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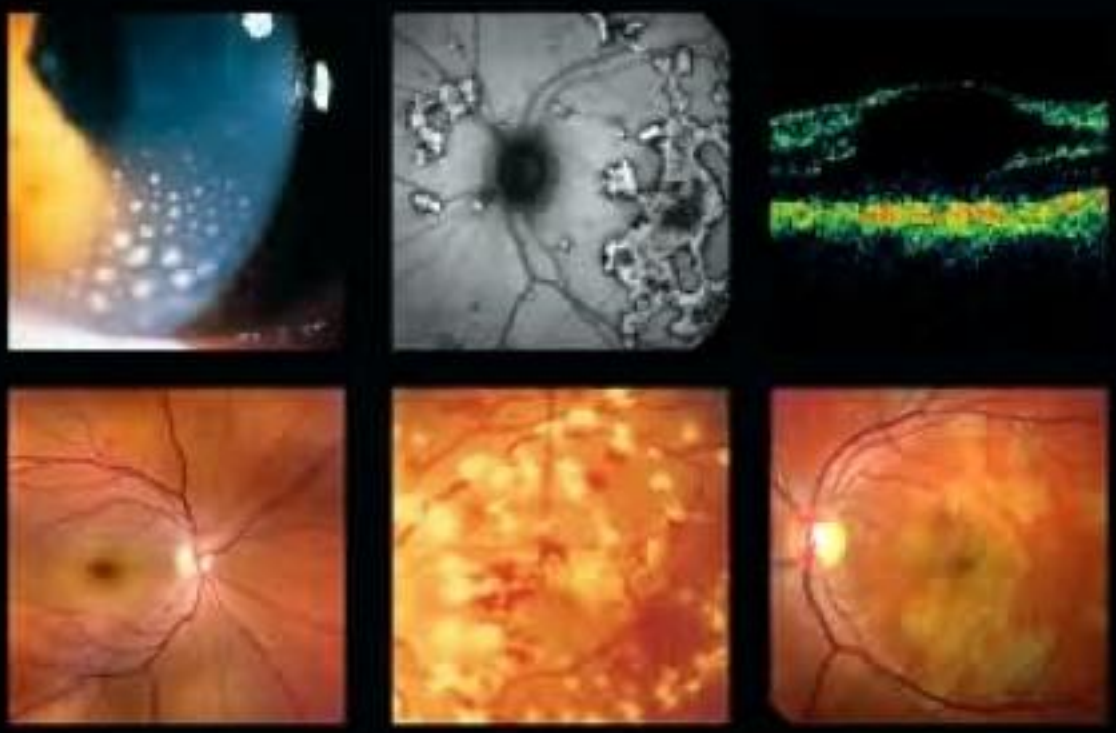
UVEITIS

FUNDAMENTALS AND CLINICAL PRACTICE



FOURTH EDITION

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UVEITIS

FUNDAMENTALS AND CLINICAL PRACTICE

Fourth Edition

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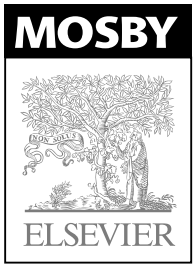

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Foreword

Since the last edition of this book in 2004, there again has been tremendous progress in understanding the basis for intraocular inflammation, and a number of novel immunotherapies for autoimmune diseases has become available for physicians. Advances in immunology, molecular biology, cell biology, imaging, and other aspects of the biomedical sciences continue to foster new approaches to the study of inflammatory diseases, both in the eye and in the rest of the body. Nevertheless, the diagnosis and treatment of uveitis remains a significant challenge for ophthalmologists and other health care practitioners.

Fortunately, scientific advances have led to improvements in our ability to study the disease and optimize the way we approach the patient with uveitis. Genetic studies have identified new pathogenic mechanisms of ocular inflammation. Since the last edition of this book, these studies have implicated the complement pathway in the pathogenesis of age-related macular degeneration. New diagnostic and analytical tools, including advances in ocular coherence tomography have improved the way we diagnose patients and assess their response to therapy.

I have had the opportunity to work closely with Dr. Whitcup and Dr. Nussenblatt for more than two decades. Both are widely recognized as leading authorities in the field of uveitis. The fourth edition of Uveitis: Fundamentals and Clinical Practice remains the authoritative text and will be of great use to ophthalmologists and other doctors who see and manage patients with ocular inflammatory disease. The book remains unique—it is not only a thorough review of the basic and clinical science of uveitis but also a practical guide to the diagnosis and management of patients with inflammatory eye disease.

