Observations in clinical and experimental ocular autoimmunity

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Outline of the thesis

Despite the introduction of steroids more than a half century ago, many people still go blind from ocular inflammation. Uveitis is the third leading cause of blindness in the United States and most of the visual impairment is brought about between the ages of 20 and 50. The social and economic impact of visual impairment in this age group is often underestimated. These individuals are denied the opportunity, through their visual impairment, to contribute actively to the well being of a nation. They are often a burden on family and friends. You only need to consider how difficult it is for these patients to visit their eye doctors, how often appointments need to be changed, how often they require assistance to be seen.

Despite having such an impact, uveitis is studied by a limited number of individuals. It does not possess the glamour of many other illnesses for which well organized patient associations raise money, or evoke the same level of fear as cancer does in our collective ethos. When compared to other autoimmune processes which can be life threatening, loss of sight seems so unimportant. Yet, these patients require care, and new alternatives.

The present thesis attempts to address two main issues (1). Understanding the relevance to human disease of the experimental autoimmune model of uveitis EAU. This is the subject of the first two sections of the thesis. The first attempts to define the specific immunopathogenic determinants of S-Ag and Interphotoreceptor Retinoid Binding Protein (IRBP), both potent uveitogens, in the experimental model EAU. An attempt is also made to determine intracellular binding mechanisms for these proteins in antigen presenting cells, identifying in the process a novel chaperone. In the second section, attention is turned to the potential role of these proteins in humans. Means of identifying relevance in a variety of uveitic conditions, as well as an attempt at devising means of following patient responsiveness over time are explored in a series of 4 articles. The second issue to be addressed is the use of the experimental model to develop novel treatment strategies. In section III are presented trials in animal models of novel anti-inflammatory therapies. Section IV discusses treatment modalities used in humans and presents some of the short and long term risks associated with the implementation of new therapies. Cyclosporine was first tested in an animal model and found to be 100% effective at preventing disease. Clinical use demonstrated a number of complications which required the development of treatment algorithms and dosage adjustments. Attempts were made to reduce toxicity by drug combination as shown. Finally, an approach using immune modulation by antigen feeding is presented. This promising technique has not produced the expected results once the study was completed, but remains an interesting and potentially useful approach. It is included here, as an example of a trial which generated much controversy, and stimulated researchers to search for new therapeutic modalities. It is the forerunner of more sophisticated approaches looking at local immune modulation in the eye (including the use of gene therapy).

While this thesis does not and cannot hope to prevent blindness in uveitis, it is hoped that some of the techniques and approaches used here may be of benefit in understanding the pathophysiology of uveitis in humans. Hopefully, it can serve as a foundation for a more systematic study of its course in humans, and lead to judicious therapeutic choices using both existing, and yet to be discovered drugs.