

REVIEW

Involvement of B cells in non-infectious uveitis

Justine R Smith¹, Andrew J Stempel¹, Arpita Bharadwaj² and Binoy Appukuttan¹

Non-infectious uveitis—or intraocular inflammatory disease—causes substantial visual morbidity and reduced quality of life amongst affected individuals. To date, research of pathogenic mechanisms has largely been focused on processes involving T lymphocyte and/or myeloid leukocyte populations. Involvement of B lymphocytes has received relatively little attention. In contrast, B-cell pathobiology is a major field within general immunological research, and large clinical trials have showed that treatments targeting B cells are highly effective for multiple systemic inflammatory diseases. B cells, including the terminally differentiated plasma cell that produces antibody, are found in the human eye in different forms of non-infectious uveitis; in some cases, these cells outnumber other leukocyte subsets. Recent case reports and small case series suggest that B-cell blockade may be therapeutic for patients with non-infectious uveitis. As well as secretion of antibody, B cells may promote intraocular inflammation by presentation of antigen to T cells, production of multiple inflammatory cytokines and support of T-cell survival. B cells may also perform various immunomodulatory activities within the eye. This translational review summarizes the evidence for B-cell involvement in non-infectious uveitis, and considers the potential contributions of B cells to the development and control of the disease. Manipulations of B cells and/or their products are promising new approaches to the treatment of non-infectious uveitis.

Clinical & Translational Immunology (2016) 5, e63; doi:10.1038/cti.2016.2; published online 5 February 2016

Autoimmune and autoinflammatory uveitis is a heterogeneous group of diseases characterized by non-infectious inflammation within the eye.¹ Although uveitis is an uncommon medical condition in the general community, it is a leading cause of visual disability and loss of sight,² and it is associated with a marked reduction in the patient's quality of life.³ Conventional immunosuppressive drugs, delivered systemically or locally, are not universally effective for uveitis, and side effects further limit their use.⁴ Today considerable research is focused on understanding the basic mechanisms of the inflammation and developing biological approaches that target key pathogenic cells or molecules.

The involvements of helper T lymphocytes and monocytes or macrophages in uveitis have been well established in many studies using experimental models, and through observations made in patients suffering from immune-mediated uveitis.^{1,5,6} In contrast, there has been relatively little investigation of the participation of B lymphocytes in the disease. However, scattered across the peer-reviewed literature are reports that implicate B cells in various forms of experimental and clinical uveitis. In addition, B-cell-targeted treatments have recently been used effectively in the clinic for some recalcitrant forms of intraocular inflammation.^{7–9}

This translational review presents the lines of evidence for B-cell involvement in non-infectious uveitis and provides discussion of the potential roles of B cells in the pathogenic and regulatory mechanisms of disease. The review begins with an overview of uveitis, and summaries of B-cell immunology and unique aspects of ocular

immunology. In the conclusion to the review, recommendations are made for future directions of study in this field.

HUMAN NON-INFECTIOUS UVEITIS AND THE EXPERIMENTAL MODELS

Definition and classification of uveitis

Uveitis is a diverse group of inflammatory diseases that involve one or more of the tissues within the eye. By convention,¹⁰ uveitis is classified anatomically, according to the primary clinical site of the inflammation: 'anterior uveitis' is based in the anterior chamber; 'posterior uveitis' is based in the retina or choroid; 'intermediate uveitis' is based in the vitreous (Figure 1). When the severity of inflammation at two tissue locations cannot be distinguished, these terms are combined (for example, anterior and intermediate uveitis). However, when inflammation is present throughout the eye, with no tissue site predominating, the term 'panuveitis' is applied.

Inflammation within the eye may be infectious or non-infectious in nature.^{1,11} Often a specific cause is identified, through consideration of the location of the inflammation, specific ocular signs, clinical course, and patient demographics and co-morbidities. Many infectious agents, including viruses, bacteria, fungi and protozoa, are causes of uveitis. However, infectious uveitis will not be considered further in this review.

Non-infectious uveitis may be the component of a systemic inflammatory disease, or it may be isolated to the eye.^{1,11} The systemic diseases most often associated with uveitis include: sero-negative

¹Eye & Vision Health, Flinders University School of Medicine, Adelaide, South Australia, Australia and ²Vollum Institute, Oregon Health & Science University, Portland, OR, USA
Correspondence: Professor JR Smith, Eye & Vision Health, Flinders University School of Medicine, Flinders Medical Centre Room 4E-431, Flinders Drive, Bedford Park, South Australia 5042, Australia.