In Part 1, the authors start with a thorough discussion of the fundamentals of inflammation and review the immunology of uveitis. In Part 2, they provide an organized description of the diagnostic approach to the patient with ocular inflammation. The ophthalmic history and examination, diagnostic testing, and guides to developing a differential diagnosis are reviewed. This section also provides an insight into the evaluation of the uveitis literature. In Part 3, the authors offer the reader a thorough approach to the medical and surgical therapy of uveitis, followed by a section on infectious uveitic conditions in Part 4, and 13 chapters related to diseases and syndromes of uveitis in Part 5.

The chapters are definitive yet practical reviews on their individual topics and they are well integrated to cover the entire field with few omissions and little duplication. Chapters are well-illustrated and this edition has been newly formatted with color figures and photographs throughout the text. For example, the chapter on acquired immunodeficiency syndrome (AIDS) remains comprehensive, up to date, yet readable. Results from important clinical trials are succinctly summarized. There is an excellent presentation of cases and photographs that emphasize both the disorder and the treatment of patients with ocular complications of AIDS.

There have been a number of important additions and updates to this new edition. In addition to the chapter on AIDS, the chapter on medical therapy has been extensively updated and reviews a number of new therapeutic approaches to patients with inflammatory disease, including biologic agents that block tumor necrosis factor. Dr. Whitcup has expanded the discussion of bacterial and fungal causes of uveitis, and this is now divided into two chapters, Chapters 9 and 10, and has added a discussion of evidence-based medicine in the section on diagnosis. Dr. Nussenblatt has written a new chapter discussing the role of inflammation in other retinal diseases including age-related macular degeneration and diabetic retinopathy. In addition to new color illustrations throughout the book, key concepts have been added to each chapter to focus the reader on the key take-home messages.

The authors have divided this edition of the book into 31 chapters and brought each of their individual strengths into this partnership. They worked together for almost a decade at the National Eye Institute, and their cohesive approach to uveitis benefits the reader. The scholarship and experience of the authors provide a unified textbook that can be read cover to cover, or used as a reference guide that is at the forefront of clinical medicine. Each chapter is authoritatively presented, well-illustrated, and practical. The authors have again given us an excellent textbook on uveitis, which ophthalmologists and other practitioners will find useful in taking care of their patients. This is a book which will be frequently used by clinicians and will improve the care of the challenging patient with uveitis.

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Preface

The 21st century may be remembered as the true golden age of medicine. Advances in molecular biology, immunology, pharmacology, and drug discovery that began and matured over the last 50 years will lead to substantive changes in the way we diagnose and treat our patients with uveitis in the decades to come. Prior to 1950, treatment for uveitis was severely limited. Many physicians treated patients with uveitis by inducing hyperpyrexia. Patients were placed into steam baths where their temperatures were raised to 40 to 41 degrees centigrade for four to six hours. Although occasionally successful, Sir Stewart Duke-Elder did note that the treatment was poorly tolerated and often dangerous for the patient. In 1949 Philip Hench and colleagues reported the successful use of corticosteroids for the treatment of rheumatoid arthritis. Ophthalmologists were quick to use corticosteroids for the treatment of ocular inflammatory disease, and interestingly, despite profound improvements in immunotherapy, steroids remain the mainstay of therapy even today.

However, many patients remain resistant or become intolerant to corticosteroid therapy. Spawned by the need for better immunosuppression for transplant surgery, a number of new and effective immunosuppressive agents have been developed. More recently, a number of novel immunologic therapies have aided physicians in the treatment of autoimmune disease. Drugs that specifically target cytokines and cytokine receptors are now commonly used in the treatment of diseases such as rheumatoid arthritis and increasingly employed in the treatment of severe uveitis. Intravitreal injections and sustained-release intravitreal implants have allowed physicians to deliver high amounts of drugs to target tissues in the eye while avoiding systemic side effects. Nevertheless, the cause of many forms of uveitis remains unknown, and vision loss is still an all too common occurrence in our patients.

