Immunology Letters 209 (2019) 4–10

Contents lists available at ScienceDirect

Immunology Letters

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

The role of ocular dendritic cells in uveitis

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ARTICLE INFO

Keywords:
Uveitis
Dendritic cells
T cells
Confocal microscopy

ABSTRACT

Dendritic cells (DCs) act as a bridge between innate and adoptive immunity. They are widely distributed in various tissues and organs. Resident ocular DCs are found in the peripheral margins and juxtapapillary areas of the retina, usually in an immature state. During inflammation, DCs are activated and participate in the development of uveitis, an ocular inflammatory disease. Herein, the characteristics and status of DCs in uveitis, the possible factors affecting the status of DCs, and the clinical methods for detecting the DCs in patients are described.

1. Introduction

Uveitis is an inflammatory disease, which can cause blindness in humans [1,2]. In developed countries, uveitis affects approximately two per 1000 people. 35% of the patients have severe visual impairment [3]. Uveitis is the inflammation of the uveal tract (i.e., iris, ciliary body and choroid), and results from a heterogeneous group of disorders with varying etiologies and pathogenic mechanisms [4]. The cause of this disease is correlated with immune disorders, including increased $CD4^+$ T cell infiltration in eyes leading to pathological damage of ocular tissue [5–8], and is associated with chronic and recurrent ocular complications. Under normal physiological conditions, the aqueous humor, cornea and a few immune cells form a natural immune barrier to prevent the invasion by foreign pathogens [7]. When inflammation occurs, these tissues are destroyed, or pathogenic microorganisms enter the eye tissues by blood flow, or autoimmune responses are induced after exposure to auto-antigens, which trigger an increase in immune cells in the eye, causing inflammation [7,8]. Meanwhile, the activation of inactivated immune cells in the eye tissues leads to inflammation. Recently, dendritic cells (DCs) were found to exist in normal eyes and their role has been gradually recognized. Herein, we reviewed the status of DCs in the ocular immune system.

2. The characteristics of dendritic cells

DCs are very effective antigen presenting cells (APCs), with the unique ability to prime and activate naive T lymphocytes [9,10]. Based on their functions, DCs are divided into three types, including immature DCs (imDCs), mature DCs (mDCs) and regulatory DCs (DC_{reg}). Under physiological conditions, DCs are widely distributed in various tissues and organs. Most of them are imDCs, which express high level of major histocompatibility complex-I (MHC-I), but low level of MHC-II and co-stimulatory molecules including CD40, CD54, CD58 and CD80, as well as low or no CD86. These cells have strong phagocytic ability, and secrete tumor necrosis factor-α (TNF-α), interleukin (IL)-12, IL-6 and other cytokines. The imDCs have high endocytic capacity, but low capability to stimulate T cells. However, imDCs can be activated to become mature DCs that typically express high levels of "activation" markers (MHC-II, CD54, CD80, and CD86) and possess strong T-cell priming ability [11]. The regulatory DCs are known to control T-cell responses [11,12]. $CD11b^{high}$ $CD11c^{low}$ Ia^{low} DCs are believed to be a subset of regulatory DCs that can inhibit T-cell activation by inducing nitric oxide (NO), IL-10, or indoleamine 2,3-dioxygenase (IDO). Additionally, $CD11c^+$ $CD3^-$ CD25- DCs are another subset of regulatory DCs that can decrease the expansion of γδ T cells and activation of $IL\text{-}17^+$ IRBP-specific T cells in autoimmune experimental uveitis (EAU) [13]. However, the existence of these regulatory DCs in the eyes and their function in EAU remain unknown. Different subsets of DCs may play different roles during different developmental/functional stages [14,15]. Regulatory DCs were found to balance the immune response in several organs (e.g., lung, spleen, and liver) [16–18]. The status of DCs changes according to the dynamic changes in the immune microenvironment. Regulating the status of DCs could be beneficial for the treatment of various diseases.

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https://doi.org/10.1016/j.imlet.2019.03.016
Received 3 October 2018; Received in revised form 19 March 2019; Accepted 25 March 2019
Available online 26 March 2019

Table 1
Characteristics of DCs in the eyes.

