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# Environmental Microbes and Uveitis: Is Microbial Exposure Always Bad?

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# Environmental Microbes and Uveitis: Is Microbial Exposure Always Bad?

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## Abstract

The eye generally is considered to be an immune-privileged organ, but this notion is being increasingly challenged as ocular antigens can be expressed in the generative lymphoid organs, resulting in attainment of self-tolerance. What triggers a break in this tolerant state is a fundamental question in autoimmunity research. The general belief is that exposure to environmental microbes can break self-tolerance in genetically susceptible individuals, leading to the induction of autoimmune responses. The molecular mimicry hypothesis has been proposed as one major mechanistic, pathway through which microbes, by generating cross-reactive immune responses, can induce ocular damage of the kind that might occur in uveitis. However, our recent data suggest that exposure to microbial products containing mimicry epitopes for retinal antigens can potentially be beneficial to the host. In this review, we discuss the immune mechanisms with particular reference to the molecular mimicry hypothesis as it relates to immune-mediated uveitis.

## Introduction

Uveitis is inflammation of the uvea, an area of the eye consisting of the iris, ciliary body and choroid layer, but when the retina is involved, the disease process is described as uveoretinitis [1]. However, based on the anatomic location of lesions, uveitis has also been categorized as anterior uveitis (cornea, anterior chamber, iris, ciliary body and lens), intermediate uveitis (vitreous humour, pars plana of the ciliary body and peripheral retina) and posterior uveitis (vitreous gel, retina, retinal vessels, choroid and optic nerve) [2]. For diagnostic purposes, identification of lesions in specific regions becomes a critical necessity, but in this review, to simplify understanding, we use the broader term *uveitis* to describe the disease process, regardless of the region of inflammation involved.

Uveitis is the fourth leading cause of blindness in the Western world, affecting approximately 300,000 individuals in the United States alone [3]. The disease incidence is high in individuals aged 25–44 years [4]. The clinical course of uveitis is characterized by sudden or insidious onset, lasting up to 3 months or even longer [5]. Uveitic conditions can be of infectious or non-infectious origin. In various eye diseases or systemic diseases affecting the eye, such as Behcet's disease, Vogt–Koyanagi–Harada (VKH) syndrome, birdshot chorioretinopathy, systemic sarcoidosis and sympathetic ophthalmia, autoimmune responses arising from recognition of eye antigens as foreign have been suspected. Generally, it is held that exposure to microbes can trigger autoimmune responses in genetically susceptible individuals and may involve a combination of various mechanisms, such as molecular mimicry, epitope spreading, bystander activation and release of cryptic antigens [6–8]. In this review, we discuss the mechanisms of immune-mediated ocular damage with an emphasis on the molecular mimicry hypothesis as it relates to the induction of cross-reactive T cells in the mediation of uveitis.

## The eye as an immune-privileged organ

Traditionally, the eye is considered an immunologically privileged organ, and several mechanisms have been postulated to explain this phenomenon. (1) The two components of the blood–ocular barrier (BOB), which is comprised of the blood aqueous barrier (non-pigmented epithelium of the ciliary body and the vascular endothelium of the iris) and the blood retinal barrier (vascular endothelium of the retinal blood vessels and the retinal pigment epithelium [RPE]), protect the intraocular components from access to lymph or blood and control trafficking of immune cells, including naïve T cells, into the eye [9]. (2) The phenomenon of anterior chamber-associated immune deviation (ACAID) causes induction of peripheral T regulatory (Treg) cells. In this process, after







SCANDINAVIAN JOURNAL OF Immunology AN INTERNATIONAL MONTHLY JOURNAL

the initial encounter with an antigen, the antigen-presenting cells (APCs) escape from the eyes and traffic selectively to the marginal zone of the spleen, promoting distinct populations of CD4 and CD8 Tregs [10]. (3) Specialized APCs cannot efficiently stimulate naïve T cells, as suggested by the finding that dendritic cells (DCs) in the eye respond poorly to conventional APC assays [11]. (4) Immunomodulatory factors in the aqueous humour, such as transforming growth factor (TGF)-$\beta$, interleukin (IL)-1 receptor antagonist, vasoactive intestinal peptide (VIP), inhibitors of C1q and C3 convertase, and macrophage migration inhibitory factor (MIF), can suppress activation of macrophages, neutrophils, T cells and the complement cascade. In these factors, TGF-$\beta$2 and $\alpha$-melanocyte-stimulating hormone favour the induction of peripheral Treg cells from the eye [12, 13]. (5) In the immune regulatory environment, resident macrophages can mimic the Treg properties of TGF-$\beta$-primed macrophages [14]. Iris, ciliary body and RPE structures also can promote Tregs [15]. It recently has been shown that RPE can express ligands for programmed death-1 receptor, cytotoxic T cell-associated antigen-2$\alpha$, and cathepsin L inhibitor that may involve induction of Tregs and suppression of the differentiation of T-helper (Th) cells [16, 17].

