# IMMUNE-MEDIATED INTRAOCULAR INFLAMMATION

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***Sworn declaration***
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## SUMMARY

Immune mediated inflammatory diseases are categorized into autoimmune and autoinflammatory. Autoimmune etiology is represented by autoreactive lymphocytes or autoantibodies, e.g. primary Sjögren's syndrome or rheumatoid arthritis. Ocular specific diseases with presumed autoimmune origin are sympathetic ophthalmia or birdshot chorioretinopathy. Autoinflammatory diseases are caused by mutations in regulatory genes for specific immunity. Hereditary periodic fevers represent monogenic autoinflammatory diseases; eye specific is Blau syndrome also named sarcoidosis with early onset.

This article reviews the actual knowledge about immune mediated uveitides, their immunological mechanisms and the possible trigger role of infection in autoimmune inflammation. Immune privilege provides a protection of the eye against any strong immune reaction to foreign antigen, based on physical, immune, humoral and molecular mechanisms. Antigens hidden within the eye are revealed in case of damage of hematoretinal barrier caused by infection or mechanical insult. These ocular antigens have not been set as tolerable during the development and immune reaction is initiated subsequently.

Current studies demonstrate that uveogenic trigger might be generated by own microbiome, particularly when dysregulated, so called dysbiosis. There is a known association between idiopathic inflammatory bowel disease with ankylosing spondylitis and anterior uveitis in humans. Intensive research is focused on microbiome and immune mediated inflammatory disease to influence therapeutically the intestinal microbiome. The animal models are used to study the immunopathological mechanisms of uveitis and the new therapeutic strategies, because of relatively low incidence of immune mediated uveitis in humans.

**Key words:** uveitis, autoimmune disease, autoinflammatory disease, immune-mediated inflammatory disease, eye, intraocular inflammation

## INTRODUCTION

Immune-mediated intraocular inflammations are a sight-threatening condition affecting patients of younger and middle age in advanced countries. Despite the fact that the therapeutic options are constantly expanding, uveitis remains resistant to treatment in a range of patients, and 10 % of these patients lose their sight as a consequence of complications of uveitis [1,2]. An understanding of the immunopathological mechanisms leading to immune-mediated intraocular inflammation is essential for the introduction of new, targeted therapeutic options. This review article aims to present the microbial theory of the origin of intraocular inflammation, and to define the group of autoimmune and autoinflammatory diseases.

### The eye and immunity

The eye ranks among the organs with immune privilege, which means that within the intraocular environment the immune reaction to a presented antigen is suppressed in various manners. Similarly, the central nervous system and testicles are distinguished by immune privilege [3]. This phenomenon is the result of evolutionary efforts to provide protection against damage to organs and tissues with a limited capacity for regeneration.

The eye is protected from damage by physical barriers and the production of anti-inflammatory and immunosuppressant factors (Table 1).

The physical barrier between the eye and the external environment is constituted on 2 levels. The blood-ocular barrier is constituted by close links between the endo-

thelial cells of the iris blood vessels and the ciliary body blood vessels, and the epithelial cells of the ciliary body. The blood-retinal barrier (Fig. 1) is constituted by close links between the endothelial cells of the retinal blood vessels and the cells of the retinal pigment epithelium (RPE). In addition to this mechanical function, the blood--retinal barrier also ensures immunological protection by means of the cells of the "neurovascular unit" (endothelium of retinal blood vessels, perivascular macrophages, pericytes, microglia, axons of the Müller cells forming the internal limiting membrane) [4,5] and the cells of the RPE, which produce immunosuppressant mediators and with the aid of retinoic acid indicate a conversion of naive T lymphocytes to T regulatory lymphocytes [6,7]. Microglia in the retina represent a heterogeneous population of migrating cells with long axons. The activated microglia change their morphology, interact with infiltrating macrophages, in case of trauma they inhibit the destruction of photoreceptors or contribute to phagocytosis of already decayed photoreceptors. It is assumed that activated perivascular microglia have a fundamental role at the beginning of the autoimmune process by influencing adherence of leukocytes and their permeability via the blood-retinal barrier [8]. The avascular cornea and minimal lymph drainage of the eye contribute to the maintenance of immune privilege.

