are consistent with Weller's analysis of lymphatic drainages in the brain but do not firmly prove that endogenous brain DCs migrate along the same paths. Another mechanism that may compensate for the restricted migration of brain DCs is the presence of other APCs, such as perivascular microglia, that may move to peripheral lymph nodes. However, microglia are unlikely to traffic to the periphery (Byram et al. 2004). Alternatively, soluble antigens (such as Aβ peptides) that move along the perivascular drainage toward lymph nodes may provide the antigen itself by directly draining to lymphoid tissue (Carare et al. 2008; Weller et al. 2009).

As proposed by Greter et al., DCs cells in the brain may inherently be non-migratory and carry out their function without moving to lymphoid tissue (Greter et al. 2005; Goverman 2009). The brain microenvironment, in part, may dictate this characteristic. For example, Ganea and colleagues (Vassiliou et al. 2008) have shown that exposure to local tissue factors such as resolvin E1, a lipid metabolite derived from eicosapentaenoic acid, alter DC chemokine expression and restrict migration of DCs to the site of infection. These and related active lipids have been recently shown to reduce inflammatory pain via an action on spinal cord pathways indicating they are found in the CNS (Xu et al. 2010). In addition, lipid accumulation by DCs reduce the ability of the cells to process antigens, further suggesting that the inflammatory environment alters the normal functional state of DC (Herber et al. 2010). Instead of migrating out, then, DCs that migrate to the CNS in the steady state may remain within the CNS during infection or inflammation. Recently, lymphoid neogenesis has been described in multiple tissues though out the body including the brain (Cipponi et al. 2012). These lymph node-like structures, called ectopic or tertiary lymph nodes, form under conditions of chronic infection and serve to host T and B-cell interactions with APC at a site close to the infection (Cipponi et al. 2012). Tertiary lymphoid structures have been found in the CNS particularly during MS and EAE, most commonly along the meninges (Peters et al. 2011). Specific chemokines such as CXCL13 and cytokines such as IL-17 appear to play a role in the formation of these ectopic sites (Aloisi et al. 2008). However, the formation of tertiary sites in the brain does not negate the possibility that brain DCs migrate to the periphery since CSF DCs have been found in cervical lymph nodes (Carson et al. 2006). The additional meningeal sites may simply give the brain the ability to interact with T-cells in multiple locations.

Effector outcomes: *Immunogenic/immunotoxic*

The dual necessity for protection against foreign antigens and for return to homeostasis after injury or infection is an underlying principle of immunity that is key to survival in

all animals (Finch et al. 2010). DCs primarily provide protection through their ability to mobilize and direct the development of effector T-cells that are associated with immune defense. This "immunogenic" response includes the production of multiple subtypes of T-cells that include CD8+ cytotoxic T lymphocytes (CTLs) and various classes of CD4+ helper T-cells with different pro-inflammatory cytokine profiles. Figure 3 shows the basic categories of effector T cells including the cytokines/factors that stimulate their production and cytokines that are produced on stimulation. Excellent reviews are available that describe in detail the transcription factors and pathways that regulate the effector action of cells involved in the immunogenic response and this topic will not be discussed here (Reis e Sousa 2006; Haftmann et al. 2012; Josefowicz et al. 2012). It is clear that immunogenic T-cell responses are critical to rid the CNS of invading organisms as shown for clearance of *sindbis* virus from the CNS (Metcalf and Griffin 2011) or to reduce infection with *Taenia solium* that causes neurocysticerosis (Gundra et al. 2011). However, this "protective" pro-inflammatory armament can be redirected to generate bystander tissue damage under specific conditions. For example, EAE in mouse and MS in humans are well-studied examples of immunogenic effector responses initiated by the adaptive immune response that are directed against self molecules and produce damage to the CNS (Fischer and Reichmann 2001; Greter et al. 2005; Goverman 2009; Munz et al. 2009; Podojil and Miller 2009; Melton et al. 2010). In contrast to *T. gondii* infection where the target is an invading organism (in this case a parasite), in EAE or MS the primary targets are auto-antigens particularly against myelin proteins. Multiple immunogenic T-cells (for example, CD4+ Th1, CD4+Th17 and/or CD8+ CTL T-cells) enter the CNS at different sites including the meninges, subarachnoid space, perivascular spaces and, as recently demonstrated, the 5th lumbar region of the spinal cord (Goverman 2009; Arima et al. 2012). T-cells expressing self-antigens against myelin proteins (most commonly myelin basic protein) are re-activated by APCs that have low avidity for the auto-antigens.