In spite of these immune barriers, the eye still can become vulnerable to infectious and non-infectious assaults, leading to the development of chronic uveitic conditions in which autoimmune responses are suspected. As exemplified in Fig. 1, the potential role of autoreactive T cells in the causation of ocular damage can be best illustrated in sympathetic ophthalmia, a bilateral granulomatous uveitic condition that can be seen after surgical procedures or traumatic injuries to the eyes [18, 19]. In this disease process, T cells that might be generated in response to ocular antigens such as uveal melanin, retinal S-antigen (S-Ag; also called as retinal arrestin), rhodopsin, interphotoreceptor retinoid-binding protein (IRBP) and recoverin released from one damaged eye can induce inflammatory response in the unaffected eye. Essentially, the naive T cells responding to the ocular antigens draining into the regional lymph nodes become activated, and the effector T cells then infiltrate the healthy eye and recruit neutrophils and macrophages, leading to damage to the previously unaffected eye [20].

## Factors that predispose to uveitis

The peripheral repertoires of healthy individuals may contain self-reactive T cells and B cells; before they are exported to the periphery, both cell types have to interact with self-antigens during their selection processes in the thymus and bone marrow, respectively [21]. Therefore, hypothetically, healthy humans can have a propensity to develop autoimmune diseases, but the clinical symptoms are manifested in very few of them. How such tolerance is maintained is fundamental to the understanding of autoimmune diseases. Two major factors have been implicated in the predisposition to autoimmune diseases: genetic susceptibility and exposure to environmental microbes.

### Genetic susceptibility

Major histocompatibility complex (MHC) genes play a role in disease susceptibility, and strong associations have been found between acute anterior uveitis and human leucocyte antigen (HLA)-B27 [22], between Behcet's disease and HLA-B51, and between VKH disease and HLA-DR4 and HLA-DQ4 haplotypes, whereas birdshot retinochoroidopathy and sympathetic ophthalmia are linked with HLA-A29 and HLA-DR4 haplotypes, respectively [23–25]. MHC locus is an important determinant of T cell responses because T cells can recognize peptide antigens presented by APCs only in the context of MHC molecules. During the maturation process within the thymus, T cells have to recognize both MHC molecules and self-antigens; high-affinity interactions lead to negative selection, as opposed to weak interactions that favour positive selection of T cells [21].

However, it is possible for T cells to escape negative selection if the antigen presentation pathways are defective [21], or if the thymus fails to express self-antigens. The latter is controlled by autoimmune regulatory element (AIRE), both a transcriptional factor and a non-MHC gene that influences central tolerance and controls the thymic expression of self-proteins [21]. Two lines of evidence support the notion that AIRE plays a critical role in central tolerance: (1) humans possessing point mutations in AIRE exhibit a wide array of autoimmune diseases [26] and (2) AIRE-deficient mice develop multi-organ autoimmunity, including uveitis, in which autoantibodies for a wide range of antigens have been demonstrated in heart, liver, testes, pancreas, adrenal glands and eyes [27]. Further, failure to express a self-antigen in the AIRE-sufficient mice can lead to organ-specific autoimmunity [28]. However, the long-standing notion that ocular antigens are sequestered and not expected to be recognized by the developing thymocytes is increasingly being challenged, as demonstrated by expression of various retinal antigens within the thymus, such as IRBP, S-Ag, recoverin, opsin, RPE-65 and melanocyte-specific antigens [29, 30]. Nonetheless, alterations, if any, in the amounts of protein expression can still affect thymic education of T cells, leading to their safe exit into the periphery [31, 32]. In genetically susceptible individuals, self-reactive T cells in such a pre-existing repertoire can be activated to become pathogenic cells that might occur in response to exposure to environmental microbes.

