
ANTIBODY RESPONSE IN UVEITIS

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The role of antibodies in uveitis is controversial. Indeed, antibodies directed at specific organisms or autoantigens could either participate in the pathogenesis or in the suppression of uveitis or could be interpreted as an epiphenomenon resulting from other processes. We will examine the role of antibodies in experimental models of uveitis: experimental autoimmune uveoretinitis (EAU), endotoxin-induced uveitis (EIU) and ocular inflammatory disorders developed in humans.

ROLE OF ANTIBODIES IN THE INDUCTION OF EAU

EAU has been described as a mainly T-cell-mediated disease. Immunisation of rats with retinal autoantigens (S-antigen (S-Ag), interphotoreceptor retinoid-binding protein (IRBP), rhodopsin, melanin-bound antigen) results in the activation of retinal-antigen specific Th1-like lymphocytes associated with delayed-type hypersensitivity to the immunising antigen.¹⁻³ The role of antibodies in the induction of EAU lesions is not clearly understood. Several lines of evidence indicate a role for antibodies in EAU induction:

1. A single immunisation with retinal autoantigens induces high titres of circulating antibodies directed at different epitopes of the S-Ag molecules from the second week after immunisation.⁴
2. Injection of hyperimmune serum to rod outer segments either in the eye or systemically results in moderate EAU.⁵ Intravenous injection of a polyclonal rat serum anti-S-Ag to a normal rat or administration of this antibody to rat eyecup preparations by bolus perfusion induces electroretinographic supernormality, indicating a direct consequence of immunoglobulin binding to its target protein and interaction with cell-surface receptors of molecules involved in photoreceptor function.⁶

3. The massive neutrophil infiltration in acute EAU might result from an immune-complex-mediated reaction, as suggested by the suppression of neutrophil infiltration by complement depletion using cobra venom factor.⁷ However, circulating immune complexes (CIC) could be involved in both the regulation and pathogeny of EAU.⁸
4. IgE antibodies specific for S-Ag, detected early in the serum of S-Ag immunised rats, may play a role in the initiation of EAU by mediating local mast cell degranulation⁹ and release of multi-functional cytokines¹⁰ which have a role in recruitment of leucocytes. The role of mast cells in the induction of EAU is further supported by several findings: mast cell degranulation occurs before the onset of EAU,⁹ development of EAU is lowered by drugs that affect mast cells¹¹ and the number of mast cells in rat choroid,¹² iris and ciliary body is correlated with the susceptibility of rats to EAU.¹³

These data would be in favour of a role of antibodies in EAU induction. However, adoptive transfer of EAU is effective with T cells without the presence of antibodies in recipients (Mochizuki^{1,14} and several reports indicate a participation of antibodies in disease suppression).

ROLE OF ANTIBODIES IN THE IMMUNOSUPPRESSION OF EAU

Regulation of EAU by Local Synthesis of Antibodies
Guinea pigs and monkeys present a chronic and subacute form of EAU characterised by lesions of photoreceptor cells with focal infiltrations of mononuclear cells of the choroid. After the acute phase of EAU, plasma cells are the most numerous cells found in the choroid infiltrates that can be detected for long periods of time in healing lesions (Fig. 1). Indeed, as detected by monoclonal antibodies directed at guinea pig leucocyte antigens, a progressive increase in B cells associated with a decrease in suppressor/cytotoxic T cells is observed in late stages of EAU.¹⁵ These findings are in favour of a role of

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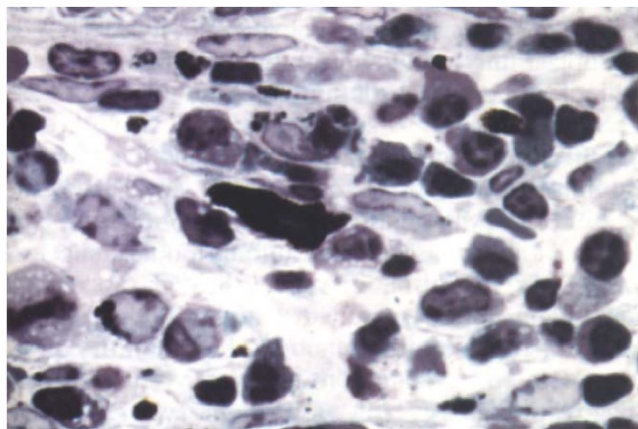


Fig. 1. Two months after one injection of purified bovine photoreceptor cells in complete Freund's adjuvant into guinea pig footpads, choroidal inflammatory infiltrate containing numerous plasmacytes is seen.

antibodies in local down-regulation on the ocular immune response.