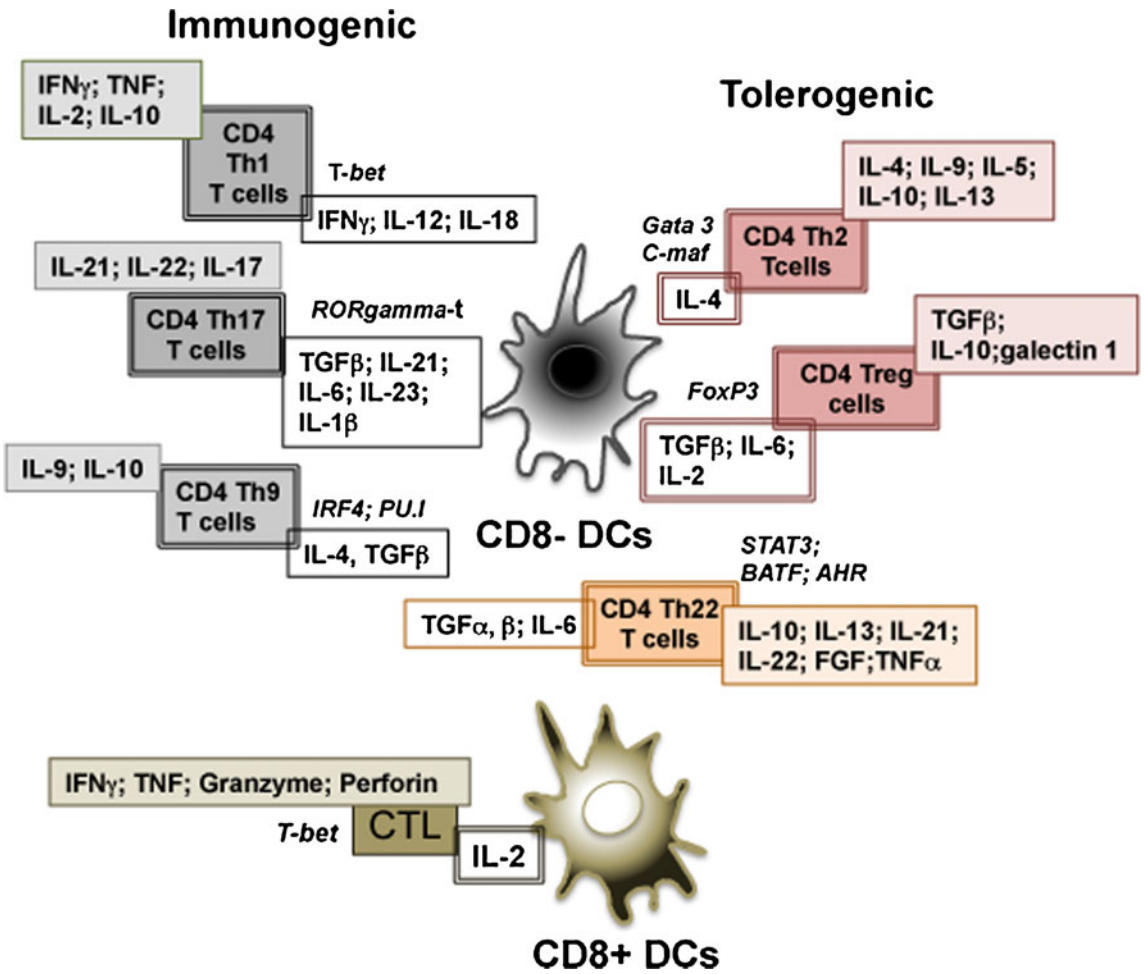

Fig. 3 Subtypes of helper T-cells generated by the interaction of DCs with naïve T-cells. DCs produce cytokines (*open boxes*) that direct development of T-cell subtypes (*darkly filled boxes*). Examples of the cytokines produced by the T-cell subtype are shown in the lightly filled boxes. Transcriptional factors are in italics