### Environmental microbes

Generally, it is believed that microbial infections can trigger autoimmune responses in susceptible individuals. A

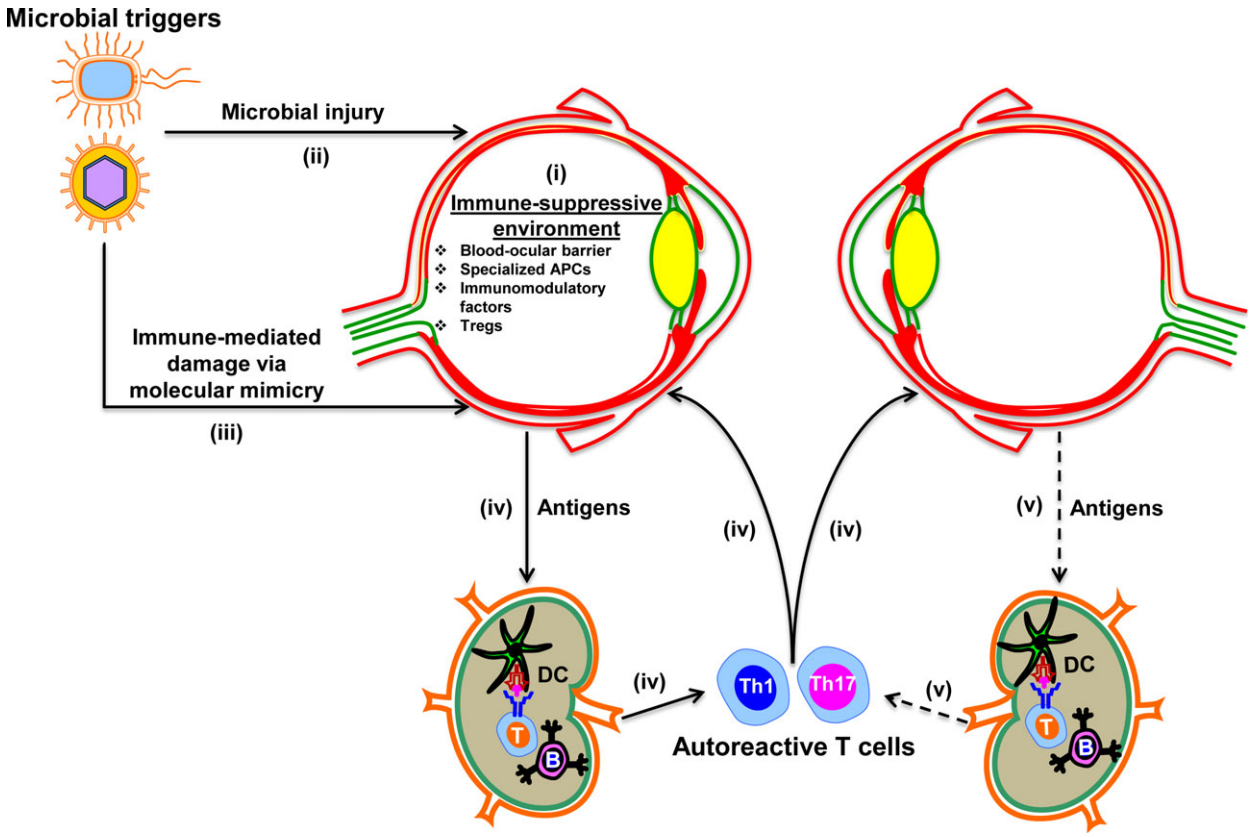


**Figure 1** Proposed immune mechanisms of uveitis. The eye is generally considered to be an immune-privileged organ, and several factors contribute to the immunosuppressive environment within the eye: blood–ocular barrier; specialized antigen-presenting cells (APCs); immunomodulatory factors such as TGF-$\beta$, VIP and macrophage migration inhibitory factor (MIF); and Tregs (i). Nonetheless, exposure to pathogens that have a tropism for the eye can lead to ocular damage by direct injury (ii). Alternatively, microbes bearing the mimicry sequences of ocular antigens can induce the generation of cross-reactive T cells in the periphery, which then enter the eyes and induce ocular inflammation through molecular mimicry (iii). Consequently, new ocular antigens can be released and drained into the local lymph nodes, leading to the generation of self-reactive T cells that are capable of producing proinflammatory Th1 and Th17 cytokines, which can then migrate back into both the affected and the healthy eye (iv). As this vicious cycle continues, chronic inflammation sets in (v).

variety of pathogens such as viruses, bacteria, protozoa and fungi have been implicated in the causation of uveitic conditions (Table S1). But, the challenge is to delineate the underlying mechanisms for the persistence of chronic inflammation in the absence of detectable infectious particles. Under these circumstances, autoimmune responses are suspected, and molecular mimicry is one major mechanism implicated in the mediation of autoimmune diseases of microbial origin [33].