Type	Phenotype	Location	Function
imDCs	Low levels of MHC; CD80, CD86, CD40, CD54 [19] 33D1 [20] TLR4, TLR2 [24,51] CD1c [52]	Corneal epithelium and stroma; iris matrix; around the ciliary epithelium and the choroidal cavity; Aqueous humor; Peripheral cornea [19,20,22,23,29,50]	Uptake of antigen Immune surveillance Immunomodulatory [19,20,24,51]
mDCs	High levels of MHC, CD80, CD86, CD40, CD54 [19,20,22,23,25,50]	Choroid; Aqueous humor; Central cornea [19,20,22,23,29,50]	Play an inflammatory role by secreting cytokines; migrate into LN to activate immune response [19,20,24]

3. Dendritic cells in the eyes

DCs are reported to exist in the peripheral margins and juxtapapillary areas of the retina in mice and rats [19–21]. Human DCs are normally found within the central and limbal epithelia, the basal lamina, and the sub-basal nerve plexus layer, at a depth of 40–60 μm [22,23]. The activation of DCs was determined based on morphology. Mature, activated DCs possess a slender cell body from which a network of long membrane processes extend, resembling dendrites of nerve cells. Immature DCs have a large body with fewer and shorter processes, if any. The peripheral cornea is populated by both these phenotypes, whereas the central cornea only has the immature phenotype. These resident DCs are in an immature state in iris tissue [21]. Both mouse and human DCs express MHC-II/HLA (human lymphocyte antigen), TLR4 and its associated LPS receptor complex, and are thought to be strategically placed along blood vessels to capture disease-causing antigens [19,20,24]. The function of DCs in quiescent retina is to promote generation of Foxp3(+) T cells and inhibit activation of naive T cells by splenic DCs and antigens [19]. Under physiological conditions, these cells are in an immature state, and are involved in immune surveillance (Table 1).

However, in the pathological state, DCs act as unique APCs to activate naïve T cells, which are also involved in the pathogenic process of uveitis [19,25–27]. In the mouse model of uveitis, ocular DCs were activated, and functionally mature DCs were found in the choroid [25], which were believed to generate antigen-specific Th1 and Th17 cells. In the aqueous humor of patients, mature DCs were found and were characterized by elevated HLA-DR [28,29]. Mature DCs pulsed with uveitogenic antigens could induce the development of EAU [19]. Pretreatment with fixed imDCs, but not fixed mature DCs, ameliorated the progression of EAU by inhibiting uveitogenic $CD4^+$ T cell activation and differentiation [26]. Additionally, impairing the maturation of DCs with drugs could prevent the generation of antigen-specific Th1 and Th17 cells to attenuate EAU [30]. Moreover, in vitro induced regulatory DCs suppressed the development of EAU [31]. These data indicated that regulating the status of DCs could be beneficial for the treatment of uveitis.

Regulatory DCs have been tested in several autoimmune diseases, but they are rarely mentioned in the study of ocular DCs. Splenic DCs could alleviate the symptoms of EAU by decreasing the expansion of γδ T cells and Th17 autoreactive T cells [13,31]. Autologous DCs were exposed to citrullinated peptide antigens in the presence of NF-κB inhibitor to induce immunomodulatory properties [32]. Several types of DCs with negative regulatory functions have been reported [33]. Most regulatory DCs can be generated in vitro by co-culture with stromal cells or immunosuppressive agents, including IL-10 or transforming growth factor β (TGF-β), or other substances such as vitamin D receptor ligands, vasoactive intestinal peptide, and thymic stromal lymphopoietin (TSLP) [12,16,34–37]. The surface protein TIGHT could induce DCs to produce IL-10 to suppress T cell activation, thereby exerting immunosuppressive effects [38]. Galectin-1 endows DCs with regulatory potential by producing IL-27, followed by inducing IL-10–producing T cells [39]. Additionally, the microenvironment in certain tissues can also induce DC development, and affect the function of DCs [16–18,34,40]. Previous studies demonstrated that splenic or lung microenvironment can drive mature DCs or stem cells to differentiate into DC_{reg} [16–18,34]. In the eye of mice, retinal pigment epithelial (RPE) cells can produce higher levels of IL-1Ra to suppress DC activation [41]. Corneal stromal cells (CSCs) could inhibit DC maturation by secreting TGF-β [42]. At the ocular surface, the expression of TSLP was linked to allergic conjunctivitis in a mouse model or patients with various types of allergic conjunctivitis in a Th2-response related manner [43–45]. TSLP could target DCs in the cornea to play a protective role in *P. aeruginosa* keratitis through IL-23/IL-17 signaling pathway [46]. These regulatory DCs induce T cell or tissue tolerance by secreting immunosuppressive cytokines, such as IL-10 and TGF-β, IDO or cell-cell contact through Fas-FasL [36,47–49]. Ocular microenvironment is essential for sustained ocular tolerance. The mechanisms underlying ocular microenvironment-mediated inhibition of DC maturation or induction of regulatory DCs in eyes need further study.