Circulating or brain restricted DCs can carry out this function but microglia or perivascular microglia are also capable of fully activating the invading immunogenic T-cells (Fischer and Reichmann 2001; Byram et al. 2004; Karni et al. 2006; Goverman 2009; Ransohoff and Cardona 2010). Reactivation, rather than direct activation, is most likely to occur. As described by Goverman (Goverman 2009) for multiple sclerosis, a high avidity T-cell for a self antigen such as myelin basic protein (MBP) ordinarily leads to removal of the T-cells expressing the self antigen-MHC complex through central tolerance. However, low avidity T-cells against self antigens may escape the elimination process and become available for later re-activation as a component of auto-immunity in diseases such as MS.

Interestingly, auto-reactive T-cells may be beneficial to a damaged CNS. Schwartz and colleagues (Schwartz et al. 1999; Kipnis et al. 2002; Walsh and Kipnis 2011) support the view that autoimmune T effector cells are critical to neuronal survival after injury or stress. For example, Cohen et al. (Cohen et al. 2006) showed that mice with severe combined immune deficiency (SCID mice) demonstrated more severe behavioral deficits with stress compared to normal mice. At least part of this effect was due to the lack of autoimmune T-cells against myelin proteins. This apparently contradictory view has been shown for optic nerve crush, for EAE and more recently for AD and clearly underscores the complexity of T-cell action in CNS disease (Moalem et al. 1999; Schwartz et al. 1999; Fisher et al. 2001; Ethell et al. 2006; Koronyo-Hamaoui et al. 2009).

Effector outcomes: *Tolerogenic/Immunosuppressive*

DCs participate in tolerogenic mechanisms by interacting with naïve T-cells to generate at least 2 different types of T-cells that can limit the extent and duration of an adaptive immune response. These mechanisms incorporate CD4+Th2 effector T-cells and CD4+Foxp3+ regulatory T-cells (T-regs), both of which have been well described (Vignali et al. 2008; Shevach 2009; Wilson et al. 2011) (Fig. 3). Th2 cells generate and secrete immunosuppressive, anti-inflammatory cytokines such as IL-4, IL-10, IL-13 and IL-9 that quell the pro-inflammatory activity of local macrophage populations at sites of inflammation (Varin and Gordon 2009; Wilson et al. 2011). In addition, these effector cells mobilize and recruit eosinophils as well as induce their maturation and regulate class switching from IgG1 to IgE. Th2 cells are also required for the maintenance of alternatively activated macrophages during parasitic infections or during tissue injury (Loke et al. 2007). Similarly to Th2 T-cells, regulatory T-cells (CD4+Tregs) are also critical to limiting the tissue response to infection. They function in the CNS to down regulate the immune response by secreting IL-10, and by either inducing anergy (i.e., killing) or reducing the ability of effector T-cells to respond. In some cases, entry of effector T-cells into the tissue may also be blocked. T-regs like Th-2-cells are most commonly generated in the peripheral lymph nodes in response to "activated" DCs and carry out their immune function in the periphery. However, T-regs can travel to the CNS. McGeachy et al. (McGeachy and Anderton 2005; McGeachy et al. 2005) showed that T-regs accumulated in the brain in animals subjected to EAE. They further showed that depletion of the brain's T-reg population worsened the disease process while adding isolated CNS T-regs to animals with EAE was beneficial. Importantly, T-regs isolated from the brain have unique properties, most likely due to their exposure to the brain's microenvironment. O'Connor et al. (O'Connor et al. 2012) have recently reported that T-regs found in EAE mice brain are resistant to IL-6, through down-regulation of the IL-6 receptor. This effect helps to maintain an immunosuppressive, tolerogenic effector outcome by preventing the T-reg cells from producing IL-17 (Zhang et al. 2008). IL-17 is a T-cell- produced pro-inflammatory cytokine that worsens tissue damage by inducing cytokines that call in activated macrophages and by enhancing the activity of TNFα and IL-1β (Fletcher et al. 2010). IL-17 is also a key cytokine involved in autoimmune diseases throughout the body (Ambrosi et al. 2012). It is believed that changes in the pro-inflammatory microenvironment during EAE or MS promote IL-17 which is then countered by altered resistance to IL-6. Unlike the brain, T-regs from peripheral lymph nodes apparently retain the ability to generate IL-17. Finally, T-regs have also been shown to reduce the activity of CD8+ effector cells in the CNS (Gobel et al. 2012), further demonstrating a wide range of protective activities of these immunosuppressive cells.