The phenomenon of "anterior chamber-associated immune deviation" (ACAID) has been known for many years [3,9]. Ignorance of the immune system may be established against any antigen – soluble, cellular, viral, tumour, autologous or allogenic. This antigen is transported with the aid of antigen-presenting cells via the blood to the spleen, where the formation of antigen-specific CD4+ and CD8+ regulatory T lymphocytes is induced, in which B lymphocytes and NK (natural killer) cells are also engaged. These regulatory T lymphocytes inhibit the induction and expression of specific Th1 and Th2 lymphocytes, which usually lead to the elimination of the antigen [10]. An analogous phenomenon of weakened immune response occurs also in the vitreous body and in the subretinal space [11,12].

Immunosuppressant substances, anti-inflammatory cytokines (transforming growth factor β (TGF- β), IL-10) and anti-inflammatory factors, e.g. α-melanocytes stimulating hormone (α-MSH), vasoactive intestinal peptide (VIP), somatostatin etc., were demonstrated in the anterior chamber fluid [13].

Fas ligand (FasL, CD95L) is expressed in the resident immune cells in the eye. If a Fas receptor (CD95) present on the surface of leukocytes is bound to Fas ligand during inflammation, a cascade of reactions is activated, leading to apoptosis of the target cell. Apoptosis induced by binding of "FasL-Fas receptor" represents a mechanism suppressing a strong inflammatory response in the immune privileged organs [14].

Molecules HLA I and II (human leukocyte antigen) contributing to the presentation of antigens to T lymphocytes are expressed either to a lesser degree or not at all on the resident immune cells in the eye. In addition, the role of the complement to remove infected cells or microbes

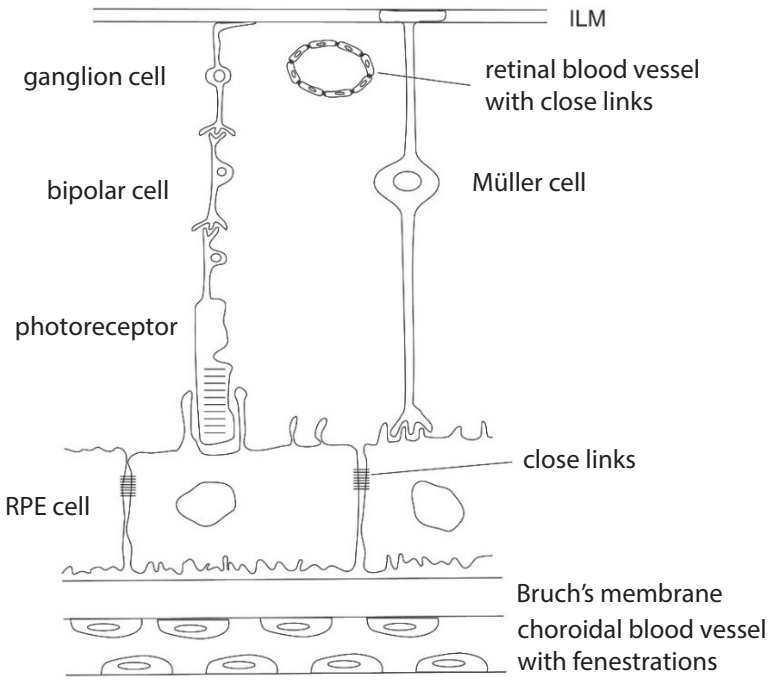


**Fig. 1.** Diagram of blood-retinal barrier. The blood-retinal barrier is secured by close links between the endothelial cells of the blood vessels and close links between the cells of the retinal pigment epithelium (RPE). ILM – internal limiting membrane.

by lysis or opsonisation for subsequent phagocytosis is radically reduced.

**Uveitis**

Uveitis arise when the immune system overcomes the mechanisms of immune privilege, resulting in a breach of the blood-ocular or blood-retinal barrier. Extravasation of plasma components takes place, with migration of leukocytes across the endothelial cells of the vessels.