Regulation of EAU by Antibodies Directed Against Cellular Components

Effective inhibition of EAU has been reported after treatment with antibodies directed at a variety of surface molecules expressed on cells participating in the immune reaction. Antibodies used for EAU treatment were directed against CD4,¹⁶ class II M antigen,^{17,18} interleukin-2 (IL-2) receptor,¹⁹ TCR²⁰ and adhesion molecules ICAM-1 and LFA-1.²¹ These antibodies are possibly acting through an inactivation of molecules expressed on ocular resident and/or inflammatory cells that express these surface molecules during the inflammatory process.

Regulation of EAU by Manipulation of the Idiotypic Network

According to the network theory of Jerne,²² interactions of idiotypes and anti-idiotypes, at humoral and cellular level, participate in the regulation of the immune response. Schematically, immunisation with an antibody directed against an antigenic determinant (epitope) of an antigen results in the formation of an anti-antibody (anti-idiotypic, anti-Id) recognising the hypervariable domain (idiotype) of the immunising antibody. This anti-Id, called the 'internal image' of the antigen, mimics the antigen through its stereochemical structure (Fig. 2).

Antibodies of different anti-idiotypic specificities have been shown to down-regulate EAU.²³⁻²⁶ This inhibitory effect on EAU was obtained by injecting rats simultaneously with the immunising S-Ag or with a rat polyclonal antibody to S-Ag prepared in conditions that do not produce disease, or with mouse monoclonal antibodies (mAb) directed at certain epitopes of S-Ag.²³ The mAb S2D2 was the most effective in EAU inhibition. Immunisation

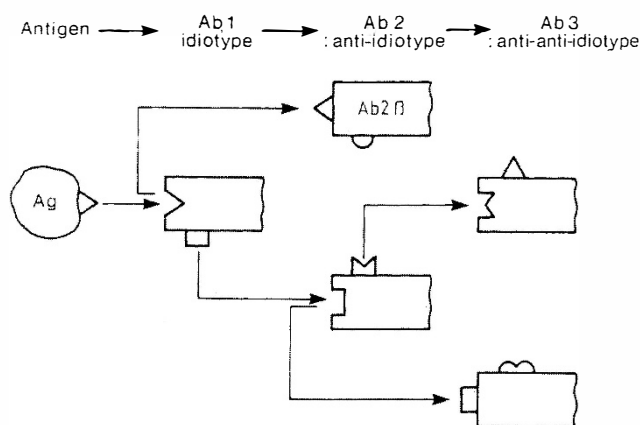


Fig. 2. Regulation of the immune response by interaction of idiotypes and anti-idiotypes (theory of idiotypic network). Ag, antigen; AB, antibody.

against the mAb S2D2 (three injections in complete Freund's adjuvant) prevented EAU induced by the injection of the whole molecule of S-Ag.²⁴ This protocol allowed the production of high levels of anti-Id antibodies, as demonstrated in an immunoassay (ELISA) by competition of anti-Id contained in rat sera with labelled S-Ag for the plate-coated mAb containing the Id. EAU suppression could be adoptively transferred by cells (anti-Id cells) from donors immunised with a polyclonal antibody directed at mAb S2D2 to recipients challenged with S-Ag. Lymph node cells from rats hyperimmunised with this anti-Id S2D2 antibody proliferated in the presence of anti-Id S2D2, mAb S2D2 and S-Ag. The suppressive effect of treatment with mAb S2D2 could result from an effect on the humoral and cellular immune network.