Molecular mimicry is a phenomenon in which the structural similarities between self- and non-self (foreign)-antigens facilitate recognition of self-antigens by cross-reactivity, which can occur at the level of T cells or antibodies [33, 34]. Antibodies can recognize linear microbial sequences, as well as homologous non-identical sequences, and they can trigger inflammatory reactions through the activation of complement cascade [35]. For T cells, cross-reactivity occurs as a result of degeneracy in the recognition of peptides presented by MHC molecules (Fig. 2a). T cell degeneracy has been noted in microbial products showing stretches of sequences identical to the self-proteins [36]. Importantly, peptide fragments bearing even minimal sequence identities can still be recognized by T cells, if the critical MHC- and T cell receptor (TCR)-contact residues are preserved in the mimicry epitopes [37, 38]. Thus, potential exists for microbes to trigger autoimmune diseases such as uveitis via molecular mimicry.

To determine the pathogenic potential of uveitis-inducing mimicry epitopes, experimental autoimmune uveoretinitis (EAU) models are commonly employed [39]. EAU can be induced in susceptible rodent species by immunizing them with proteins or their peptides extracted primarily not only from the retina but also from iris and ciliary body, in complete Freund's adjuvant. The uveitogenic proteins include S-Ag, IRBP, rhodopsin, recoverin, phosducin, RPE-65 and type I collagen [40–42]. Although the CAR and PVG strains of rats are susceptible to S-Ag-mediated EAU, the disease can be induced in Lewis rats with both S-Ag and IRBP [7, 41]. In contrast, EAU can be induced in mice only with IRBP; its

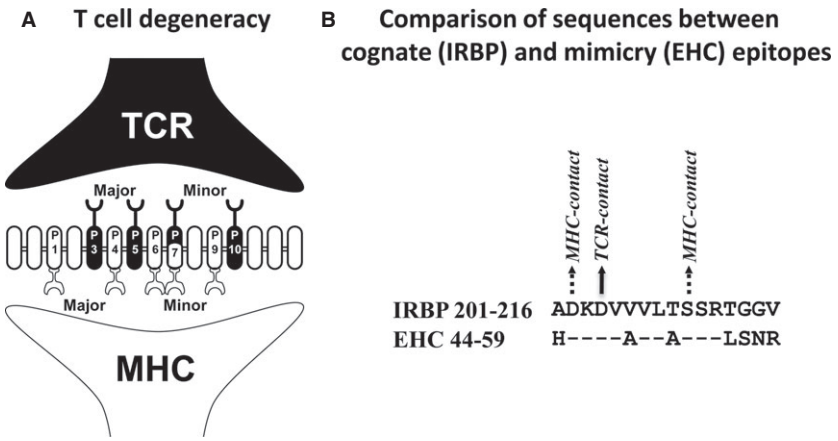


**Figure 2** T cell degeneracy in the recognition of major histocompatibility complex (MHC)-bound peptides. (a) T cell degeneracy. T cells recognize peptides in the context of MHC molecules through their receptors. The peptides are comprised of critical residues with extended side chains that anchor the peptide to the MHC molecule, whereas the side chains from the solvent-exposed residues interact with the T cell receptors (TCRs). The major and minor contact residues at indicated positions (P) corresponding to MHC and TCR contacts are shown. In some instances, a single residue as shown at P7 can interact with both MHC and TCR. T cell recognition of peptides is degenerate, which can be explained by the fact that peptide recognition can occur even if the major MHC or TCR contacts alone are conserved in the peptide. This forms the basis for the phenomenon of molecular mimicry in which microbial epitopes that share partial sequence identity, but with conserved critical residues, can lead to the activation of cross-reactive immune responses. (b) Comparison of sequences between cognate [interphotoreceptor retinoid-binding protein (IRBP)] and mimicry [*Ehrlichia canis* (EHC)] epitopes. The amino acid sequences between IRBP 210-216 and EHC 44-59 showing an overall identity of 56% were compared to indicate the similar and dissimilar residues between the two.

