Anterior chamber associated immune device (ACAID)

Eye Learn

All about the Eye

Dr. Krati Gupta

Dr. Saurabh Deshmukh

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ACAID

1. Anterior chamber associated immune device (ACAID) - definition, mechanism and its useful effect. J2010

Definition

- ACAID is a stereotyped immune response to the antigens introduced into the eye , requires an anatomically intact eye and spleen, and depends upon the antigen specific signal in the eye that traffics via the blood into the spleen
- It is a phenomenon that induces immune-tolerance to antigens injected into the eye´s anterior chamber, provoking the reduction of such immune response.
- As the mechanisms that limit immune cell entry and induce immune suppression, the eye also contains active immune cells that act upon the detection of foreign antigens.
- These cells interact with the immune system to induce unusual suppression of the systemic immune system response to an antigen introduced into the eye.
- This is known as Anterior Chamber Associated Immune Deviation (ACAID).

Immunoregulatory Systems

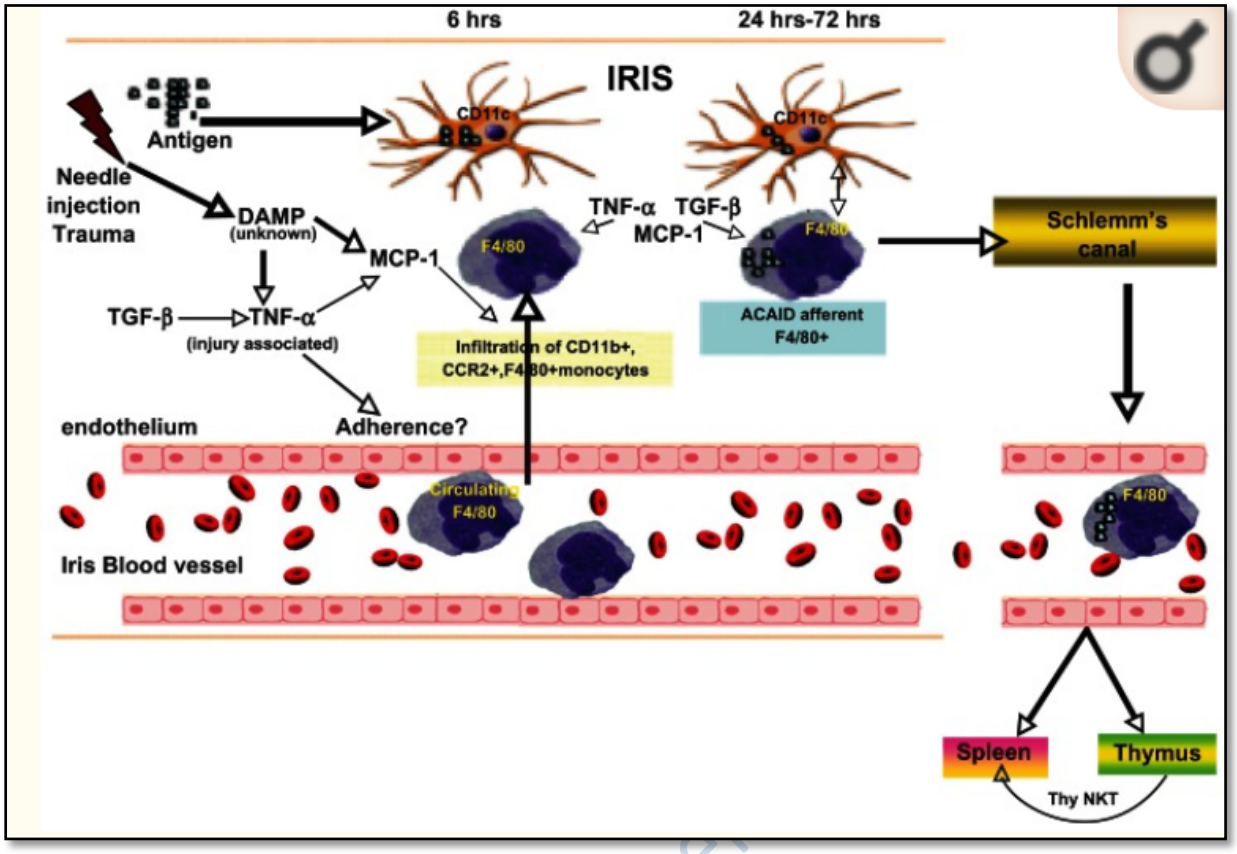
- A variety of immunoregulatory mechanisms have thus evolved to modulate intraocular immune responses.
- This concept, termed immune privilege, arose from the observation that tumor implants or allografts survive better within an immunologically privileged region, whereas a similar implant or graft is rapidly rejected by immune mechanisms within the skin or other non-privileged sites.
- Other immune-privileged sites include the subretinal space, brain, and testes.
- Ocular immune privilege has been observed with a wide variety of antigens, including alloantigens (eg, transplantation antigens), tumor antigens, haptens, soluble proteins, autoantigens, bacteria, and viruses.