E-mail: justine.smith@flinders.edu.au

Received 8 November 2015; revised 4 January 2016; accepted 4 January 2016

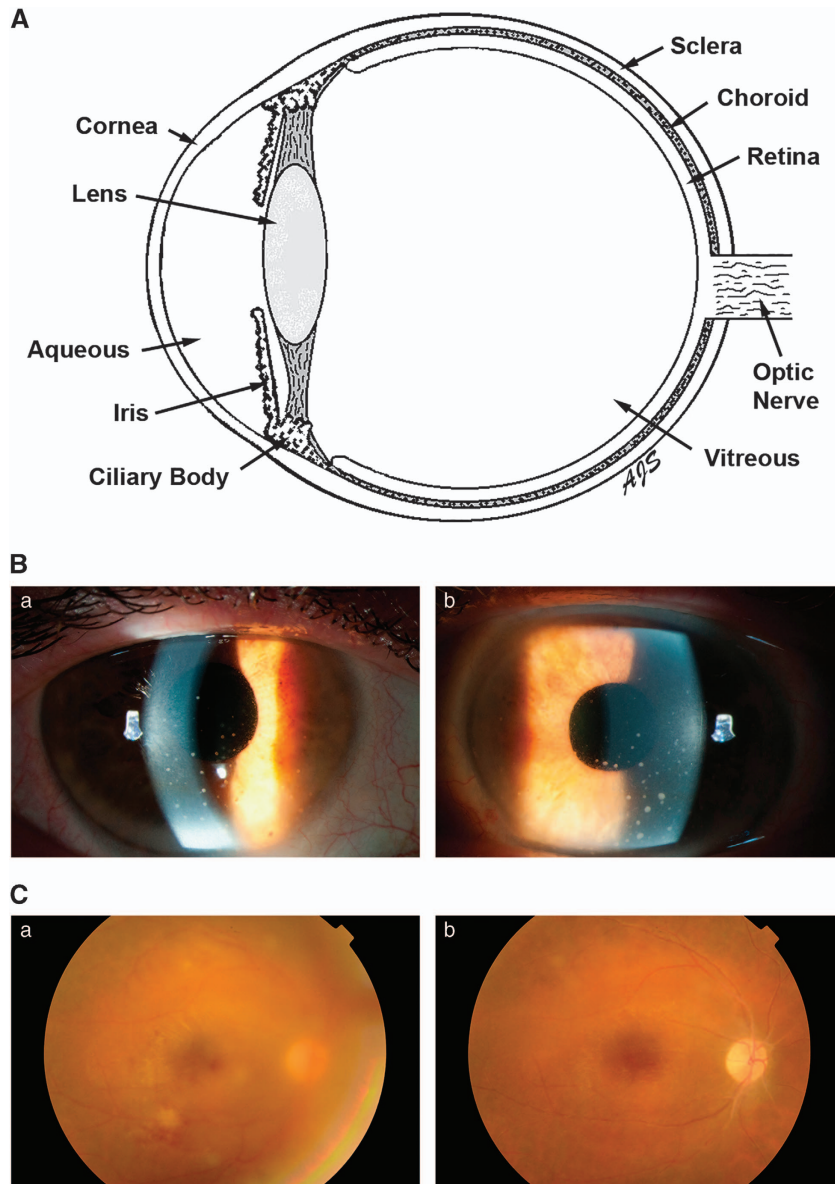


Figure 1 (A) Cartoon of the human eye in cross-section. Anterior uveitis is based in the anterior chamber, which is the space bordered by the cornea, the iris and the lens, that is filled with aqueous. Posterior uveitis is based in the retina and/or choroid. Intermediate uveitis is based in the vitreous. (B) Clinical photographs of the right (a) and left (b) anterior eyes of a patient with anterior uveitis. Circular white spots (keratic precipitates), formed by collections of leukocytes, are present on the interior surface of the cornea. (C) Clinical photographs taken through the dilated pupil of the right posterior eye in a patient with posterior uveitis. When uveitis is active (a), there are fluffy white patches of retinal inflammation with hemorrhages, and the view is hazy due to secondary inflammation in the vitreous. As the uveitis goes into remission (b), the vitreous inflammation resolves, and there is a crisp view of the retina, which is without whitening or hemorrhages.

HLA-B27-positive spondyloarthropathies; juvenile idiopathic arthritis; sarcoidosis; multiple sclerosis; inflammatory bowel disease; tubulointerstitial nephritis; Behçet disease; and Vogt–Koyanagi–Harada syndrome. Relatively rare, but recently highlighted as inherited syndromes that include non-infectious uveitis, are: familial juvenile systemic granulomatosis and neonatal-onset multisystem inflammatory disease (NOMID).⁶ Systemic vasculitis seldom co-exists with uveitis, although it is commonly associated with scleritis, which is an inflammation of the external scleral coat of the eye.¹² Diseases confined to the eye may have characteristic clinical pictures. This applies particularly to the ‘white dot’ forms of uveitis, including entities such as birdshot retinochoroidopathy and serpiginous

choroidopathy, which present with focal inflammation of the retina and/or choroid.¹³

Current management of non-infectious uveitis

Non-infectious uveitis is often challenging to manage, requiring drugs to suppress the abnormal immune response within the eye.⁴ The first treatment for most patients is corticosteroid, which may be delivered to the anterior eye by eye-drop, but requires either injection around (periocular) or into (intravitreal) the eye, or systemic administration, for intermediate or posterior uveitis. The side effects of corticosteroid generally limit the duration of such treatment. Corticosteroid given systemically has diverse side effects, such as weight gain with

cushingoid features and skin striae, psychiatric disturbances, accelerated cardiovascular disease and bone pathology. Locally delivered corticosteroid may precipitate or progress opacification of the lens (cataract) and/or elevate the intraocular pressure, which ultimately may irreversibly damage the optic nerve (glaucoma).

When extended anti-inflammatory intervention is needed, patients are prescribed 'conventional immunosuppressive drugs'.⁴ Drug classes include anti-metabolites, which disrupt nucleic acid synthesis (for example, methotrexate, azathioprine and mycophenolate mofetil), and calcineurin inhibitors, which reduce proliferation and activation of immune cells (for example, cyclosporine). These drugs achieve control of the inflammation within 12 months in just 30–51% of patients, and to maintain control, many of those individuals require additional treatment with corticosteroid.^{14–17}

Over the past decade, 'biologic immunosuppressive drugs' that inhibit specific inflammatory mechanisms and that have revolutionized the course of systemic inflammatory diseases, have also been employed to treat non-infectious uveitis. In particular, antibodies that target the inflammatory cytokine, tumor necrosis factor (TNF)- α , are being used with increasing frequency to treat recalcitrant uveitis. The use of antibody-based TNF blockade in uveitis was discussed in a recent expert panel review of 400 publications over 15 years.¹⁸ In essence, patients with various forms of non-infectious uveitis who fail conventional immunosuppressive drugs frequently show response to this treatment. Challenges include the high cost of the medication, and the potential for life-threatening side effects, including serious infections, new autoimmune disease and malignancy, particularly for uveitis that is confined to the eye. Hypersensitivity reactions and immune-mediated drug resistance may also complicate TNF blockade. Multiple other biologic immunosuppressive drugs with a range of targets (for example, lymphocytes, inflammatory cytokines and co-stimulation) have been used to treat uveitis, but in relatively small groups of patients and/or at relatively few centers.⁴

Burden of uveitis

Uveitis is a cause of substantial visual morbidity that reduces quality of life and has a high economic cost. The incidence of uveitis is 17–52/100 000 person years in Western nations, and higher in the developing nations.¹ Uveitis causes vision loss in 70% of individuals who present to a specialist service, with 55% of these persons experiencing legal blindness; and uveitis begins during the working years in up to 90% of patients.² Thus, based on calculations made with US data, the total annual cost of blindness from uveitis equals that of blindness from diabetic eye disease, although uveitis is far less common.¹ For one in two patients, conventional immunosuppressive drugs will not adequately control the disease and/or treatment-limiting complications will develop.^{14–17} Quality of life in persons with uveitis is considerably lower than would be expected, based on level of vision alone.³