uveitogenic epitopes include IRBP 161-180, IRBP 171-190 and IRBP 541-560 in B10.RIII mice; IRBP 201-216 in B10.A, B10.BR and A/J mice; and IRBP 1-20, IRBP 461-480 and IRBP 651-670 in C57BL/6 mice. In all these models, autoreactive T cells are implicated in the disease pathogenesis [7, 43–45]. As in other autoimmune diseases, the skewed T-helper cytokines (most importantly, Th17 cytokines) are considered to be proinflammatory in EAU pathogenesis, whereas Th2 cytokines mediate a disease-suppressive role, suggesting that the pathogenic mimicry epitopes induce Th17 cytokine-producing cross-reactive T cells [46, 47].

Mimicry epitopes capable of inducing uveitis have been reported from various sources including self-protein, milk protein and microbes. Peptides from the HLA-B (HLA-B27PD 125-138), bovine α2-casein (Cas 73-84) and the viral outer capsid protein (VP) 4 of rotavirus (VP4 591-601) that mimic the cognate epitope, S-Ag 341-355, have been shown to induce uveitis in Lewis rats through the induction of cross-reactive T cells (Table S2) [48, 49]. Similarly, a panel of disease-inducing mimicry epitopes for another epitope of the S-Ag (S-Ag 303-320) also has been identified from a number of sources. These include two peptides from the hypothetical protein of *Escherichia coli* (ECHP 9 and ECHP 11); three viral peptides, one each from hepatitis B virus DNA polymerase (HBVDP 404-415), gag-pol polyprotein of AKV murine leukaemia virus (AKVMLVGP 347-358) and gag-pol polyprotein of baboon endogenous virus (BEVGP 354-365); and a peptide from the potato proteinase IIa (Table S2) [50–52].

It is a common belief that exposure to microbes containing mimicry epitopes for self-antigens leads to the induction of pathogenic cross-reactive T cells or autoantibodies [33, 53, 54]. However, recently, using IRBP 201-216 as a target antigen, we identified a total of 48 novel mimicry sequences from various microbial sources, and one of these, *Ehrlichia canis* (EHC) 44-59, induced cross-reactive T cells for IRBP 201-216 (Fig. 2b) [55]. Of note, EHC is a species-specific rickettsial pathogen that can induce uveitis and optic neuritis in dogs, but autoimmune responses have not been investigated in the affected animals [56, 57]. In our hands, in spite of its ability to produce uveitogenic Th1 and Th17 cytokines, EHC 44-59 failed to induce EAU. Rather, the mimicry epitope suppressed EAU induced with IRBP 201-216, an effect attributable to its ability to act as a naturally occurring altered peptide ligand (APL). Such a phenomenon also has been previously reported for one other self-antigen, myelin basic protein 87-99, in the context of experimental autoimmune encephalomyelitis [58], raising the question as to the relevance of molecular mimicry in the mediation of autoimmune diseases, ocular diseases in particular. Furthermore, similar to T cells, cross-reactive autoantibodies can also be generated in response to exposure to environmental microbes carrying the mimicry epitopes, such as streptococcal M protein for S-Ag; leptospiral recurrent uveitis (lru) A-associated proteins for alpha-crystallin B and lru B for vimentin and beta-crystallin B2 [59]; and *Klebsiella* components for vitreous humour antigens [60, 61]. Likewise, reports indicate that

autoantibodies can be present in microbial infections independent to the generation of cross-reactive immune responses. For example, rabbits infected with *Toxoplasma gondii* show antibodies for S-Ag and retinal peptide-35 [62]. Similarly, autoantibodies to the human retinal extract have been demonstrated in patients affected with chronic toxoplasmosis showing no apparent symptoms [63]. Likewise, antibodies to retinal Gal-1 and S-Ag were found to be elevated in patients with toxoplasmic retinochoroiditis [64, 65]. Although, similar associations have been reported for various other microbes, such as *Yersinia* spp [66, 67], *Mycobacterium* spp [68], *Bartonella* spp [69], *Helicobacter pylori* [70] and *Leptospira interrogans* [71], the pathological significance of autoantibodies in all of these infections is not known.