Mechanisms of immune privilege

- Antigens from immune privileged regions have been found to interact with T cells in an unusual way inducing tolerance as previously opposed to a destructive response.
- Immune privilege has emerged as an active rather than a passive process.
- Physical structures surrounding privileged sites cause a lack of lymphatic drainage, limiting the immune system's ability to enter the site.
- Other factors that contribute to the maintenance of immune privilege include:
    1. low expression of classical MHC class Ia molecules
    2. expression of immunoregulatory non-classical, low polymorphic class Ib MHC molecules
    3. increased expression of surface molecules that inhibit complement activation
    4. local production of immunosuppressive cytokines such as TGF-β
    5. presence of neuropeptides
    6. constitutive expression of Fas ligand that controls the entry of Fas-expressing lymphoid cells.

- The nature of isolation of immunologically privileged sites from the rest of the body's immune system can cause them to become targets of autoimmune diseases or conditions, including sympathetic ophthalmia in the eye.

Mechanism of ACAID



Hypothetical model for events in the anterior chamber following the intracameral injection of antigen.

- The trauma of injection induces damage associated molecular pattern (DAMP) molecules that induce the production of MCP-1 and TNF-α.
- TNF-alpha is also induced and/or maintained by TGF-β in aqueous humor.
- TNF-a increases the production of MCP-1.
- MCP-1 attracts circulating F4/80+ cells that enter the anterior chamber and obtain antigen from resident iris/ciliary body F4/80+, CD11c+ cells.
- The infiltrated monocytes are influenced by TGF-β and exit the anterior chamber via Schlemm's canal.
- These cells recirculate to the thymus and spleen where they participate in the induction of regulatory thymocytes and splenic T cells.

- The best-studied model of immune privilege in the eye is called anterior chamber– associated immune deviation (ACAID).
- Whereas subcutaneous immunization with antigen elicits a strong, delayed-type sensitivity, immunization into the anterior chamber with the identical antigen results in a robust antibody response but a virtual absence of delayed-type hypersensitivity.
- In fact, preexisting delayed-type hypersensitivity can be suppressed by the ACAID response.
- Once ACAID is induced by injection of antigen into the anterior chamber, specialized macrophages residing in the iris recognize and phagocytose the antigen.

- The APC function of these uveal macrophages has been altered by exposure to immunoregulatory cytokines present within aqueous humor and uveal tissue, especially transforming growth factor β2 (TGF-β2).
- These TGF-β2–exposed, antigen-stimulated, ocular macrophages exit via the trabecular meshwork and Schlemm canal to enter the venous circulation, by which they migrate to the spleen.
- Within the spleen, the antigen signal is processed, resulting in activation of not only helper T lymphocytes and B lymphocytes but also regulatory T lymphocytes.
- These CD8+ regulatory cells serve to alter CD4+ helper T-lymphocyte responses in the spleen and downregulate CD4+ T-lymphocyte DH responses to the specific immunizing antigen at all body sites.
- Thus, the resulting effector response is characterized by a selective suppression of antigen-specific DH and a selectively diminished production of complement fixing isotypes of antibodies.
- Splenectomy eliminates ACAID, demonstrating the importance of this site for generation of immune deviation.
- ACAID represents an attenuated effector arc.
- The eye is further protected from severe inflammation by another modulating system termed effector blockade, by which Th1 lymphocytes, cytotoxic T lymphocytes, natural killer cells, and complement activation appear to function less effectively in the anterior uvea than elsewhere.
- For instance, the anterior uvea is relatively resistant to induction of a secondary purified protein derivative DH response after primary immunization with mycobacteria in the skin.
- There are several mechanisms of effector blockade, but one of the most important and best studied involves the Fas ligand (FasL, or CD95 ligand).
- The FasL is constitutively expressed on the iris and corneal endothelium and is a potent trigger of programmed cell death, or apoptosis, of lymphocytes expressing the Fas receptor.
- Thus, even if an immune response develops to an ocular antigen, the inflammation can be downregulated by this mechanism of effector blockade.
- It should be noted that ACAID and other effector blockades can be overcome by sufficient immune stimulation. Following an episode of inflammation, ACAID may be only partly restored, thus potentially reducing the eye's immune protection.

Clinical applications

- There is great potential for use of molecular mechanisms present in immune privileged sites in transplantations, especially allotransplantations.
- Compared to skin allografts, which are rejected in almost 100% of cases, corneal allografts survive long-term in 50-90% of cases.
- Immune privileged allografts survive even without immunosuppression, which is routinely applied to different tissue/organ recipients.
- Research suggests that the exploitation of anterior chamber-associated immune deviation (ACAID), aqueous humor and its anti-inflammatory properties and the induction of regulatory T cells (Treg) may lead to increased survival of allotransplants.
- Sympathetic ophthalmia is a rare disease which results from the isolation of the eye from the systemic immune system.
- Usually, trauma to one eye induces the release of eye antigens which are recognized and picked up by local antigen presenting cells (APC) such as macrophages and dendritic cells.
- These APC carry the antigen to local lymph nodes to be sampled by T cells and B cells.
- Entering the systemic immune system, these antigens are recognized as foreign and an immune response is mounted against them.

- The result is the sensitization of immune cells against a self-protein, causing an autoimmune attack on both the damaged eye and the non-damaged eye.
- In this manner, the immune-privileged property has served to work against the eye instead.