Uveitis is divided according to etiology into infectious and non-infectious [15]. In cases of non-infectious uveitis, autoimmune etiology is assumed, similarly as in organ-specific autoimmune processes, where autoantigens are known. According to some authors, it is probable that cases of non-infectious or idiopathic uveitis may be caused by infection, either directly or indirectly [7,16]. The influence of microbiome dysregulation as a trigger of immune-mediated intraocular inflammation has been demonstrated experimentally. Even after the disappearance of the infectious agent, an immune reaction causing destruction of tissue may persist. This theory assumes that infection contributes more and auto-immunity less in the pathogenesis of these cases of uveitis [7].

**Autoimmune and autoinflammatory diseases**

A common feature of the group of diseases referred to by the term immune-mediated inflammatory diseases (IMID) is inflammation, despite the fact that the etiology in certain diseases has not been clarified. Advances in the understanding of the pathogenesis of immune-mediated diseases are leading to their division into autoimmune and autoinflammatory diseases (Table 2) [7,16,17,18]. Autoimmune diseases above all affect acquired immunity, and are characterised by the generation of autoantibodies or autoreactive T lymphocytes recognising specific cells or tissues [18]. Individual autoantibodies are specific for individual autoimmune diseases, although their precise role in the pathogenesis of the disease is unknown. The mere presence of antibodies does not mean the presence of autoimmune disease. In the case of autoinflammatory diseases, inflammation is caused by genetic mutations, and the innate immune system is influenced by means of macrophages and neutrophils [16,18].

**Autoimmune diseases** occur through dysregulation of the immune system, when activation of the immune cells directed against autoantigens leads to damage to the body's own tissue (Table 3). Mechanisms directed against healthy tissue are triggered as a consequence of an acquired (also referred to as adaptive or specific) immune response mediated with the aid of T and B lymphocytes. Destruction of tissues is then a result of the activity of autoantibodies or autoreactive T lymphocytes (Th1 and Th17). Some antibodies are specific for certain disorders, e.g. in the case of rheumatoid arthritis rheumatoid factor (RF) and antibodies against cyclic citrullinated peptide (anti-CCP). The majority of patients with primary Sjögren's syndrome have positive antibodies against Ro and La (anti-SSA/Ro and anti-SSB/la, anti-Sjogren's syndrome antigen A, B, antibodies against Sjogren's syndrome antigen type A and B, termed Ro and La).

**Table 1.** Mechanisms of immune defence of the eye

| **Cellular mechanisms** |
|---|
| Physical barriers (blood-ocular and blood-retinal barrier) |
| Absence of lymph drainage |
| Specific immunological mechanisms of neurovascular unit (glial and endothelial cells) |
| |
| **Molecular mechanisms** |
| Soluble immunomodulatory factors in chamber fluid (including complement) |
| Immunomodulatory ligands on surface of parenchymal cells (Fas ligand and others) |
| Antigen-presenting cells leading to immune tolerance (reduction of expression of HLA I and HLA II) |

**Table 2.** Characteristics of autoimmune and autoinflammatory diseases [18]

| **Autoimmune diseases** |
|---|
| Inflammation directed against own tissue, in which abnormal dendritic cells, B and T lymphocytes, which lead to a breach of tolerance and immune reaction against own antigens, are generated in primary (thymus and bone marrow) and secondary (spleen, lymph nodes and mucosal immune system) lymphatic organs. Illness results especially by means of an acquired immune response. Production of organ-specific antibodies may precede damage to the target organ and manifestation of illness by years. |
| |
| **autoinflammatory diseases** |
| Inflammation directed against own tissue predisposed to manifestation of illness, in which activation of innate immune cells takes place, including macrophages and neutrophils, and destruction of the target tissue. An example is disruption of homeostasis of the cytokine signalling cascade (in periodic fevers) or erroneous sensitivity to bacteria (in Crohn's disease) |

Some antibodies are non-specific (e.g. ANA, anti-nuclear), they are present also in healthy individuals and need not mean the presence of an autoimmune disease [19]. ANA antibodies are examined as standard in child patients with juvenile idiopathic arthritis (JIA), since it is known that positivity for ANA antibodies increases the risk of uveitis [20].