Microenvironment regulation of DCs

It is clear from the above discussions that the localized environment in which the DC-T-cell interaction takes place allows a subtle interplay between the disease process and the immune response. The diverse inflammatory conditions are a prime factor in the initiation of maturation of DCs and can orchestrate or modify the immunogenic or tolerogenic/immunosuppressive outcomes. These disease or injury-specific signals interact with pattern recognition receptors on DCs to initiate a variety of maturation programs (Reis e Sousa 2006, 2011). The signaling pathways that are activated facilitate endosomal acidification and the degradation of the ingested protein antigens and the MHCII components (Trombetta et al. 2003) (Table 1). Beyond these specific functions, the activation signals appear to be critical to directing the downstream maturation process that allows DCs to shape T-cell fates.

DCs respond directly to pathogens such as bacteria or virus, to specific carbohydrate groups (glycans) and to cytokines or interferons that are indirectly released during an injury or inflammatory process (McMahon et al. 2006; Mollen et al. 2008; Boele et al. 2009; Mascanfroni et al. 2011). The timing of expression and the mixture of the corresponding receptors expressed on the surface dictate the overall response of the DC, that is, if the effector outcome will be immunogenic or immunosuppressive. An excellent example of the complex duality of DC activation is shown by the exposure of DCs to prostaglandins E2 (PGE2). PGE2 is a cyclooxygenase metabolite of arachidonic acid and is a member of the eicosanoid family. The presence of PGE2 and TNFα, commonly found in inflammatory environments, induces DC maturation that leads to Th-1 cells and an immunogenic outcome. However, depending on which PGE2 receptor is involved, the actions of PGE2 can be the opposite (Milatovic et al. 2011). Obermajer et al. (Obermajer et al. 2011) demonstrated that exposure to PGE2 early in the maturation process produces an immunosuppressive DC phenotype that included the expression of arginase 1, IL-10 and indolamine oxygenase (IDO). In addition, this immunosuppressive phenotype inhibited CD8 cytotoxic T-cells. Other cytoactive components found in inflammatory environments can promote an immunosuppressive/tolorgenic DC phenotype and outcome. These include neuropeptides such as vasoactive peptide (VIP) and pituitary adenylate cyclase activating polypeptide (PACAP) (Delgado et al. 2005a, b; Gonzalez-Rey and Delgado 2005), Neuropeptide Y (NPY) (Zukowska et al. 2003; Prod'homme et al. 2006) and somatostatin (Herberth et al. 2006). The levels of these neuropeptides are altered in many brain diseases. For example, at autopsy NPY neurons were shown to decrease in humans with AD and in the CVN mouse model of AD suggesting that loss of these factors late in disease may contribute to an inflammatory profile. (Chan-Palay et al. 1986; Wilcock et al. 2008)

An additional class of cytoactive agents that activate DCs and other APCs is the alarmins, a diverse group of immune mediators that include defensins, eosinophil derived toxins and damage associated molecular patterns (DAMPS) such as high mobility group box-1 (HMBG -1) and ATP. Defensins are a proteotypic alarmin and are rapidly induced by cytokines and interferon type 1 and type 2 at sites of inflammation (Yang et al. 2007, 2009). In general, they function to recruit immature DCs and phagocytes to the injury site, to promote antigen presentation by inducing maturation of DC and to facilitate DC migration to lymph nodes by changing the chemotactic receptor profile of DCs. Defensins also act as an anti-microbial agent to kill or inactive infectious agents and are considered part of the anti-microbial peptide family (AMPs) (Zaiou 2007). In an interesting study, Soscia and colleagues (Soscia et al. 2010) have shown that Aβ peptide acts as an antimicrobial "defensin-like" molecule and in addition, is capable of killing or inactivating pathogens. These data would suggest that the delivery of Aβ to the perivascular space and to the CSF may promote maturation of immature DCs located in these regions of the brain.