Experimental models of non-infectious uveitis

The most widely used model of non-infectious uveitis is experimental autoimmune uveoretinitis (EAU), in which a pathological immune response is directed against one of several retinal photoreceptor-associated antigens.¹⁹ Inflammation is based in the retina, but also involves the anterior chamber and vitreous. The model may be induced in many animals, including non-human primates.²⁰ Commonly EAU is induced in the mouse, against interphotoreceptor retinoid-binding protein (IRBP); this was originally performed as a primary immunization, requiring adjuvant, but today adoptive transfer

with pathogenic T-cell lines is popular.⁵ Severity of inflammation and structural damage may be graded grossly and histologically.

There are many other experimental models of non-infectious uveitis. Spontaneous uveitis occurs in horses as recurrent equine uveitis,²¹ HLA-A29 transgenic mice²² and autoimmune regulator knockout mice.²³ Intraocular inflammation accompanies some experimental models of systemic inflammation, such as mouse proteoglycan-induced spondylitis²⁴ and rat experimental autoimmune encephalomyelitis.²⁵ Uveitis may be produced in rodents that are challenged with proteins expressed from transgenes within the retina, and by intraocular injection of inflammatory cytokines or chemokines. Uveitis also may be induced in rodents by intraocular or systemic injection of bacterial products, including lipopolysaccharide and muramyl dipeptide.²⁶

B-CELL IMMUNOLOGY

Development of B cells

B cells coordinate the adaptive immune response, alongside T cells. In humans, B cells arise in the bone marrow from CD34⁺ hematopoietic stem cells that are maintained by several populations of stromal cells.²⁷ Studies in mice implicate CXCL12-producing reticular cells and osteoblast precursors in this process.²⁸ B-cell precursors pass from common lymphoid progenitor, through early B cell, pro-B cell and pre-B-cell stages, as they acquire expression of CD19 and then assemble the B-cell receptor, which is fully functional in the CD34⁻CD10⁺CD19⁺IgM⁺ immature B cell. Immature B cells enter the circulation and travel to spleen, becoming CD10⁻ mature naive B cells, which are capable of specific antigen recognition via their B-cell receptor. Subpopulations of transitional B cells are distinguished in the human on the basis of cell surface markers and functional responses.²⁹ Autoreactive B cells are identified for negative selection at the conversions from the pre-B to immature B cell (central tolerance) and transitional stages (peripheral tolerance).³⁰

Most mature naive B cells recirculate to secondary lymphoid organs, including lymph nodes, tonsils and mucosa-associated lymphoid tissue, where they enter lymphoid follicles. Here they interact with particulate and soluble antigens, presented in immunological synapses by subcapsular macrophages, dendritic cells and follicular dendritic cells.³¹ Chemokines and cholesterol metabolites direct B-cell movement within the follicle.^{32,33} CXCR5-expressing mature B cells are directed into the follicle by the chemokine, CXCL13, which is expressed on follicular dendritic cells. CXCL13–CXCR5 signaling also promotes B-cell receptor-mediated B-cell activation.³⁴ After internalizing and processing the B-cell receptor and antigen, B cells move to T-cell area under the direction of receptor–ligand interactions involving oxysterol and Epstein–Barr virus-induced G-protein coupled receptor 2, and CCR7 and CCL21, to present antigen to follicular helper T cells and become fully activated.

Differentiation of B cells

After activation, some B cells secrete specific immunoglobulin M (IgM) as short-lived plasma cells. Other activated B cells move to germinal centers for clonal expansion, and selective somatic hypermutation and class-switch recombination, which enable production of high affinity, class switched antibodies.³⁵ These B cells become long-lived CD19⁻ plasma cells or CD27⁺CD19⁺ memory B cells. Shlomchik and Weisel³⁶ hypothesize that early germinal center reactions generate memory B cells, and late reactions generate plasmablasts destined become long-lived plasma cells. Memory B cells reside in lymphoid and non-lymphoid organs when not in the circulation.³⁷ Long-lived plasma cells are maintained in the bone marrow. According to mouse

studies, eosinophils maintain these plasma cells by secreting proliferation-inducing ligand (APRIL) and interleukin (IL)-6.³⁸

In addition to conventional B cells, also known as follicular or B-2 B cells, the B lymphocyte population includes innate-like B-1 B cells and marginal zone B cells. These subsets are well described in the mouse, but their existence in humans continues to be discussed. B-1 cells, which develop from common lymphoid progenitors, are characterized by spontaneous secretion of natural antibodies that have broad reactivity against microbial and other danger signals. Rothstein³⁹ has taken a functional approach in building a case for a human B cell with this capacity, albeit with different cell surface markers and more specifically directed antibody than characterizes mouse B-1 cells. Marginal zone B cells develop from transitional B cells and are located in the marginal zone of the spleen, for early contact with circulating microbes. Their polyreactive B-cell receptor binds many molecular patterns and they express Toll-like receptors (TLRs) at high levels. Cerutti *et al.*⁴⁰ argue that human marginal zone B cells are not simply memory B cells, as suggested by others.

Regulatory B cells

A small proportion of B cells have regulatory activities that include production of the immunomodulatory cytokine, IL-10. Rosser and Mauri⁴¹ provide a comprehensive summary of present understanding of these regulatory B cells, which were first described just over 10 years ago. Regulatory B cells have been equated functionally with regulatory T cells. They may be generated at different stages of B-cell development and differentiation, according to microenvironmental conditions, including activation of TLRs or CD40, or by cytokines. Originally described in mice, regulatory B cells also exist in the human, and diverse involvements have been reported. Iwata *et al.*⁴² identified IL-10-producing B cells in newborns and adults, and in a large group of patients suffering from inflammatory diseases that ranged from rheumatoid arthritis to multiple sclerosis; some patients had expanded numbers of these cells. Flores-Borja *et al.*⁴³ showed that human CD19⁺CD24^{hi}CD38^{hi} B cells inhibited differentiation of naive CD4⁺ T cells into helper subsets, and promoted differentiation of effector CD4⁺ T cells into regulatory T cells. These activities were curbed in patients with rheumatoid arthritis, who had low numbers of regulatory B cells in blood, but relatively high numbers of such cells in inflamed joints.