A large group comprises autoimmune diseases in which no specific antibody has been identified. These diseases include sympathetic ophthalmia and birdshot chorioretinopathy, in which an antibody against structures of the posterior segment is assumed. In the case of Vogt-Koyanagi-Harada (VKH) syndrome, an antibody against melanocytes is assumed, in multiple sclerosis antibodies against myelin, in JIA antibodies against joint cartilage. In the case of tubulointerstitial nephritis with uveitis (TINU) antibodies against modified C-reactive protein (mCRP) are present, in autoimmune retinopathy recoverin, alpha-enolase, carboanhydrase II, tubby-like protein 1, in systemic lupus erythematodes there are present antibodies ANA, ENA (against extractable nuclear antigens), anti SM (anti-Smith, named after the first patient in whom these antibodies were detected), ANCA (against cytoplasma neutrophils), anti-dsDNA (against double-stranded DNA) [18].

It is assumed that autoimmune reactions against retinal antigens play a fundamental role in various types of uveitis. Direct evidence of autoimmune pathogenesis has been repeatedly described in retinopathy associated with certain tumours (CAR – cancer-associated retinopathy; MAR – melanoma-associated retinopathy) with the aid of transfer of autoantibodies [21]. Despite this, demonstration of autoimmune reactions and triggering antigens in uveitis is limited.

Autoimmune uveitis can be assumed in clinical units with a strong link to HLA, for example in VKH syndrome (HLA-DRB1*0405) [22,23], sympathetic ophthalmia (HLA--DRB1*04 and DQA1*03) [24] and birdshot chorioretinopathy (HLA-A29) [25].

In addition to autoimmune diseases is the group of autoinflammatory diseases, which are caused by genetic mutations in areas involved in the regulation of innate (also referred to as non-specific) immune mechanisms (Table 4). In the case of these diseases there is a known genetic disposition, and it is assumed that the triggering mechanisms are environmental factors, infection (pathogen associated molecular pattern – PAMP) and damage to tissues (damage associated molecular pattern – DAMP).

Monogenic autoinflammatory diseases incorporate hereditary periodic fevers, e.g. cryopyrin associated periodic syndrome (CAPS), familial Mediterranean fever (MEFV), and TNF receptor associated periodic syndrome (TRAPS). These diseases are characterised by episodic fevers, skin rashes, serositis, arthralgia and myalgia. These episodes usually subside spontaneously and are not linked with the formation of autoantibodies or autoreactive lymphocytes [26].

Blau syndrome (also referred to as early onset sarcoidosis – EOS) is an example of a monogenic autoinflammatory process affecting the eyes, caused by an acquired mutation of the gene NOD2. It is usually manifested in the first year of life through dermatitis, at the age of 1-2 years by granulomatous polyarthritis; uveitis appears around the second year in 60-80 % of patients. Arthritis may result in the presence of permanent flexion of some fingers (camptodactyly). Characteristic lesions reminiscent of sarcoidosis are present on the retina [16,27].

**Table 3.** Autoimmune diseases with characteristic autoantibodies (*) and assumed autoimmune diseases

| Systemic autoimmune diseases with potential ocular manifestations | Autoimmune diseases isolated to eye |
|---|---|
| Primary Sjögren's syndrome* | Sympathetic ophthalmia |
| Rheumatoid arthritis* | Birdshot chorioretinopathy |
| Systemic lupus erythematodes* | Autoimmune idiopathic retinopathy |
| Certain cases of vasculitis (ANCA-associated etc.)* | |
| Tubulointerstitial nephritis with uveitis* | |
| Autoimmune retinopathy associated with tumours (CAR, MAR)* | |
| Multiple sclerosis | |
| Juvenile idiopathic arthritis | |
| Vogt-Koyanagi-Harada syndrome | |

**Table 4.** Examples of monogenic autoinflammatory diseases

| |
|---|
| Cryopyrin associated periodic syndrome (CAPS) |
| Familial Mediterranean fever (MEFV) |
| TNF receptor associated periodic syndrome (TRAPS) |
| Blau syndrome |

In the case of some diseases it is assumed that groups overlap or the classification is not unequivocal. According to certain authors, autoimmune-autoinflammatory, polygenic or complex autoinflammatory diseases include e.g. Crohn's disease, morbus Behçet, HLA B27 uveitis, ankylosing spondylitis, psoriasis/psoriatic arthritis and reactive arthritis, age-related macular degeneration, JIA, and TINU [7,28].