While defensins are released primarily from epithelial cells, HMG proteins, a subtype of damage associated molecular patterns (DAMPS), are released from badly injured/dying cells or from sterile injuries such as cerebral ischemia (Rubartelli and Lotze 2007). ATP is another principal factor released during injury, although the levels released will depend on how much ATP was used by the dying cell. Apoptosis but not necrosis requires ATP (Leist et al. 1997). ATP is also released normally during synaptic transmission but excessive activity as seen in excitotoxicity can result in ATP signaling to the immune system (Koles et al. 2011). Microglia, macrophages and DCs express varied complements of P2X or P2Y purinergic receptors that mediate the ATP response. Receptor binding produces activation of the inflammasome as well as the primary pro-inflammatory cytokines, IL-1 and IL-18 (Miller et al. 2011; Rock et al. 2011). Interestingly, ATP can be metabolized to adenosine by the sequential enzymatic action of nucleoside triphosphate diphosphohyrdolase and 5′ribonucleotide phosphohyrdolase. Adenosine receptors on the membrane of microglia, DC and T-cells respond to adenosine to produce a strong anti-inflammatory signal. This signal includes increased production of IL-10, direct inhibition of LPS mediated events and decreased T-cell proliferation (Drygiannakis et al. 2011). Again, immunotoxicity or immunosuppression is dictated by the brain's microenvironment.

Can microglia become dendritic cells?

Recent studies on the ontogeny of microglia have significantly altered our understanding of their origin and ultimately, of their function. Data from Ginhoux et al. (Ginhoux et al. 2010) show that microglia arise from an embryonic cellular source that is distinct from bone marrow derived -monocytic cells. In other words, microglia arise from a second, mononuclear phagocyte lineage that is apparently different from cells of the bone marrow -derived lineage. This concept has been strengthened very recently by the discovery that Kupffer cells, Langerhans cells and pleural lung macrophages are similarly derived from the yolk sac- based precursors rather than bone marrow stem cells. While there are clearly many similarities between the two cell lineages, Schulz et al. (Gomez Perdiguero et al. 2012; Schulz et al. 2012) have shown several unique characteristics of macrophages derived from yolk sac compared to those derived from hemopoietic stem cells. The primary

differences are 1) the lack of dependence on the proto-oncogene, *myb*, in the development of the yolk sac precursor, 2) the expression by lineage cells of the transcription factor *maf*, and of the chemokine receptor, CX3CR1, 3) high expression of F4/80 and 4) low *Flt3* expression indicating a restricted dependence on Flt3 ligand for expansion. Data also suggest that the expression of myeloperoxidase (MPO) in DC may be restricted to yolk sac lineage cells (Scholz et al. 2004). The addition of this separate, independently renewable line of macrophagic cells in the body adds an interesting twist to our ability to distinguish the cell types that participate in the brain's immune response, including the possibility that microglia can form DCs that are unique when compared to hemopoietic lineage DCs.

Whether microglia or perivascular microglia/macrophages can become DCs remains unresolved. The conversion of monocytes/mononuclear phagocytes to a DC-like cell, often termed "inflammatory" DCs, has been a controversial idea, but is now generally accepted. The discovery that mononuclear phagocytes could generate DCs was originally made because of the scientific need for isolation of large populations of cDCs (Romani et al. 1996). This was accomplished by treatment of monocytes in culture with GM-CSF usually in combination with cytoactive factors such as TGFβ, IFNγ or IL-4. Monocytes treated in this manner produce DC-like cells that, on maturation, present antigen, express CD11c and can migrate to lymph nodes (van de Laar et al. 2012). Part of the controversy surrounding the firm identification of these cells as DCs has stemmed from the non-selectivity of CD11c as a DC marker. In addition, questions were raised about the translation of the in vitro finding to an in vivo condition. The recent use of genetic strains of mice expressing Lysozyme M coupled to EGFP strongly imply that DCs do not arise from monocytes under *normal* conditions but do arise from monocytes on exposure to an i*nflammatory* environment. (Liu et al. 2007; Hume 2008a, b; Jakubzick et al. 2008; Geissmann et al. 2010a; van de Laar et al. 2012).