OCULAR IMMUNOLOGY AND INFLAMMATION

Ocular immune privilege

Detection of Ebola virus inside the eye of a physician who survived Ebola virus disease recently focused world interest on the phenomenon of ocular immune privilege.⁴⁴ Beginning in the 1970s, Streilein expanded on the experimental work of Medawar, Billingham and Brent, which had established the concept of the eye as an immune-privileged site;⁴⁵ he worked from the principle that 'immune-privileged sites allow foreign grafts to survive for extended, often indefinite intervals', and identified microanatomical, cellular and molecular components of ocular immune privilege. This privilege functions to limit inflammation within the eye, where scarring is likely to result in blindness and disadvantage to survival. Thus ocular immune privilege impacts the course of ocular immune responses, and some systemic immune responses

The blood–ocular barriers are microanatomical barriers that restrict the movement of leukocytes into the eye.⁴⁶ The intraocular vascular bed of the anterior eye is located in the iris; tight junctions between iris endothelial cells combined with tight junctions between cells of the posterior iris epithelium and the contiguous non-pigmented ciliary

body epithelium form the 'blood–aqueous barrier'. In the posterior eye, an equivalent 'blood–retinal barrier' exists as tight junctions between endothelial cells lining the retinal blood vessels and cells of the retinal pigment epithelium. The absence of blood vessels and/or lack of lymphatic drainage of certain ocular surface and intraocular tissues may also limit leukocytic infiltration. However, the extent of a lymphatic-based barrier is unclear as new research suggests a more extensive lymphatic network within the eye than was previously believed.⁴⁷

Deviant immune responses occur when foreign antigens are placed within the eye, in the anterior chamber (anterior chamber-associated immune deviation), vitreous cavity or subretinal space.⁴⁸ This phenomenon has been extensively investigated in the mouse. Spleen-based interactions between ocular F4/80⁺ antigen-presenting cells (believed to be macrophages), B cells and natural killer (NK) T cells and conventional T cells, promote the development of CD8⁺ regulatory T cells that suppress systemic immune responses to antigens previously introduced into the eye.^{49,50}

The eye contains multiple soluble and cell-bound immunomodulatory molecules.⁴⁵ Transforming growth factor (TGF)- β 2 is produced within the eye in latent form, and is converted to active form in the presence of inflammatory cytokines.⁵¹ This cytokine suppresses activation of infiltrating lymphocytes and macrophages, and confers tolerance-promoting properties on antigen-presenting cells. Other intraocular immunomodulatory cytokines include IL-10, IL-1RA and macrophage migration inhibitory factor. Various neuropeptides— α -melanocyte stimulating hormone, vasoactive intestinal peptide, somatostatin and calcitonin gene-related peptides—also suppress immune responses in the eye.⁵² Constitutive expression of Fas ligand permits the eye to eliminate Fas-bearing infiltrating leukocytes by apoptosis.⁵³ Other intraocular immunomodulatory molecules include indoleamine 2,3-dioxygenase, thrombospondin-1 and programmed death-ligand 1. The eye demonstrates low levels of complement activity, along with multiple complement regulatory proteins. Binding of complement C3 fragment iC3b to CR3 on antigen-presenting cells induces the production of TGF- β 2.⁵⁴

Mechanisms of non-infectious uveitis

Non-infectious uveitis is a result of failed ocular immune privilege. In human patients and experimental models, the inflammation is characterized by a mixed intraocular infiltrate of leukocytes.^{55,56} Studies conducted primarily in mouse EAU indicate a cell-mediated autoimmune response directed against antigens normally confined to the retina, which is coordinated by T cells and macrophages. The obvious human example of autoimmune uveitis is the devastating disease known as sympathetic ophthalmia, in which an injury to one eye is followed by explosive panuveitis in both eyes, as sequestered ocular antigens are suddenly exposed to the systemic immune system.⁵⁷

Experimental autoimmune uveoretinitis is controlled by CD4⁺ helper T cells. Anti-CD4 antibody prevents EAU,⁵⁸ and inflammation is transferred passively by a CD4⁺ T-cell line.⁵⁹ In different forms of EAU, the Th17 subset—characterized by synthesis of IL-17A and other inflammatory cytokines—or the Th1 subset—characterized by synthesis of interferon (IFN)- γ —direct the inflammation. Antibody neutralization of IL-17 limits EAU when B10R/III wild-type mice are immunized with IRBP peptide 161–180 in complete Freund's adjuvant; the same blockade has no effect on EAU induced by infusion of an activated CD4⁺ Th1 cell line that recognizes the same peptide.⁶⁰ These observations suggest that the effector response—Th1 or Th17—depends on the context of antigen presentation.

Table 1 The evidence for involvement of B cells in non-infectious uveitis

Observations	Studies (reference)
B cells in intraocular leukocytic infiltrate in forms of uveitis including: juvenile idiopathic arthritis-associated uveitis, diffuse subretinal fibrosis uveitis syndrome, Vogt–Koyanagi–Harada syndrome, multifocal choroiditis and sympathetic ophthalmia	57,79–82,84–88
Schlieren caused by vitreous immunoglobulin in juvenile idiopathic arthritis-associated uveitis	83
Remission of juvenile idiopathic arthritis-associated uveitis coincident with onset of combined variable immunodeficiency	91
Effectiveness of rituximab in forms of uveitis including: juvenile idiopathic arthritis-associated uveitis, Behçet disease, isolated chronic anterior uveitis, diffuse subretinal fibrosis uveitis syndrome, Vogt–Koyanagi–Harada syndrome, autoimmune lymphocytic hypophysitis-associated uveitis	7–9,95–99
Elevated level of B-cell-activating factor in serum of patients with juvenile idiopathic arthritis when uveitis co-exists	92
Prominence of B cells in leukocytic infiltrate of eyes of non-human primates with experimental autoimmune uveoretinitis	20