4. Possible factors affecting ocular DCs

Many factors could affect the status of DCs. Studying the factors that affect ocular DCs could improve the understanding of the pathogenic mechanism of DCs in eyes, and provide new targets for uveitis therapy. DCs exhibit plasticity in developing either pro-inflammatory or immune-regulatory characteristics depending on their environment. Activation of the resident DCs by foreign pathogens, increase in inflammatory cytokines, components of aqueous humor, cell-cell contact, etc., participate in regulating the status of ocular DCs.

4.1. Aqueous humor

Aqueous humor is produced by ciliary epithelial cells, and plays a significant role in sustaining the immune tolerance microenvironment [29,53,54]. In the normal eyes, aqueous humor is rich in TGF-β, IL-10 and NO, which sustain the tolerance environment of eye. However, multiple cytokines and chemokines were found within the aqueous humor of uveitis patients, including IL-1β, IL-6, IL-10, IL-17α, IL-21, IL-25, IL-31, IFN-γ, TNF-α, and sCD40 L [54,55]. Except for IL-10, these molecules might correlated with disease activity in patients. In the EAU experimental model, aqueous humors collected at disease onset failed to suppress T cell proliferation [56]. At the early stage, IFN-γ, IL-8 and TNF-α were produced by aqueous humors that activated mature DCs, and contributed to the inflammation [56]. At the late stage, the recovery could be attributable to a greater role of the immunosuppressive levels of IL-10, which affect the activation of DCs [29]. Soluble CD83 (sCD83) level was also increased in the aqueous humor of the EAU mouse model [57,58]. It can indirectly affect the cytoskeleton and the calcium release in DCs to suppress the activation of T cells [57]. Besides numerous inhibitory cytokines, the aqueous humor of animals and humans also contains soluble molecules such as NO, IDO, PGE2, etc [59–63]. The synergistic effects of them were involved in the inhibitory

role of aqueous humor. Thus, aqueous humor can affect the activation of DCs, leading to proliferation and activation of T cells. These results demonstrated that local conditions in the retina determined APC function and affected the pathogenesis of EAU by T cells [19,29]. Thus, the inflamed ocular microenvironment contributes to immune cell responses and intraocular inflammation [28,64]. The dynamic changes of soluble molecules in the aqueous humor influence the development of disease. The balance of inflammatory and anti-inflammatory soluble molecules determines whether the disease will worsen or subside.

4.2. Cell-cell crosstalk

During inflammation, numerous natural killer (NK) cells, DCs, γδ T cells and $CD4^+$ T cells infiltrated into the inflamed eyes of the animal model [19,65–67]. These immune cells could interact with resident DCs to promote their activation and maturation. NK cells are innate immune cells that kill target cells and produce pro-inflammatory cytokines, including IFN-γ, granzyme and perforin. The interaction between NK cells and DCs leads to activation and maturation of both cell types and production of cytokines, including IFN-γ and TNF by NK cells, and IL-12, 15 and 18 by DCs [68–71]. The resident DCs are activated and migrate to the draining lymph nodes, where they produce IL-12 and IL-18 to activate NK cells to produce IFN-γ, which in turn induces CXCR3 ligands and IL-27 expression in DCs [66]. This recruits peripheral CXCR3-expressing NK cells and induces them to produce more IFN-γ, which in turn will induce more IL-27 secretion from DCs, in a positive feedback loop [66]. Moreover, IL-27 along with IL-18 from DCs promote NK cells to secrete IFN-γ [72]. However, over-expression of IFN-γ could induce tolerance in DCs, which would suppress T cells and cure the disease. This is the negative feedback loop. If the positive or negative feedback loops are disrupted, it will lead to relapse and chronic infection.