A number of studies have used similar in vitro culture and differentiation techniques to demonstrate that microglia express markers of DCs. Fischer and Reichman (Fischer and Reichmann 2001) cultured adult brain microglia in the presence of GM-CSF for 6 days and found CD11c+cells within the cultured microglia. They further showed that the CD11c +cells were capable of T-cell stimulatory activity. Butovsky et al. (Butovsky et al. 2007) confirmed these observations by demonstrating a similar increase in CD11c expression for IL-4 or IFNγ-treated cultured microglia. In vivo confirmation has been obtained using flow cytometry on cell populations in diseased brain. In their study Beena et al. (Beena 2011) used brain lysates from mice infected with *Toxoplasma gondii* compared to uninfected mice. As judged by surface antigen profiles, the primary cell type expressed in normal, non-infected mice were typical of microglia. However in infected brain, multiple subtypes of CD11c +DCs were found. DC function was also tested by detecting increased proliferation of OT1 T-cells which are CD8+ T-cells prepared from a transgenic mouse (Wright et al. 2005). Thus, the combination of CD11c expression with the functional outcome supports the premise that microglia may be converted to DCs. The future development of unique cell specific sets of identifying markers will firmly establish this process for microglia, which is particularly important (as stated above) since microglia are not derived from the same hemopoietic precursors as monocytes.

Functions of monocyte/macrophage derived DCs

The maturation of DCs in an inflammatory environment is an important step in connecting the innate immune response in that tissue to the adaptive arm. As discussed above, one of the principle functions of DCs is to instruct T-cells which then carry out a specific subset of activities. These may be tolerogenic and thus subdue pro-inflammatory events or immunogenic and promote toxicity. TIP- DCs (TNFα-iNOS producing DC cells) are one example of an immunogenic monocyte/macrophage derived DC. These cells are formed during *Listeria monocytogenes* infection of spleen or *Trynanosoma bruceii* infection of the liver. The production of TNFα and NO by DCs is a major factor in pathogen clearance and is in addition to the M1 response associated with innate immunity. NO is a critical component to the immunotoxicity, not necessarily because of a direct toxic effect on the pathogens, but rather though NO's ability to regulate specifically the differentiation of Th-1 T-cells. Niedbala et al. (Niedbala et al. 2006) showed a concentration dependent increase in Th-1 cell populations in the presence of NOC-18, a well controlled and specific NO donor. Increased levels of Th-1 cells were found only at low NO levels while high levels of NO inhibited T-cell proliferation. High levels also impaired T-cell trafficking into the infected tissue, decreased E-selectin, an adhesion molecule involved in T-cell entry across membranes and inhibited indolamine dioxygenase (Thomas et al. 1994; Niedbala et al. 2006). Human NO levels produced by immune activated inducible nitric oxide synthase (iNOS) are much lower than NO levels found under similar conditions in rodents (Weinberg et al. 1995; Colton et al. 1996; Wink et al. 2011). Thus, the effect on Th-1 cells generated by low NO in humans provides a boost to the immunotoxic response during inflammatory challenges in humans. In contrast, for rodents that generate higher levels of NO, NO's effects are more varied. Interestingly, formation of TIP-DCs is dependent in large part on the interaction of CCL2 and its receptor CCR2. CCR2 deficient mice do not show the formation of TIP-DC in inflamed tissue (Serbina et al. 2003).