Consistently, ligation of different TLRs on dendritic cells induces different ratios of IL-17:IFN- γ production by co-cultured IRBP-reactive CD4⁺ T cells.⁶¹ Th1 and Th17 cells may also act together to induce pathology.⁶² Research using transgenic B10RIII mice, which express a T-cell receptor specific to IRBP peptide 161–180 and spontaneously develop EAU, show that IRBP-specific T cells may be activated by non-cognate antigen present in intestinal microbiota.⁶³ CD4⁺FoxP3⁺ regulatory T cells expand in the eye during the course of EAU and act to resolve the uveitis.⁶⁴ Regulatory T cells also occur in spleens of mice that have recovered from EAU.⁶⁵

Macrophages are primarily responsible for the tissue destruction that occurs in EAU. Although the retina contains resident macrophages (microglia), newly recruited macrophages effect the destruction of retina by the production of free radicals. This was elegantly demonstrated in independent studies using chimeric mice with bone marrow reconstituted from mice expressing green fluorescent protein (GFP) in their monocyte population; the majority of cells infiltrating the photoreceptor layer at the peak of inflammation were GFP⁺, implying migration from the blood.^{66,67} Normal retinal structure is retained when early infiltration by macrophages is prevented.^{67,68} As the severity of EAU peaks, retinal-infiltrating macrophages produce nitric oxide, which is consistent with the M1 macrophage phenotype.⁶⁹

Recently there has been widespread recognition that some forms of non-infectious uveitis are the result of autoinflammation, not autoimmunity.⁶ Innate immune cells are triggered when pathogen-associated or damage-associated molecular patterns interact with extra- or intra-cellular pattern recognition receptors, activating inflammasomes, and the IL-1 family of cytokines.⁷⁰ Clear examples of autoinflammatory uveitis are provided in two hereditary syndromes with gain-of-function mutations: familial juvenile systemic granulomatosis, caused by mutations in the *NOD2* gene; and NOMID, caused by mutations in the *NLRP3* gene. It has been suggested autoinflammation may also contribute to more common forms of uveitis (for example, inflammatory bowel disease-associated uveitis and Behçet uveitis).⁶ Experimental autoinflammatory uveitis may be induced by bacterial lipopolysaccharide or the muramyl dipeptide component of bacterial peptidoglycan.²⁶

B-CELL INVOLVEMENT IN NON-INFECTIOUS UVEITIS

In contrast to the intensive research on the roles of T cells and monocytes/macrophages in non-infectious uveitis, there has been little work focused on B-cell involvement in the disease. Most descriptions of B cells and uveitis come from clinical or translational studies involving human ocular tissues or cells. This also contrasts with the situation for T cells and monocytes, for which most work has been conducted in animal models. The evidence for B-cell

involvement in non-infectious uveitis includes histopathological and immunocytochemical analyses of intraocular tissues and fluids from patients with uveitis, as well as reports of the therapeutic impact of manipulating B cells (Table 1). The relevance of mouse models to human inflammatory diseases has been actively debated recently.^{71,72} In relation to B cells in particular, there are substantial differences in B-cell development, phenotypes of differentiated B cells, and immunoglobulin and class switching between man and mouse.^{73–75}

Human histopathological and immunocytochemical observations

Removal of ocular fluid from eyes of patients with uveitis is a common procedure for diagnostic purposes. Measurement of a high ratio of microbial-specific antibody in ocular fluids versus serum is used routinely to diagnose infectious uveitis.⁷⁶ There are many published reports from different groups that detail the phenotype of leukocytes in aqueous and/or vitreous of patients with various forms of non-infectious uveitis.^{55,77,78} B cells are usually present in this exudate, although the proportion ranges widely from being the least common cell to the predominant cell. In contrast to fluid analysis, microscopic evaluations of eye tissue from patients with uveitis are quite uncommon. However, examinations of eyes with forms of uveitis that involve the anterior and/or posterior eye identify B cells in the infiltrate; in some cases these cells outnumber other leukocytes, as described below.

Histopathological assessments conducted over 30 years ago of ocular tissues from four children with uveitis secondary to juvenile idiopathic arthritis consistently described a plasma cell-rich infiltration of the iris and, if examined, the ciliary body.^{79–81} This impression was recently confirmed by Parikh *et al.*,⁸² who performed a comprehensive immunohistochemical analysis of the whole eye from a boy with juvenile idiopathic arthritis-associated uveitis; CD20⁺ B cells and Ig-expressing plasma cells (primarily IgG, but also IgM and IgA) vastly outnumbered CD3⁺ T cells and CD68⁺ macrophages, leading the authors to conclude that 'JIA (juvenile idiopathic arthritis)-associated nongranulomatous iridocyclitis is a primarily B-cell-infiltrative process'. Consistent with this observation, vitreous schlieren (optical heterogeneity), detected during ocular surgery in a girl with juvenile idiopathic arthritis-associated uveitis, was the result of high vitreous levels of IgG, IgM and IgA.⁸³

In studies dating from the 1980s, tissues from eyes of patients with various forms of posterior uveitis or panuveitis were examined microscopically. In separate reports, The Laboratories of Immunology and Pathology at the National Eye Institute^{84–86} described immunohistochemical findings in diffuse subretinal fibrosis uveitis syndrome and Vogt–Koyanagi–Harada syndrome. Both diseases were characterized by a predominantly lymphocytic infiltration of the retina and choroid; lymphocytes included CD4⁺ and CD8⁺ T cells and CD22⁺ B

cells, but B cells clearly predominated in diffuse subretinal fibrosis uveitis syndrome. B cells, defined on the basis of CD20 expression, were also the most commonly observed lymphocyte in multiple cases of multifocal choroiditis.^{87,88} The authors of a most remarkable 65-year-long clinicopathological evaluation of 105 eyes with sympathetic ophthalmia reported, 'Plasma cells are said to be characteristically absent, but 65.0% of steroid-treated and 85.7% of cases before the steroid era showed plasma cell infiltration.'⁵⁷

