The natural history of uveitis

Robert B. Nussenblatt
National Eye Institute, National Institutes of Health, Bethesda, Maryland, USA

Accepted 12 April 1990

Key words: uveitis, T-cell, Sandimmune, S-antigen, EAU, HLA, cyclosporine

Summary

Inflammatory diseases of the eye were known to the ancients, but only recently have the underlying mechanisms to this problem become better defined. During the middle portion of this century, most cases of uveitis thought to be caused by infectious agents, such as those responsible for syphilis and tuberculosis. Since then, it has become clear that endogenous mechanisms of immunomodulation play an important role in these disorders, which along with environmental and genetic factors make up an important triad. Animal studies have indicated the pivotal role of the T-cell in many of these disorders. The development of T-cell lines has helped to further delineate cell to cell interactions that occur during an ocular inflammatory event. The presence in the eye of uveitogenic antigens raises the strong possibility of autoimmune driven processes as well, similar to what is seen in the animal models. The better understanding of ocular inflammatory mechanisms has led to improved therapeutic strategies, including Sandimmune, and more recently Cyclosporine G, a related compound that may be less nephrotoxic. Newer therapeutic strategies will focus on even more novel modes of immunomodulation, probably without the use of medications.

Introduction

Intra-ocular inflammatory disease or uveitis is a collection of conditions that were known to the ancients [1]. Reports of ocular inflammations by both the ancient Greeks and Chinese expertly describe many conditions that we recognize today as distinct entities, such as Behcet's disease. Today, uveitis is a condition that causes about 10% of the visual handicap in the Western World. The incidence of this condition in the Third World still needs to be determined. In the United States, it is responsible for about 30,000 new cases of legal blindness each year.

The causes of uveitis have been a source of intense interest for many years, pre-occupying the minds of many in ophthalmology. Of interest is the observation early in this century by Uhlenhuth [2] that autoimmune responses could be elicited after immunization with lens antigen, and the theory proposed by Elschnig [3] that an uveitogenic substance was present in the eye. This concept has been accepted for a small minority of ocular conditions, of particular note sympathetic ophthalmia. However, in the past, the majority of thought concerning mechanisms centered around an infectious cause. For many, the diagnosis centered around two disorders, that of syphilis and tuberculosis [4]. With time, it became clear that these two diagnoses could not fully explain the disorders being seen, and that clearly other mechanisms were at play. Antibody mediated mechanisms became an area of active interest in the 1960's and 70's. Immune complex mediated disease (type III hypersensitivity reactions) was hypothesized as mediating a large if not almost majority of the disease noted [5]. This
observation was certainly supported by the presence of circulating immune complexes in uveitis patients [6]. However, histologic evaluation of uveitic eyes in the main does not support such a mechanism of action, and more recent observations would support rather that immune complexes could be having a salutary effect [7] rather than a detrimental one.

During the 1960's and seventies, the capacity to do widespread histocompatibility (HLA) testing became feasible. Even the initial observations implicated diseases with ocular complications as being part of the group of disorders with a genetic predisposition. These observations have had a significant impact on the development of concepts concerning inflammatory disease mechanisms. As with all areas of study, the gaining of additional information has in the end emphasized the large gaps in our knowledge.

More recently, endogenous dysregulation has been investigated in depth. The role of T-cells and their interaction with parts of the immune system as well as resident ocular cells has gained a great deal of attention [8]. Coupled with the identification of uveitogenic ocular antigens, in vitro and animal systems were developed to explore many basic questions of inflammatory disease of the eye. At the present, it would appear that three dominant themes play an interdigitating role which leads to the ultimate expression of uveitis: the environment, immunogenetics, and endogenous dysregulation, the latter possibly autoimmune driven (Fig. 1). The attempt of this monograph is to explore some of these recent observations, and to demonstrate how an improved understanding of immune mechanisms can lead to more refined therapeutic approaches.

Fig. 1. Diagram showing the major themes stressed in this manuscript and the potential areas where they may affect the ocular inflammatory response.