Interestingly, the most effective mAb responsible for EAU suppression – S2D2 – recognises an epitope (S2) situated in the N-terminal region of S-Ag (contained in peptide S2, amino acid sequence 40–50 of bovine S-Ag; peptide 4, 31–50 of human S-Ag; peptide 5, 41–60 of human S-Ag). This sequence is distant from the known pathogenic sites. The S2 epitope displays a sequence homology with an epitope of tumour necrosis factor alpha (TNF- α) (amino acid sequence 39–45 of human TNF- α , peptide RRAN). Peptides from S-Ag and TNF- α containing this common epitope have been shown to stimulate TNF- α mRNA expression and TNF- α release by human monocytes *in vitro*.^{27,28}

It has to be noted that antibodies directed against the homologous sequence in S-Ag (peptides S2, 4, 5) and TNF- α are detected in the serum of rats simultaneously injected with S-Ag and mAb S2D2 and not developing EAU.⁴ Idiotypic regulation by S2D2 would induce cells reactive to S2D2 and anti-S2D2 mimicking the S-Ag/TNF- α epitope and antibodies, internal image of epitope S2 and RRAN (Ab2), inducing Ab3 (anti-peptide S2 and RRAN)

responsible for the blockade of TNF- α and suppression of TNF- α mediated inflammation. This regulation of EAU by immunointervention on the idiotypic and cytokine networks could give an explanation for the suppressive effect of mAb S2D2 on EAU. Indeed, TNF is detected in aqueous humour and vitreous body at the onset of EAU²⁹ and could originate either from ocular resident cells, retinal Müller glial cells and retinal pigmented epithelium³⁰ in the posterior segment of the eye and/or from infiltrating inflammatory cells.^{29,31,32}

Prevention of Uveitis by Human Immunoglobulin Preparations for Intravenous Use

Human immunoglobulin preparations for intravenous use (IVIg, Sandoglobulin, Central Laboratories of the Swiss Red Cross, Bern, Switzerland) are preparations of normal polyspecific IgG obtained from large pools of healthy donors. IVIg have been shown to be an efficient therapy for immunodeficiency, bacterial infections³³ and a variety of autoimmune diseases, both organ specific and systemic.^{34,35} The beneficial effect of IVIg administration has been demonstrated in clinical situations such as idiopathic thrombocytopenic purpura,³⁴⁻³⁶ chronic inflammatory demyelinating polyneuropathy³⁷ and Kawasaki disease.³⁸ IVIg treatment was also shown to improve the clinical signs of ocular inflammation observed in birdshot retinochoroidopathy.³⁹

IVIg have been demonstrated to protect against EAU in rat⁴⁰ a Th1 cell dependent autoimmune disease in which high levels of IL-2, IL-4, interferon gamma (IFN- γ) and TNF are produced in response to S-Ag immunisation.^{41,42} This experimental model is considered an experimental model for various human ocular diseases with an autoimmune component such as sympathetic ophthalmia, Vogt-Koyanagi-Harada syndrome and birdshot retinochoroidopathy. Five daily infusions of IVIg starting on the same day as S-Ag immunisation protected rats against EAU, decreased lymphocyte proliferation S-Ag and Concanavalin A and the antibody response to S-Ag, and inhibited IL-2 production by lymphocytes in the presence of S-Ag. This suppression was not dependent upon generation of suppressor cells.⁴⁰

IVIg infusions were also shown to be effective in an ocular inflammation induced in rats by systemic injection of the lipopolysaccharide component of Gram-negative bacterial outer membranes: endotoxin-induced uveitis (EIU; unpublished data). In this ocular inflammation associated with the release of numerous cytokines, mainly IL-1, IL-6 and TNF- α ,²⁹⁻³¹ five intravenous injections of IVIg, the last given at the same time as LPS challenge, inhibited EIU and TNF synthesis in serum and ocular media. *In vitro* experiments demonstrated that

IVIg can suppress the necrotising activity of TNF on fibroblast line L-929 and inhibit TNF production by retinal Müller glial cells stimulated *in vitro* by LPS + IFN- γ .³⁰