Immunosuppressive DCs also play critical roles in regulating the immune environment in an ongoing immune response. As described by Mellor and Munn (Mellor and Munn 2008) immunosuppression can create "immunoprivilege" where the tissue has limited responsiveness to foreign or self antigens. Immunosuppression is of great value in the CNS to reduce damage caused by pathogens or by untoward responses to self-antigens or innocuous substances. Even in the "resting" state, a number of suppressive mechanisms are found in the CNS that serve to signal challenges and to restrain immune responsiveness (Carson et al. 2006; Ransohoff and Cardona 2010). During disease, however, multiple types of suppressive cells including pDCs and polarized macrophages such as alternatively activated (M2) macrophages play a role in shaping the immune response in the complex inflammatory milieu. While immunosuppressive macrophage derived DCs in inflamed tissue show cellular heterogeneity, there are at least 2 subtypes that have been routinely identified. These are tumor infiltrating regulatory DCs (TIDC) and myeloid derived suppressor cells (MDSC), both of which are contributors to tumor genesis in the CNS as well as elsewhere in the body. These subtypes are primarily characterized by their profile of surface antigens and can be reasonably distinguished by the expression levels of CD11c, MHCII and CD33 (Norian et al. 2009; Lechner et al. 2011). TIDCs express high levels of CD11c, and MHCII with low levels of CD33 while MDSC express high CD33 but low to no CD11c or MHCII. As we have discussed, however, using surface antigens as an identifying criterion alone is problematic. Interestingly, CD33 represents a family of sialic acid binding immunoglobulin like lectins (Siglec) which are ITIM (immunoreceptor tyrosine based inhibitory motifs) receptors. ITIMS and its functional opposite, immunoreceptor tyrosine based activating motifs, or ITAMS, are expressed on multiple immune cells including immature and mature DCs, B cells, activated T cells and natural killer (NK) cells as well as on many tumor-based immune cells. CD33 is activated by binding to sialylated glycoproteins or glycolipids (collectively called glycans), which are molecules commonly associated with extracellular matrix and cell surface glycocalyx, although specific binding partners are unknown (Rabinovich et al. 2007b; Walter et al. 2008a, b; Di Lella et al. 2011; Mascanfroni et al. 2011; Crocker et al. 2012). Along with C-type lectins and galectins, the large siglec family of receptors is a rapid evolving, evolutionarily adaptable system that participates primarily in immunoregulation. Siglecs respond to specific brain glycoproteins found in myelin and have recently been found as a critical gene for AD from the genome wide association studies on humans with AD (Kamboh et al. 2012).

The immunosuppressive mechanisms used by TIDC and MDSC are currently thought to be primarily tolerogenic, that is, they alter the number and responsiveness of T-cells, increase the number of T-regs and alter the secretion of IFNγ, TGFβ or other cytoactive factors that are critical to the development of immunosuppression (Gabrilovich and Nagaraj 2009; Gregory et al. 2009; Nagaraj et al. 2009). The mechanisms to control T-cells used by these cells are the same as those used by cDCs and T-regs and are primarily based on nutrient deprivation. For example, increased utilization of arginine by increased expression of Arginase 1 and increased utilization of tryptophan by increased expression of indolamine dioxyenase (IDO) both generate amino acid starvation and are used to kill surrounding cells. A number of excellent reviews are available for more detailed information (Rabinovich et al. 2007a; Kahler and Mellor 2009). It is important to realize, however that immunosuppressive DCs themselves can also influence surrounding tissue by mediating the production of anti-inflammatory cytokines and other immunosuppressive pathways. Furthermore as shown particularly in tumors, the population of immunosuppressive cells increases significantly in the affected tissue thereby promoting immune protection of the "immunogen", i.e., the tumor cells, rather than immune mediated clearance (Sinha et al. 2005a, b; Gabrilovich and Nagaraj 2009).

Final thoughts

The description of the CNS as "immune privileged" was based on the blood brain barrier and the normally low immune responsiveness of the brain and spinal cord. There are clearly a number of inherent mechanisms involved in this specialized status and DCs participate in preserving privilege while also fighting infections and responding to injury. Similarly to the innate immune response, antigen-specific directed-responses by DCs provide both defense-based killing mechanisms and counter -regulatory "brakes" to the system. Also similarly to the innate response, both the defense and protection can be exploited or corrupted. Imperfections in either side can be useful but also create disease. For example, decreasing the strength of the immunogenic response by shifting the balance to immunosuppressive effectors as seen in Theiler's murine encephalomyelitis virus (TMEV-a type of demyelinating disease) infected SJL/J mice, promotes disease (Richards et al. 2011). Although initial toxicity is decreased, the increased immunosuppressive pathway (in this case T-regs that kill CD8+ T-cells) does not eliminate virus but instead slows the time course of disease, changing from an acute to a chronic profile. Whether the effect is located to lymphoid tissue outside of the CNS, to tertiary lymphoid tissue within the CNS or to

the brain parenchyma, the importance of this finding to chronic CNS disease cannot be underestimated.

Conflict of interest The authors declare they have no conflict of interest.

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