Results of studies in experimental models

Although the most common laboratory animal for EAU is the mouse, many other animals are susceptible. Non-human primates develop a disease that is comparable to forms of posterior uveitis syndromes seen in humans, characterized by vitritis, retinitis, retinal vasculitis and chorioretinal lesions.⁸⁹ Fujino *et al.*²⁰ described the phenotype of infiltrating leukocytes in 10 *Mucaca mulatta* immunized intradermally with S-antigen emulsified in complete Freund's adjuvant. At 70 days after first immunization, the predominant ocular infiltrating cell was the lymphocyte. For the 7 monkeys that developed clinically apparent uveitis, the proportions of CD22⁺ B cells and CD4⁺ T cells were equal in 3, while in 4 the number of B cells was higher than the number of T cells. In a separate publication,⁹⁰ the same team reported a contrasting picture in mice. B10.A mice were pre-treated with cyclophosphamide and immunized in the footpad and then into the muscle with IRBP in complete Freund's adjuvant, plus *Bordetella pertussis* vaccine. As followed at weekly intervals for 10 weeks after first immunization, EAU was characterized by a macrophage and helper T-cell-rich infiltration, with only rare B cells. B-cell infiltration is also not reported to be a prominent feature of other rodent uveitis models, including lipopolysaccharide-induced uveitis.²⁶

Effect on uveitis of manipulating B cells

A remarkable 'natural experiment' supports the key role of B cells in uveitis.⁹¹ A patient with unilateral juvenile idiopathic arthritis-associated uveitis from the age of 3 years, developed severe complications of the inflammation and became legally blind in the affected eye over 14 years despite treatment with conventional systemic immunosuppressive drugs. At the age of 17 years, her uveitis—and the associated joint inflammation—went into remission spontaneously. However, at the same time, she developed recurrent infections and leukocytopenias. Ultimately she was diagnosed with intercurrent common variable immunodeficiency and successfully treated with intravenous immunoglobulin. The basic feature of this immunodeficiency is failure of B-cell differentiation and hypoglobulinemia. Resolution of the juvenile idiopathic arthritis-associated uveitis after development of common variable immunodeficiency was consistent with significant B-cell involvement in the uveitis. Interestingly, ELISA (enzyme-linked immunosorbent assay) of serum from patients with

oligoarticular juvenile idiopathic arthritis detects increased levels of the cytokine, B-cell-activating factor, when uveitis co-exists.⁹²

Additional evidence for the participation of B cells in human uveitis comes from results of depleting B cells in patients with uveitis using rituximab. Rituximab is a human–mouse chimeric monoclonal antibody that targets the surface antigen, CD20.⁹³ This antigen is first expressed on B cells when they reach the pre-B-cell stage, and expression ceases with differentiation to the plasma cell.⁹⁴ The drug is typically administered in a 2-infusion cycle every 6 months. Various mechanisms of B-cell depletion by rituximab have been described, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and B-cell apoptosis.

Multiple small clinical studies have described therapeutic benefit of treatment with rituximab in patients with different forms of uveitis, including those characterized by B-cell infiltration of the eye. Two retrospective case series^{8,9} describe the use of rituximab in a total of 18 children with active juvenile idiopathic arthritis-associated uveitis who had failed treatment with TNF blockade; 15 children experienced remission of intraocular inflammation after commencing rituximab, and 13 of these children were able to cease or reduce the dose of prednisolone and/or other systemic immunosuppressive drugs. In a prospective clinical trial involving 20 patients with Behçet disease who were randomized to treatment with rituximab and methotrexate or cyclophosphamide and azathioprine, plus prednisolone, the rituximab and methotrexate group experienced significantly better total adjusted disease index activity at 6 months.⁷ Recalcitrant cases of idiopathic chronic anterior uveitis,⁹⁵ and posterior uveitis caused by the diffuse subretinal fibrosis uveitis syndrome⁹⁶ and Vogt–Koyanagi–Harada disease^{97,98} also have been treated effectively with rituximab. An unusual case of uveitis associated with autoimmune B-cell-rich lymphocytic hypophysitis entered long-term remission following treatment with the drug.⁹⁹

PATHOGENIC AND REGULATORY ROLES FOR B CELLS IN NON-INFECTIOUS UVEITIS

There are multiple potential mechanisms by which B cells might incite or perpetuate inflammation within the eye (Table 2). Antibody production is one unique characteristic of B cells. Antibody may contribute to inflammation within the eye by activating complement and/or activating innate immune effector cells that are either resident within the eye or recruited during the course of inflammation. B cells may also promote intraocular inflammation by production of inflammatory cytokines, antigen presentation to T cells—which may occur locally—and/or support of T-cell survival. These activities are likely balanced by immunomodulatory mechanisms of ocular immune privilege. New research provides evidence that B cells themselves may exert immunomodulatory effects in uveitis, as regulatory B cells or through effects on transendothelial migration of T cells.

Table 2 Inflammatory and immunomodulatory activities of B cells that may contribute to the development and/or progression of non-infectious uveitis

Inflammatory activities	Processes involving immune complexes Activation of innate immune effector cells (for example, granulocytes, monocyte/macrophages, mast cells, NK cells) Antigen presentation to CD4 ⁺ T cells by dendritic cells Complement activation by classical pathway Antigen presentation to CD4 ⁺ T cells Production of inflammatory cytokines (for example, IFN- γ , IL-17, TNF- α , IL-6) Promotion of CD8 ⁺ T-cell survival and proliferation
Immunomodulatory activities	Production of immunomodulatory cytokines (for example, IL-10, IL-35) Regulation of T-cell migration across vascular endothelium

Antibody-directed mechanisms

In the 1970s and 1980s, there was healthy debate around whether antibodies had a direct pathogenic effect in uveitis.¹⁰⁰ Elevated levels of serum antibodies to retinal S-antigen were reported in patients with various forms of uveitis, but they were also detected in normal controls and in patients with other eye diseases.¹⁰¹ High doses of S-antigen produced a histopathological picture of granulocytic and monocytic infiltration that was consistent with an immune complex disease.¹⁰² However, there were conflicting reports about the ability of systemic injection of photoreceptor hyperimmune serum to induce EAU in guinea pigs,¹⁰⁰ and as the important role of CD4⁺ T-cell-mediated pathology in EAU was recognized,^{19,59} the field moved away from this debate. Yet, the relatively recent description of 'humanized' EAU in the HLA-DR3 transgenic mice suggests that antibody within the eye is directly inflammatory: adoptively transferred EAU is more severe when serum and cells are transferred, in comparison to transfer of cells alone.¹⁰³