Different mechanisms might be involved in the inhibitory effect of IVIg on EAU and EIU. The presence in IVIg of anti-idiotypic antibodies directed against disease-associated autoantibodies suggests that IVIg might be effective through V region-dependent interaction with autoantibodies and/or receptors on T and B cells.^{35,43} The inhibitory effect of IVIg was related to a state of functional inactivation/anergy of T lymphocytes. Indeed, lymph node cells from IVIg-treated rats did not proliferate in the presence of S-Ag and did not secrete IL-2 after antigen stimulation; protection was not related to suppressor cells. The protective effect could also be due to the ability of IVIg to suppress the production of numerous cytokines, mainly TNF- α , IL-1 α ,^{44,45} IL-6,⁴⁶ IL-2, IFN- γ and lymphotoxin.⁴⁷ Autoantibodies directed against different antigenic specificities including anti-TNF, anti-IL-1 α and anti-IL-8 are present in the serum from healthy individuals.⁴⁸ The presence in IVIg of antibodies to adhesion molecules⁴⁹ and to CD4,⁴⁹ which are expressed in ocular tissue during EAU²¹ and EIU,^{50,51} might play a role in the inhibitory activity of IVIg in EAU and in EIU, suggesting an effect of IVIg through the V region. Reversible Fc receptor blockade by infused IVIg might also be operative as observed in autoimmune cytopenias.^{34,35,52} The beneficial effect of IVIg on EAU and EIU could be related to the blockade of Fc receptors on cells of the reticulo-endothelial system and possibly on ocular resident cells such as epithelium of the iris/ciliary body and retinal Müller glial cells.

Interestingly, patients with birdshot retinochoroidopathy treated with IVIg for long periods of time (12-53 months) show an improvement in visual acuity without side effects.⁵³ IVIg therapy might represent an alternative in the treatment of birdshot retinochoroidopathy.

ANTIBODIES TO RETINAL ANTIGENS IN HUMAN UVEITIS

According to the network theory of Jerne, autoantibodies and anti-Id antibodies are present in serum from normal individuals. Indeed, natural antibodies to retinal antigens are detected in the healthy population.⁵⁴⁻⁵⁶ Antibodies to S-Ag (detected by ELISA) are found in patients with uveitis,^{57,58} but no clear difference is detected between patients and controls.⁵⁴⁻⁵⁶ However, other reports show that antibodies to retinal antigens are involved in pathological manifestations. Autoantibodies against ocular antigens are demonstrated by immunostaining techniques in Vogt-Koyanagi-

Harada (VKH) syndrome and in Behçet's disease, selectively binding the outer portion of the retina.⁵⁹ Antibodies found in patients with Behçet's disease adhere to the lip of guinea pigs^{60,61} and might not be specific to Behçet's disease as they are found in other inflammatory situations.⁶² Patients with retinal vasculitis present antibodies to S-Ag with lower affinity than controls.⁶³ In the serum of patients suffering from cancer-associated retinopathy (CAR), antibodies to recoverin and visinin have been detected.⁶⁴ Recoverin is a calcium-binding protein of rod outer segments and visinin may be the cone homologue of recoverin and could be the CAR antigen in cones. Autoantibodies from patients with CAR are directed at tumour antigens and cross-react with shared epitopes in the nervous system, inducing degeneration of the photoreceptors. In serum from patients suffering from cutaneous melanoma-associated retinopathy (MAR), autoantibodies against a melanoma antigen cross-react with bipolar cells and induce abnormalities of the rod and cone systems that are specific for MAR.⁶⁵

IMMUNE COMPLEXES IN UVEITIS

Circulating immune complexes have been detected in inflammatory situations including Behçet's disease,^{66,67} and have been demonstrated in the eye.^{67,68} However, in recent reports low levels of circulating immune complexes were detected in the serum of patients with severe retinal vasculitis while high titres of immune complexes often correlate with mild inflammation.^{57,69} As proposed by the authors, this finding could indicate that immune complexes are composed of idiotypic and anti-idiotypic antibodies representing a defence against potential harmful effects of antibodies.

The role of retinal antibodies in the development of uveitis, regulatory or epiphenomenal, is speculative. However, new prospects for diagnosis and treatment could arise from analysis of the immune response of patients to retinal antigens and their fragments,⁷⁰ the determination of new retinal antigens involved in pathology such as CAR antigen, and from immunointervention on the idiotypic and cytokine networks.

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