EBioMedicine 70 (2021) 103516

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Tailoring immune cell behavior to stop autoimmune disease

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ARTICLE INFO

Article History:
Received 19 July 2021
Accepted 19 July 2021

While the ocular microenvironment normally expresses within its tissue microenvironment potent suppressors of inflammation, it is still susceptible, albeit rare, to autoimmune disease. Uveitis is a general term for intraocular inflammation that includes idiopathic inflammation assumed to be autoimmune in nature. The incidence rate of uveitis is 17−115 cases per 100,000 persons [1,2]. This makes it the third leading cause of blindness in the United States, and the standard therapy, like for most inflammatory diseases, is corticosteroids. This treatment is effective for many; however, as much as 60% of treated patients will have a recurrence of uveitis within 5 years and almost 18% of the patients become unresponsive to corticosteroid treatment to suffer chronic uveitis [3]. Therapeutic alternatives like biologics rely mostly on a trial-and-error approach to find an effective dose that balances between suppressing uveitis and susceptibility to infections and side effects [4]. Each time an attempt fails vision is further degraded by the uveitis. Therefore, therapies that focus on the autoimmune activity targeting the eye with minimal side-effects would improve the health and quality of life for patients with chronic uveitis.

The most common used animal model for uveitis is Experimental Autoimmune Uveitis (EAU) in mice. Many research groups have used EAU to not only understand the immunobiology of uveitis, but also evaluate the effects of therapeutic approaches to suppress uveitis. This model differs from human uveitis in that it is not spontaneous. Also, it resolves without intervention; however, there is substantial damage to the retina. This self-resolution of EAU is mediated by emergence of Treg cells with retinal-antigen specificity [5,6]. This has suggested that an approach that can augment Treg cell activity during uveitis can promote resolution, provide long term resistance to recurrence, and hopefully preserve vision.

In the manuscript by Chen et al. [7] they demonstrated an approach to expanding retinal-antigen specific Treg cells during EAU using anti-CD4-antibody (αCD4 Ab) therapy along with injecting retinal antigens. This generated antigen-specific Treg cells that suppress EAU. The approach to use αCD4 Ab is based on the idea that a systemic depletion of CD4 T cells would stop severe autoimmune disease with augmentation of Treg cells, which are refractory to αCD4 Ab-depletion [8,9]. The depletion of CD4 T cells raises concerns about losing resistance to infection and tumor growth. As others have shown, Chen et al. showed that their approach did not diminish resistance to tumor growth; however, they did not test the possibility of impaired defense from infection. While the αCD4 Ab-therapy had induced a generic Treg cell response, which was effective in suppressing EAU, only when antibody-therapy was combined with retinal antigen injections was there seen substantial suppression of EAU and IL-17 production by effector T cells. This approach demonstrates the potential to drive *in vivo* an antigen-specific Treg cell.

To explain the outcome of the therapy, Chen et al. propose that the antigen presenting cell (APC) uptake of apoptotic CD4 T cells along with the retinal antigen makes the APC present antigen in a manner to induce antigen-specific Treg cells. While their results support this possibility there are some interesting parallels with their findings and what is found when the mice self-resolve EAU [5,6]. Chen et al. show an antigen-specific accumulation of Treg cells in the eye. The accumulation of Treg cells within the eye is important for the self-resolution of EAU [5]. Also, there is in the spleens of self-resolving mice an APC that induces retinal-antigen specific Treg cells. Chen et al. found a Treg cell-inducing APC in the spleen; however, this induction of Treg cells is TGF-β-dependent, whereas in self-resolving EAU mice it is melanocortin and adenosine-dependent induction of Treg cells by the APC [6]. Interestingly, there is a known TGF-β-dependent pathway in the eye that induces an APC to mediate systemic tolerance to foreign antigen placed into the eye [10]. Whether the αCD4 Ab-treatment induces a similar APC is to be seen, but the ocular microenvironment is effective in inducing apoptosis in immune cells and could be the same apoptotic-inducing mechanism between αCD4 Ab treatment and injecting antigen into the eye. Since, the αCD4 Ab-therapy depletes the effector T cells this may be enough to enhance the self-resolving mechanisms with antigen specificity. While there remain many questions whether this can be translated into a safe and effective therapy for uveitis in humans, the approach does demonstrate the strength of looking at autoimmune disease therapy in a new way. Instead of applying general immunosuppressive or anti-inflammatory drugs with the hope that suppressing the inflammation will accord the tissue site and the immune system time to revert to normal, the work of Chen et al. promotes an approach

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.103496.
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https://doi.org/10.1016/j.ebiom.2021.103516

that directly manipulates the behavior of immune cells from mediating an autoimmune disease to the ultimate desired mediators of antigen-specific tolerance.

Contributors

The work was solely written by AWT.

Declaration of Competing Interest

AWT is a scientific consultant and recipient of a sponsored research agreement from Palatin Technologies, NJ, USA

Acknowledgement

AWT is supported in part by a grant from the National Institutes of Health EY025961.

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