Following classical immunology teaching, antibody within the eye might trigger inflammation by activation of effector leukocytes and/or by activation of complement. These possibilities are discussed below. However, an additional consideration is direct cell toxicity, as occurs in the rare retinal degeneration termed autoimmune retinopathy. Autoimmune retinopathy is characterized by the production of auto-antibodies directed against photoreceptor antigens, such as recoverin and α -enolase.¹⁰⁴ This may occur as a paraneoplastic syndrome (that is, cancer-associated retinopathy, melanoma-associated retinopathy and bilateral diffuse uveal melanocytic proliferation) or an isolated disease. Retinal degeneration is mediated through antibody-triggered apoptosis of retinal photoreceptors, with sequential activation of caspase 9 and caspase 3, in the absence of a primary inflammatory response.¹⁰⁵

Antibody complexed with antigen within the eye also might contribute to intraocular inflammation by stimulating effector responses from Fc receptor-bearing leukocytes. Innate effector mechanisms that are triggered when immune complexes bind activating Fc receptors include: mast cell and/or basophil release of vasoactive substances and chemoattractants; neutrophil release of chemoattractants and cytotoxic substances; macrophage oxidative burst, cytotoxicity and release of pro-inflammatory mediators; and antibody-dependent cytotoxicity, effected primarily by NK cells.^{106,107} Granulocytes, monocytes and NK cells that infiltrate the eye in uveitis, along with resident macrophages and mast cells, could be responsive to immune complexes. Dendritic cells phagocytose antigen-antibody complexes, and present processed antigen to T-cell subsets, including CD4⁺ helper T cells. Classically this interaction takes place in secondary lymphoid organs, but it also may occur within the eye, as discussed below.

Immune complexes trigger complement activation via the classical pathway. Administration of cobra venom, which depletes complement, reduces the severity of EAU induced in guinea pigs with high doses of S-antigen.¹⁰⁸ Consistently, mice that are genetically deficient in the complement component, C3, develop significantly less severe EAU than wild-type control animals.¹⁰⁹ Anterior and posterior segments of the human eye exhibit a low level of complement activity, and aqueous of patients with uveitis contains activated complement fragments, C3a, C4a and C5a, at high ratios to total protein, consistent with intraocular complement activation.¹¹⁰ Thus the potential exists for intraocular antibody to activate complement and drive inflammation. Indeed, one rationale for the development of the Fab, ranibizumab, for targeting vascular endothelial growth factor in age-related macular degeneration, was the possibility that complement-mediated or cell-dependent cytotoxicity might complicate intravitreal injection of whole antibody.¹¹¹ Fortunately, however, clinical inflammation

infrequently complicates the injection of various therapeutic antibodies into the eye for non-uveitis indications, including macular degeneration and vitreoretinal lymphoma.^{112,113}

Other pro-inflammatory activities of B cells

It is well established that B cells capture antigen via the B-cell receptor, internalize and process this complex, and present antigenic peptide in association with MHC Class II molecule to T cells in secondary lymphoid organs.³¹ Clearly this process might contribute to the pathogenesis of uveitis in patients, with presentation of auto-antigens to helper T cells. As has been studied extensively in relation to multiple sclerosis,¹¹⁴ presentation of antigen at the site of inflammation is also reported in the eye.¹¹⁵ Fluorescence videomicroscopy was applied to a mouse model of anterior uveitis: labeled T cells from transgenic DO11.10 mice were injected intravenously into BALB/c mice, and the endothelium was activated with lipopolysaccharide. Eyes injected with ovalbumin saw a significantly higher percentage of T cells in contact with antigen-presenting cells than eyes injected with control antigen. In this model, antigen-presenting cells were defined on the basis of labeled ovalbumin uptake and believed to be myeloid-derived. However, it is tempting to speculate the potential for B cells infiltrating the eye in uveitis to also present antigen locally, thereby perpetuating inflammation.

B cells have the capacity to produce inflammatory cytokines. Experiments conducted 15 years ago in the mouse demonstrated conversion of naive B cells to B effector (Be) -1 or -2 cells, with cytokine profiles characteristic of Th1 or Th2 immune responses, when co-cultured with Th1 or Th2 helper T cells, respectively.¹¹⁶ Subsequent work has shown human B cells have the capacity to produce inflammatory cytokines, including IFN- γ , IL-17, TNF- α and IL-6.¹¹⁷⁻¹¹⁹ Studies of cytokine levels in ocular fluids and/or cells from patients with uveitis have identified multiple inflammatory cytokines within the eye, including each of these cytokines; moreover, comparison of cytokines produced in different forms of uveitis suggests that particular profiles may be associated with different uveitis subtypes.¹²⁰ Infiltrating helper T cells and monocytes, and resident macrophages have been considered the primary sources of inflammatory cytokines in uveitis.^{5,56} However, given that B cells have the capacity to synthesize pro-inflammatory cytokines, it is reasonable to suggest that B cells also contribute to the inflammatory cytokine milieu present in an eye with uveitis.

Independent of antigen presentation, B cells interact with activated CD8⁺ cytotoxic T cells, in part through engagement of CD27 (expressed by B cells) and CD70 (expressed by T cells), to promote survival and proliferation of the T-cell subset.¹²¹ CD8⁺ T cells in blood from patients with uveitis express markers of cytotoxicity, including CD107a, and demonstrate enhanced target cell lysis (Hirani S, *et al*. IOVS 2013;54: ARVO E-Abstract 2026). CD8⁺ T cells appear to be particularly important in Behçet uveitis, and have been identified in the aqueous fluid of patients with this disease.¹²²

Immunomodulatory processes

B cells may also have a role in modulating non-infectious uveitis. The involvement of regulatory B cells in mouse uveitis was demonstrated convincingly in a series of experiments published by the Egwuagu Laboratory.¹²³ A population of IL-10-producing regulatory B cells, including a subpopulation that also produced IL-35, was generated by exposing splenic B cells to recombinant IL-35. Mice that were genetically defective in IL-35 signaling did not generate these cells and developed more severe EAU, and mice treated with regulatory B cells after induction of EAU experienced substantially less intraocular

inflammation than mice treated with IL-10⁻ B cells. The work is yet to be translated to patients with uveitis. However, the group showed that recombinant human IL-35 substantially expanded the population of IL-10-producing B cells in isolates of human peripheral B cells. This population inhibited B cell proliferation induced with phorbol 12-myristate 13-acetate. Thus the authors raised the possibility of using IL-35 or IL-35-producing regulatory B cells to treat uveitis.