γδ T cells are a unique and conserved population of lymphocytes that contribute to many types of immune responses. They form a bridge between innate and adaptive immunity [73]. Activated γδ T cells promote maturation of DCs by cytokine secretion or cell-cell contact. The $CD11c^+CD3^-$CD25- DC subset accounted for the decreased activation and expansion of γδ T cells, leading to decreased activation of IL-17^+ IRBP-specific T cells in the EAU mouse model [13]. It is likely that the recorded changes are accompanied by several reciprocal interactions between γδ and αβ T cells, and between γδ T and DCs. LFA-ICAM-1 interaction between γδ T and DCs was found to be helpful for γδ T-DC contact [74]. IFN-γ secreted by γδ T cells might facilitate the activation and maturation of DCs.

Additionally, mature DCs from draining lymph nodes could migrate into the eyes to affect the activation of resident ocular DCs by cytokines [13,52,75] (Fig. 1). Immature ocular DCs take up the antigens in the eye to become mature and secret cytokines to influence the intraocular immune microenvironment. These activated ocular DCs also migrate into lymph nodes to induce antigen specific T cell activation or enhance NK cell or γδ T cell activation. Infiltrating cells in the eyes also associate with CSCs or RFP to influence the ocular microenvironment [41,42] (Fig. 1). Cytokine axis and the recognization between receptor and ligand on cell-cell contact are important for cell-cell regulation. The mechanism of cell-cell regulation in the eyes needs further study.

4.3. Cytokines

Cytokines are important factors that influence the status of DCs. The cytokines come from the aqueous humor, resident cell secretion, or effusion from the blood or lymphatic vessels. Granulocyte-macrophage colony stimulating factor (GM-CSF) along with IL-4 are important stimulators for DC maturation. RPE cells secrete GM-CSF that affects the function of choroidal DCs. TNF-α can promote the expression of GM-CSF receptors on the surface of $CD34^+$ stem cells to increase the expression of CD86 and CD40 on the surface of the DCs to promote their differentiation and maturation [77]. IL-10 and TGF-β down-regulate the expression of co-stimulatory molecules on DC surface to inhibit the maturation of DCs [20,78]. The aqueous humor is rich in IL-10 and TGF-β, which maintain the tolerance of DCs. IL-37 can downgrade the expression of CD40, CD80 and CD86 on DCs, and inhibit DC proliferation by inhibiting the extracellular regulated protein kinases (ERK) 1/2, c-Jun N-terminal kinase (JNK) and p38-MAPK pathway to suppress the Thl and Thl7 responses [79].

Th1 is believed to be important inflammation effectors for uveitis. The ratio of Th1 and Th17 was correlated with the development of uveitis [80]. Higher percentage of Th1 would facilitate remission of uveitis, while lower percentage of Th1 would facilitate pathogenesis of uveitis. Th1 produce copious amounts of IFN-γ, which increase in the serum and humor of uveitis patients and EAU model [55,80]. The expression of IFN-γ mRNA is temporally correlated with the onset of uveitis, suggesting involvement of IFN-γ in the induction and pathogenesis of uveitis [81,82]. IFN-γ may activate distinct immunomodulatory pathways in mice and rats during uveitis. IFN-γ accelerates the inflammation of EAU in transgenic rat [83] but IFN-γ protects the development of EAU in mouse [84,85]. IFN-γ is secreted by Th1 cells, γδT cells and NK cells, and it could induce DC activation and maturation. However, higher dose of IFN-γ and /or longer IFN-γ stimulation was believed to increase the tolerance of DCs to induce IDO expression [86–88]. The exact mechanism of IFN-γ on the status of DCs in EAU needs further studying.