Berge et al. [28] in a cohort of 1327 patients with uveitis and/or scleritis determined that autoimmune disease was the cause in only 5 % of cases, while in 15 % this concerned autoinflammatory disease and in 14 % a combination of autoimmune and autoinflammatory disease. The most common autoimmune diseases were rheumatoid arthritis and granulomatosis with polyangiitis, and the most common manifestation was scleritis, in 53 % of cases. The low number of patients with autoimmune inflammation out of the total number of uveitis patients confirms that the designation of autoimmune uveitis should be reserved for cases of clear autoimmune origin.

Indirect evidence of autoimmunity in uveitis has been observed in animal models. Uveitis was induced following the immunisation of animals by a human retinal antigen, the immune reaction was potentiated by Freund's adjuvant containing killed mycobacteria and pertussis toxin. These animal models of experimental autoimmune uveitis (EAU) enable the study of the pathogenesis of uveitis. Various antigens have been applied (e.g. retinal antigens interphotoreceptor retinoid-binding protein or S-arrestin or lipopolysaccharide endotoxin) primarily on mouse models, causing intraocular inflammation imitating human uveitis. In other models uveitis was induced by the transfer of specific T lymphocytes against retinal antigens [29].

Cases of autoimmune uveitis in humans provide only indirect evidence of autoimmune pathogenesis, for example an increasing number of Th17 lymphocytes during active uveitis and scleritis, and their reduction during treatment [30]. The autoimmune mechanism of uveitis in humans has been demonstrated only if it was a component of a systemic autoimmune disease, and it is very probable in sympathetic ophthalmia. It is possible that damage and subsequent exposure of previously concealed retinal or choroidal antigens causes autoimmune reactions, which may play a role in certain types of uveitis [31].

The infection theory of origin of "non-infectious uveitis", now referred to by some authors as undifferentiated or idiopathic uveitis, is appearing ever more frequently in the literature [7,16]. The autoimmune theory is derived from mechanisms of uveitis in animal models, in which a breach of the blood-retinal barrier occurs, with stimulation of acquired immune reaction against retinal antigens. Nevertheless, if inflammation does not affect the retina, innate immune reaction and autoinflammatory process may predominate. An example is anterior uveitis in a mouse model induced by endotoxin (also referred to as lipopolysaccharide, which is a toxin released upon lysis of bacteria) applied in a location far from the eye – subcutaneously, intravenously or intraperitoneally. Similarly in humans, anterior uveitis occurs in 50 % of patients with ankylosing spondylitis [32,33]. Ankylosing spondylitis is associated with idiopathic bowel disease in 6-14 % of patients, and more frequently with Crohn's diesease or ulcerative colitis. Asymptomatic inflammatory changes of the intestinal mucosa are observed in as many as 60 % of patients with ankylosing spondylitis [34]. Activation of the immune system by bacterial products is assumed, in which bacterial fragments may act as an adjuvant activating innate immune reactions and probably secondarily also acquired immune reactions [35].

## CONCLUSION

New observations in immunopathology and more available genetic testing are now enabling the division of non-infectious diseases into autoimmune and autoinflammatory, and are referred to using the broader term immune-mediated inflammatory diseases. The assumed line from autoimmune to autoinflammatory diseases provides the possibility of classifying within this group illnesses with an unclear pathogenesis, in which an immune origin is assumed.

In ophthalmology the term "undifferentiated" or "idiopathic" uveitis is replacing the original term "non-infectious", due to the possible primary reaction to an infectious agent. At present it is acknowledged that chronic inflammation and tissue damage probably occurs as a consequence of excessive reaction to an infectious stimulus. The source of infectious antigens may also be the individual's own microbiome. It is possible to assume that a persistent microbial stimulus triggers chronic or recurrent uveitis. Dysregulation of the microbiome may be a predisposition or source of uveogenic stimuli..

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