Newly described, peptide inhibitor of transendothelial migration (PEPITEM) is a B-cell product that regulates memory T-cell migration across the vascular endothelium during inflammation.¹²⁴ The peptide is produced under the control of adiponectin and binds cadherin 15 on the vascular endothelium; binding results in synthesis of sphingosine-1-phosphate, which in turn binds sphingosine-1-phosphate receptors on T cells as they interact with the endothelium, limiting activation of lymphocyte function-associated antigen-1 and restricting transendothelial migration. This mechanism is compromised in human autoimmune diseases, rheumatoid arthritis and type I diabetes mellitus. Relevance to uveitis was studied in mouse lipopolysaccharide-induced uveitis; treatment of mice with PEPITEM significantly reduced the number of T cells in the intraocular infiltrate.

Clearly immune privilege may impact any inflammatory activities perpetrated by B cells. The Mochizuki Laboratory¹²⁵ have considered this issue, working in the C57BL/6 mouse. In this animal, TGF- β produced by the retinal pigment epithelium limited B-cell proliferation and IgG production by B cells, following stimulation with anti-CD40 antibody, lipopolysaccharide and IL-4. Although the report concentrated on events occurring within the retina, the published data indicated that iris pigment epithelial cells and ciliary body pigment epithelial cells similarly had the capacity to limit B-cell proliferation.

B-cell entry into the eye

In order for B cells to participate in uveitis, they must first migrate from the circulation into the eye. Leukocytes move from the blood stream into peripheral tissues through complex molecular interactions with the local vascular endothelium.¹²⁶ Tissue-specific combinations of endothelial adhesion molecules and chemokines mediate steps that include tethering, rolling, arrest, firm adhesion and diapedesis. Our group has a long-standing interest in the molecular basis of leukocyte migration across the human retinal vascular endothelium, as occurs in non-infectious posterior uveitis. Endothelial cells may be isolated from human retina dissected from cadaver donor eyes, by a process of enzymatic digestion and selection on the basis of CD31 expression; these cells may be expanded by transduction with lentivirus encoding the human papilloma virus E6/E7 genes.¹²⁷ We have showed that human retinal endothelial cells constitutively express an array of adhesion molecules and chemokines, and the expression of many of these migration signals is increased by inflammatory stimuli.

Recently we have investigated the signals that are used by human B cells for transmigration of retinal endothelium (manuscript under review). We migrated B cell isolates that were prepared from individual healthy adults through transwells populated with human retinal endothelial cells. We examined the effect of antibody blockade of key immunoglobulin superfamily proteins, intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1 and observed a role for ICAM-1, but not VCAM-1, in B cell transendothelial migration for a majority of the adult subjects. The B cells migrated in significantly higher numbers in the presence of CXCL13, which is a B-cell-selective chemokine that we have detected in human retina. In an unrelated study by another group, aqueous fluid collected from 11 children with juvenile idiopathic arthritis-associated anterior uveitis was found to contain increased soluble ICAM-1, but not

VCAM-1, in comparison to control fluid collected from children who did not suffer from uveitis.¹²⁸ This finding suggests ICAM-1 may also be involved in B-cell migration across the iris vascular endothelium, as occurs in anterior uveitis.

CONCLUSIONS

Although basic research in non-infectious uveitis continues to focus on the involvement of various T cell and myeloid cell populations, it is clear that B-cell subsets, including plasma cells, participate in the pathogenesis of this vision-threatening disease. Recent high impact basic publications have highlighted specific roles for B cells in uveitis, and should stimulate interest in clarifying other roles for these cells and their products. For example, re-visiting the question of antibody involvement in uveitis could be informative. Consideration should be given to models in experimental animals other than the mouse, given the apparent lack of major involvement of B cells in mouse EAU. Studies in animal models will need to be translated to the human condition. Although human models are necessarily *in vitro*, it also may be important to use these in elucidating the roles of B cells in uveitis.

In parallel with new basic science studies, recent clinical case series support the possibility of targeting B cells for treatment of uveitis. Treatments that modulate B-cell mechanisms, not B cells directly, will be worthy of consideration, given the roles of B cells not only in promoting, but also in modulating, the process. Options might include targeting B-cell migration into the eye, or augmenting B cell regulatory activities. Clinical trials in humans will ideally progress past non-controlled case series to randomized controlled clinical trials. It may be advisable to initially target specific uveitis syndromes, in which there is strongest evidence for B-cell involvement, such as juvenile idiopathic arthritis-associated uveitis or sympathetic ophthalmia. Such trials will require enrollment across multiple centers, given the low prevalence of uveitis.

Finally, it is worth noting that research on the involvement of B cells in uveitis may have implications for research and development in other ocular diseases. The obvious example is vitreoretinal lymphoma. This highly malignant tumor is almost always of diffuse large B-cell type.¹²⁹ Treatment with intravitreal rituximab, in addition to standard chemotherapeutic drugs, is gaining popularity, but is not a definitive cure for the cancer.¹¹³ Knowledge of the molecular mechanisms by which B cells access the eye, and the activities of B cells within the eye, is likely to be highly informative in developing more effective treatments for vitreoretinal lymphoma.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by grants from National Eye Institute/National Institutes of Health (R21 EY022009) and Australian Research Council (FT130101648). The authors wish to thank Professor Keryn Williams, Flinders University (Adelaide, Australia) for helpful discussions, and Ms. Angela Chappell and Ms. Carly Emerson, Ophthalmic Imaging, Flinders Medical Centre (Adelaide, Australia) for capturing the clinical images shown in Figure 1.

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