Therapeutic Implications of Immune-Privilege Mechanisms: Emphasis on ACAID

Dr. Hossam M Ashour PhD

Department of Microbiology and Immunology, Faculty of Pharmacy, Cairo University, Egypt

Anterior chamber-associated immune deviation (ACAID) is a unique example of immune privilege of the eye that culminates in systemic peripheral tolerance. ACAID is maintained by antigen-specific regulatory T cells (Tregs) that control harmful immune responses, which if not curbed, can lead to injury of the bystander cells incapable of regeneration. ACAID involves intricate cellular interactions between $F4/80^+$ ocular antigen presenting cells (APC), B cells, gamma delta (γδ) T cells, NK T cells, $CD4^+CD25^+$ Tregs, and $CD8^+$ Tregs[1,2]. This whole cascade of events is induced by simply introducing antigens into the anterior chamber (AC) of the eye. Antigens injected into the AC are processed by $F4/80^+$ antigen presenting cells (APC), which migrate to the thymus and the spleen. In the spleen, ocular APC elicit the generation and expansion of antigen-specific splenic B cells that express both MHC I and MHC II, present antigens, and are required for ACAID induction[3-5].

During the past three decades, many significant findings have been reported in the field using murine models. These findings certainly have therapeutic implications. However, the therapeutic applications of these findings to human subjects have not yet been adequately accomplished. In order to move on towards therapy, researchers have to give more attention to studies on human cells. For instance, studies have shown that by treating with TGF-β2, adherent monocytes isolated from human samples down-regulated IL-12 production and CD 40 expression in a manner similar to what was reported with murine ACAID APC, suggesting that adherent human monocytes acquired the properties of inducing ACAID by treatment with TGF-β2[6]. The striking similarities between TGF-β2-treated human monocytes and TGF-β2-treated murine APC lends promise to the relevance of conclusions drawn from murine models to human ACAID.

It is noteworthy that from a therapeutic angle, ACAID and immune privilege can cause desirable, as well as, undesirable side effects. On one hand, ACAID can help prolong the survival rates of corneal allografts, usually permitting them to persist indefinitely. On the other hand, ACAID can promote the growth of tumor cells injected into the AC of the eye. This can result in death due to the tumor extension into the brain. It is absolutely crucial to maintain the balance of immune privilege mechanisms, so as to avoid harboring tumors that can result from excessive immune privilege mechanisms and to avoid destructive ocular inflammations that can result from poor immune privilege mechanisms. Thus, the goal should be to take advantage of ACAID in therapy without compromising other functions of the host. Here are some examples that are intended to shed light on how to take advantage of ACAID in therapy and medicine.

For example, it is now known that both Th1 and Th2 cells can produce immunogenic inflammation that causes tissue destruction[7,8]. The target specificities of the T helper cells that get activated during inflammation can be tissue-restricted autoantigens (autoimmune diseases), or exogenous antigens in organs vulnerable to attack by activated T effector cells (immunopathogenic diseases). The T cells of patients of autoimmune or immunopathogenic diseases are already sensitized to the disease-associated antigens. ACAID has been shown to suppress Th1 and Th2 effector mechanisms in an antigen-specific manner, even after the generation of the immune response[9]. The ability of ACAID to inhibit the expression of immune response in the sensitized immune T cells can be utilized medically.

An ACAID-based therapy can involve the generation of antigen-specific ACAID-inducing APC *in vitro*. This can be simply done by treating conventional APC from the peripheral blood of patients with TGF-β2 followed by pulsing with the antigen associated with this particular disease. These cells can then be injected intravenously. Results of experiments on animals and humans suggest that this approach could be successful in suppressing antigen-specific autoimmunity and

immunopathogenesis[10,11]. Thus, ACAID could be adapted to induce tolerogenic immunotherapy in humans in cases of Th1 or Th2-induced inflammation.

The beauty of the aforementioned approach is that it can be used even if the target antigen is unknown, as in the case of some autoimmune and immunopathogenic diseases. This is because of the immunosuppressive factors present in the aqueous humor that can convert the patient's T cells into antigen-specific Tregs. Given that the patient's peripheral T cells contain the subpopulation of sensitized effector cells against the unknown antigen, one can induce the generation of antigen-specific Tregs by incubating the patient's T cells *in vitro* with aqueous humor, as was shown before in animal models[12].

Another ACAID-based intervention can be applied in the area of corneal transplantation in order to make corneal grafts more favorable. Graft recipients can be pretreated with their own APC that have been converted into ACAID-inducing APC by incubating them with TGF-β2 together with the donor alloantigens *in vitro.*

If treatment strategies, which are based on immune privilege mechanisms, prove to be successful, they would be expected to cause much less toxicity and side effects than some present therapies. Therefore, we have to re-consider immune privilege mechanisms as plausible alternatives to some current therapies, particularly in the areas of autoimmunity, immunopathogenesis, and corneal transplantation tolerance.

REFERENCES

1. Ashour HM, Niederkorn JY. Gammadelta T cells promote anterior chamber-associated immune deviation and immune privilege through their production of IL-10. *J Immunol.* 2006 Dec;177(12):8331-7.
2. Niederkorn JY. See no evil, hear no evil, do no evil: the lessons of immune privilege. *Nat Immunol.* 2006 Apr;7(4):354-9.
3. Ashour HM, Niederkorn JY. Expansion of B cells is necessary for the induction of T-cell tolerance elicited through the anterior chamber of the eye. *Int Arch Allergy Immunol.* 2007;144(4):343-6.
4. Ashour HM, Niederkorn JY. Peripheral tolerance via the anterior chamber of the eye: role of B cells in MHC class I and II antigen presentation. *J Immunol.* 2006 May;176(10):5950-7.
5. Ashour HM, Seif TM. The role of B cells in the induction of peripheral T cell tolerance. *J Leukoc Biol.* 2007 Nov;82(5):1033-9.
6. Shi FD, Ljunggren HG, Sarvetnick N. Innate immunity and autoimmunity: from self-protection to self-destruction. Trends Immunol. 2001 Feb;22(2):97-101.
7. Skundric DS, Cai J, Cruikshank WW, et al. Production of IL-16 correlates with CD4+ Th1 inflammation and phosphorylation of axonal cytoskeleton in multiple sclerosis lesions. *J Neuroinflammation.* 2006 May;3:13.
8. Temann UA, Laouar Y, Eynon EE, et al. IL9 leads to airway inflammation by inducing IL13 expression in airway epithelial cells. *Int Immunol.* 2007;19(1):1-10.
9. Kosiewicz MM, Okamoto S, Miki S, et al. Imposing deviant immunity on the presensitized state. *J Immunol.* 1994 Oct;153(7):2962-73.
10. Hara Y, Caspi RR, Wiggert B, et al. Suppression of experimental autoimmune uveitis in mice by induction of anterior chamber-associated immune deviation with interphotoreceptor retinoid-binding protein. *J Immunol.* 1992 Mar;148(6):1685-92.
11. Takeuchi M, Keino H, Suzuki J, et al. Possibility of inducing anterior chamber-associated immune deviation by TGF-beta2 treatment of monocytes isolated from Behcet's patients. *Exp Eye Res.* 2006 Oct;83(4):981-8.
12. Namba K, Kitaichi N, Nishida T, et al. Induction of regulatory T cells by the immunomodulating cytokines alpha-melanocyte-stimulating hormone and transforming growth factor-beta2. *J Leukoc Biol.* 2002 Nov;72(5):946-52.

Dr. Hossam M Ashour
Associate Editor
Email: hossamking@mailcity.com