4.4. Surface molecules on DCs

Surface receptors on DCs can also influence the status of DCs. The activation of Toll-like receptor 4 (TLR4) signaling pathway is important for DC maturation. TLR4 is expressed on the DCs in iris, but not on DCs in other ocular tissues [24]. The activation of TLR4 pathway would initiate the activation of DCs [24]. Additionally, TLR2–P38–MAPK pathway activation also promoted the maturation of DCs, which further activated Th17 in EAU [51]. The external antigen activates the corresponding ligand of lectin C receptor, which promotes mouse DC maturation, secretion of IL-10 and IL-2, and further regulates T cell activation and differentiation. Additionally, higher CXCL16 expression was found on DCs of patients with Behçet's disease (BD), and was correlated with the secretion of IFN-α [89]. CXCL16 is a member of CXC chemokine, and plays a role in binding, uptake and accumulation of CpG D ODN in early endosomes but not lysosomes, thereby causing high interferon-alpha secretion.

The balance between activating and inhibitory signals is important for immune regulation of cellular activation. TLRs including TLR2, TLR4 and TLR7 are essential for DC activation by enhanced MAPK/NF-κB signal pathway [24,27,51]. Co-stimulatory molecules and MHC are also important for DC activation. Tumor necrosis factor receptor super family member 9 (TNFRSF9) was associated with the maturation of DCs from an immature to antigen-presenting phenotype [90]. However, many inhibitory signals expressed on DCs regulate the status and function of DCs, but few have been studied in the ocular DCs. For example, dendritic cell immunoreceptor (DCIR) is an ITIM-containing CLR that is reported to be associated with systemic lupus erythematosus and experimental autoimmune encephalomyelitis [91–93]. Paired immunoglobulin-like receptor-B (PIR-B) is another inhibitory receptor that comprises multiple ITIMs, and has been demonstrated to modulate IFN-I response and DC maturation [94–97]. PDL-1, FasL, CD155, etc., are also inhibitory receptors expressed on DCs [98–102]. They may play an important role in autoimmune disease development and have potential for intervention. However, little is known about their expression and contribution towards uveitis pathogenesis.

5. Clinical detection of DCs in the eyes

Owing to the important role of ocular DCs in eyes, the clinical

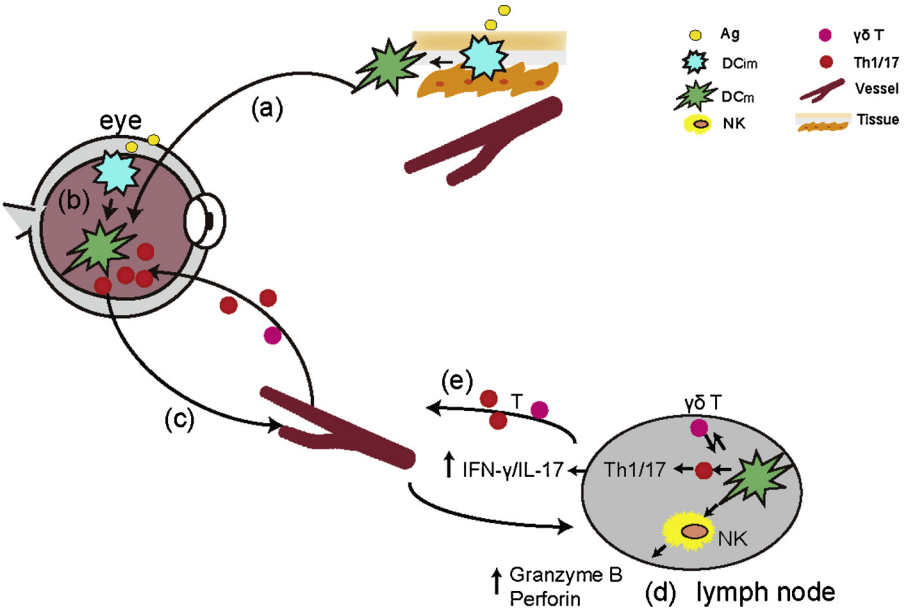

Fig. 1. The function of DCs in eyes. Mature DCs (DC_m) increase in the eyes of the EAU model, and these cells originate by two ways: (**a**) Immature DCs (DC_{im}), circulating in the peripheral blood and tissues, are activated to migrate into eyes under the action of chemokines or cytokines; and **(b)** immature ocular DCs take up the antigens in the eye to become mature and express high levels of MHC and co-stimulatory molecules. (**c**) DC_m migrate into draining lymph nodes via the blood vessel or lymphatic vessels. (**d**) In the draining lymph node, DC_m educate naïve T cells to become Th1 and Th17 cells depending on the signals. DC_m also promote NK cells to secret granzyme B and perforin [58,66,76]. Activated γδ T cells migrate into lymph nodes to enhance the function of DCs. (**e**) Educated T cells migrate into eyes to secrete cytokines, which causes non-infectious uveitis.