As illustrated in Fig. 3, microbes can cause ocular damage regardless of their tropism for eyes, but their disease-inducing mechanisms may vary. Oculotropic pathogens can break the BOB, causing direct physical injury to the tissues, resulting in acute uveitis. Tissue destruction also can be mediated by toxins and proteases secreted by microbes leading to the release of ocular antigens, such as IRBP, recoverin, uveal melanin, retinal S-Ag, phosducin, rhodopsin/opsin or tyrosinase-related proteins 1 and 2, which may be then recognized by the immune system as foreign [72–74]. As infections become established, inflammatory cells are recruited to the local milieu, further aggravating tissue damage. Ocular diseases induced by microbes, however, can be spontaneously resolved as the pathogens are cleared with or without treatment. But if the pathogens continue to persist, affected individuals can develop chronic disease. Alternatively, exposure to environmental microbes carrying the mimicry epitopes for retinal antigens, regardless of their tropism for eyes, can have three consequences: (1) immune-mediated damage can occur as a result of the induction of pathogenic cross-reactive T cell responses, leading to the induction of acute and chronic damage to the eyes. During this process, new ocular antigens can be released, which may become targets for immune recognition resulting in the activation of a new repertoire of autoreactive T cells. This phenomenon is termed '*epitope spreading*', the outcome of which is perpetuation of inflammation [75]. (2) Induction of cross-reactive T cells with no pathologic outcomes, or so-called sterile responses, can occur. (3) Cross-reactive T cells that appear may prove to be beneficial for the host, as we have shown with the mimicry epitope, EHC 44-59, which has the ability to suppress the disease induced with IRBP 201-216 by acting as APL [55]. Alternatively, given that Treg cells play a critical role in suppressing the expansion of autoreactive effector T cell responses, it may be possible that T cell recognition of microbial antigens carrying the mimicry epitopes may lead to the generation of Treg cells, thereby suppressing the pathogenic cross-reactive immune responses as previously proposed [76].

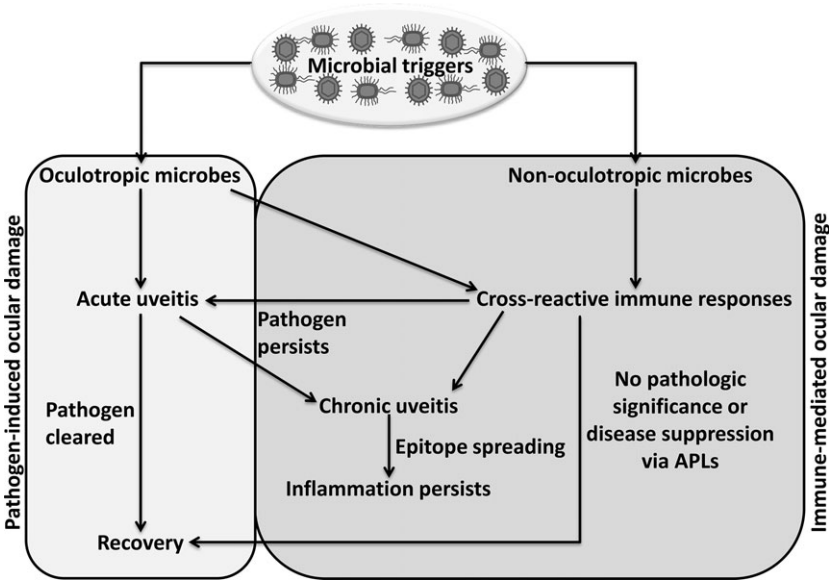


**Figure 3** Hypothetical outcomes of ocular diseases of infectious origin. Oculotropic microbes can cause acute uveitis, and the inflammation is resolved as the pathogen is cleared spontaneously or with treatment. But when pathogens persist, they can lead to chronic inflammation. Conversely, exposure to microbes bearing mimicry epitopes, regardless of their specificity for eyes, can induce cross-reactive immune responses with varying outcomes, including chronic disease, no disease or disease suppression via altered peptide ligand (APL) mechanism. Nevertheless, if chronic inflammation sets in as a result of initial damage caused by the pathogen *per se* or through the induction of uveitogenic cross-reactive immune responses, then new ocular antigens can be released as a result of epitope spreading and may become targets for immune attack. The outcome of these events is perpetuation of inflammation. This is a likely reason for the persistence of chronic inflammation in the absence of detectable infectious particles, where autoimmune responses are suspected in ocular infections.