detection of ocular DCs is widely used to judge the severity of the disease. Optic neuropathy, retinal pathology with maculopathy and retinal neovascularization have been described in uveitis [103,104]. The use of instruments to detect the density of ocular immune cells and neurocyte damage has been extensively studied. Since DCs exhibit the typical morphology of synaptic processes after activation, confocal microscopy was used to examine the presence of DCs in the eyes. DCs were examined by confocal microscopy to determine their morphology, distribution, and density in both the central cornea and limbus [22,23,50].

Studies using optical coherence tomography (OCT) have demonstrated a significant reduction in the thickness of the retinal nerve fiber layer [105], ganglion cell and inner plexiform layers in uveitis patients [106]. However, the cellular morphology was not clearly visualized. So confocal microscopy was developed to detect DCs, in order to better evaluate the immune status of patients. In vivo confocal microscopy was performed on patients under topical anesthesia with 0.4% oxybuprocaine eye drops using a digital corneal confocal laser-scanning microscope (HRT III Rostock cornea module; Heidelberg Engineering GmbH, Dossenheim, Germany). The confocal examination lasted five minutes, and none of the patients experienced significant complications at the end of the session. The mean density of DC in the central cornea and the entire limbus of every patient was obtained after examination [23]. In vivo confocal microscopy was also used to detect different subtypes of anterior uveitis, in order to explore the inflammatory cells [22].

Corneal confocal microscopy (CCM) is a non-invasive imaging technique, which allows detailed quantification of the corneal subepithelial nerve plexus and DCs, which are reported to be increased in inflammatory processes [107]. In vivo CCM can detect corneal small fiber damage and immune cell density. It was recently used to assess central corneal sensitivity, corneal sub-epithelial nerve plexus morphology and DC density in patients with BD, a type of autoimmune uveitis [50]. CCM demonstrated corneal sub-basal nerve fiber loss and increased DC density in the eyes of patients, providing a non-invasive method to identify peripheral neuropathy and inflammation in patients with BD [50]. The development of detection technology will promote the clinical detection of DC in eyes, the judgment of uveitis diseases, and the underlying mechanism of DCs in the eyes.

6. Summary

Uveitis is commonly classified by anatomical location of inflammation into anterior, intermediate, posterior, and pan-uveitis. About 30–45% of uveitis patients are believed to have a systemic disease, which is usually ignored by the doctors, owing to the subtle systemic symptoms. Some uveitis patients have rheumatological, Crohn's or infectious diseases [4]. Thus, uveitis is a systemic disease that is correlated with disorder of immune response. The immune disorder in uveitis patients is mainly caused by the increase in Th1 and Th17 cells involved in adaptive immunity. Many recent studies focused on the disorders of innate immunity in uveitis, which includes DCs, NK cells and γδ T cells. Innate immunity is the first line of defense of the immune system. Dysfunction of innate and adaptive immune systems can result in unregulated, inappropriate and detrimental autoimmune diseases including uveitis [108]. DC is an important immune cell in innate immunity. Owing to its special morphological characteristics and unique function, DC has become a new target for diagnosis and treatment. Cell-based therapy using ex vivo manipulation of mature DCs or regulatory DCs has been used in autoimmune disease to induce tolerance [109–111]. Thus, in-depth study of the mechanism of DCs in uveitis is required to find a new target to regulate the ocular DCs in order to provide a new strategic treatment for uveitis. The visual detection of DCs in eyes will be helpful for the evaluation of the immune status of uveitis and the judgment of disease progression. This could become a research hotspot in the future.

Funding

This work was supported by grants from the Natural Science Foundation of China (No.81500710); the key research and development plan of Shandong Province (No.2016GSF201088); projects of medical and health technology development program in Shandong province (No.2015WS0194); the science and technology program from Shandong Academy of Medical Sciences (No. 2015-25); and the Innovation Project of Shandong Academy of Medical Sciences.

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