## Conclusion

Previously, mimicry epitopes identified for various retinal antigens have been shown to induce EAU in Lewis rats. Based on our data in the mouse model of EAU [55], we propose that exposure to microbes bearing the mimicry epitopes for ocular antigens does not necessarily lead to disease; rather, the mimics can suppress the disease. Ironically, such a phenomenon has been documented for one other immune-privileged organ – the central nervous system [58]. We theorize that in typical host–parasite relationships, microbes carrying mimicry epitopes can induce pathogenic cross-reactive immune responses, and such outcomes are not favourable for survival of parasites. Alternatively, it may be possible that as parasites coexist with hosts, they can acquire the host's genetic material, leading to their survival by promoting tolerance [77].

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## Supporting Information

Additional supporting information may be found in the online version of this article:

**Table S1.** Potential infectious and non-infectious triggers of uveitis.

**Table S2.** Mimicry epitopes that can induce EAU in Lewis rats.

**Supplementary Table 1. Potential infectious and non-infectious triggers of uveitis**

| Infectious triggers | Reference | Non-infectious triggers | Reference |
|---|---|---|---|
| Viruses | | Physical/traumatic injuries | [1] |
| Varicella zoster virus | [2] | Chemical injuries | [3] |
| Herpes simplex Virus | [4] | Surgical maneuvers | [5] |
| Cytomegalovirus | [6] | Radiation exposure | [7] |
| Epstein Barr virus | [8] | Ocular tumors | [9] |
| West Nile virus | [10] | | |
| Dengue virus | [11] | | |
| Chikungunya virus | [12] | | |
| Rift valley fever virus | [13] | | |
| Influenza A (H1N1) | [14] | | |
| Human T-lymphotropic virus | [15] | | |
| Parvovirus B19 | [16] | | |
| Hepatitis C virus | [17] | | |
| Human herpes virus 6 | [18] | | |
| Human parechovirus | [19] | | |
| Human immunodeficiency virus | [20] | | |
| Rubella virus | [21] | | |
| Bacteria | | | |
| *Treponema pallidum* | [22] | | |
| *Mycobacterium tuberculosis* | [23] | | |
| *Rickettsia* spp | [24] | | |
| *Brucella abortus* | [25] | | |
| *Staphylococcus aureus* | [26] | | |
| *Pseudomonas aeruginosa* | [27] | | |
| *Borreilia burgdorferi* | [28] | | |
| *Leptospira* spp | [29] | | |
| *Bacillus cereus* | [30] | | |
| *Enterococcus faecalis* | [31] | | |
| Protozoa | | | |
| *Toxoplasma gondii* | [32] | | |
| *Toxocara canis* | [33] | | |
| *Onchocerca* spp | [34] | | |
| *Cysticercus cellulosae* | [35] | | |
| Fungi | | | |
| *Aspergillus* spp | [36] | | |
| *Candida* spp | [37] | | |
| *Histoplasma* spp | [38] | | |

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**Supplementary Table 2. Mimicry epitopes that can induce EAU in Lewis rats**

| Retinal antigen | Source of mimicry epitopes | Peptide sequence‡ | Reference |
|---|---|---|---|
| S-Ag 341-354 | | FLGELTSSEVATEV | |
| | VP4 591-601 | WTEVSEVATEV | [1] |
| | Cas 73-84 | SEESAEVATEEV | [1] |
| | HLA B27PD 125-138 | | [1] |
| S-Ag 303-320 | | DTNLASSTIIKEGIDKTV | |
| | HBVDP 404-415 | LTNLLSSNLSWL | [2] |
| | BEVGP 354-365 | PTNLAKVRTITQ | [2] |
| | AKVMLVGP 347-358 | PTNLAKVKGITQ | [2] |
| | PPI IIa 25-36 | DTNIASYKSVCE | [2] |
| | Histone H3 peptide 106-121 | DTNLAAIHAKRVTIQK | [3] |
| | ECHP 9-22 | DWLANLASSTQLCK | [4] |
| | ECHP 11-24 | LANLASSTQLCKKN | [4] |

‡Similar residues are underlined.

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