Even since the publication of the third edition of our book, there have been a number of significant advances in basic science, technology, and clinical medicine that impact our approach to uveitis. First, the field of immunology continues to move forward. New cytokines and inflammatory pathways have led to a better understanding of disease pathogenesis and novel therapeutic targets. The roles of IL-23 and Th17 cells in autoimmune disease and uveitis have been described and new therapies are being developed that target this pathway. Second, new technologies are changing the way we diagnose and follow our patients. Ocular coherence tomography is now commonly used to evaluate macular edema and assess the response to therapy. PCR is more frequently used to diagnose infectious etiologies for uveitis and allow specific antimicrobial therapy for patients who were previously misdiagnosed. Third, we have new therapies in our armamentaria, including novel immunosuppressive agents and biologics that target key inflammatory cytokines, cell adhesion molecules, inflammatory cells, or other critical components of the inflammatory response. Fourth, advances in drug delivery allow us to administer high amounts of drugs directly to the diseased tissues and minimize systemic exposure and treatment-limiting side effects.

The goal of this fourth edition of Uveitis: Fundamentals and Clinical Practice remains the same as that of the first three – to provide a comprehensive text presenting a practical approach to the diagnosis and treatment of various forms of the disease. The book includes a review of the fundamentals of ocular immunology but focuses on the clinical aspects of the disease. We believe that our book will be of value not only to ophthalmologists, optometrists, and other eye care providers, but also to internists, rheumatologists, and other physicians who see patients with diseases associated with uveitis.

Again, the text is divided into five parts. Part 1 includes a single chapter on the immunology of uveitis. Part 2 on diagnosis includes detailed discussion of the medical history, clinical examination, and diagnostic testing in the patient with uveitis. Part 3 includes two chapters covering the medical and surgical therapy of uveitis. In Part 4, uveitic syndromes with known infectious etiologies are reviewed. In Part 5, a number of other uveitic diseases and syndromes are included – some which may have an infectious etiology that has not been elucidated. With improvements in our diagnostic testing, we are identfying specific infections as the cause for more forms of uveitis. We now know that *Tropheryma whipllei* causes Whipple's disease, and the section on uveitis associated with this disease has now been moved from the chapter on anterior uveitis to the chapter on bacterial and fungal diseases. Finally, we have added a chapter on the role of inflammation in diseases other than uveitis, including macular degeneration.

We have based this book, to a large extent, on our clinical experience, both at the National Eye Institute where both of us spent time seeing patients together, and at the Jules Stein Eye Institute. We owe a great deal of thanks to Alan Palestine who helped make the first edition of the book a reality and continue to express our gratitude to Chi-Chao Chan, Igal Gery, and Rachel Caspi for their knowledge and friendship and to our fellows for their inquisitiveness and comradeship. We must also thank the photographers of the National Eye Institute and a number of our colleagues for obtaining the artful clinical photographs. Importantly, we must thank our patients who value the opportunity to contribute to the understanding of their disease in an attempt to help others.

Finally, we thank our families and friends for their support and tolerance in allowing us to work on yet another edition of the book.

Scott & Bob

Dedication

To Rosine, Veronique, Valerie, and Eric.
Bob

I would like to dedicate this book to my father whose love, support, humor, and inquisitiveness will always be a part of me; and to my family and friends.
Scott

For our colleagues and patients.

Acknowledgments

We would like to thank the photographers and ophthalmic technicians of the National Eye Institute for their assistance in obtaining photographs, angiograms, and other materials for the book. We also want to thank our colleagues who supplied outstanding images that help to bring our text to life.

Elements of the Immune System and Concepts of Intraocular Inflammatory Disease Pathogenesis

Robert B. Nussenblatt

Key concepts

- T cells play an important role in the pathogenesis of uveitis.
- The eye is very active immunologically, with ocular resident cells interacting with the immune system.
- Uveitogenic antigens are found in the eye, and immunization of animals with these antigens induces experimental uveitis, often resembling the human condition.
- Similar immune responses can be seen in the experimental models of uveitis as in the human condition.

In an ever-changing field, a review of the immune system is the subject of numerous books, courses, and scientific articles. However, certain principles have been established that, in the main, have survived the test of time and rigorous scrutiny. The aim of this chapter is to provide the reader with the essentials needed to follow a discussion on mechanisms proposed for intraocular inflammatory disease; therefore, topics relevant to the understanding of that subject are addressed. In addition, selected themes thought to be important in understanding the unique ocular immune environment and pathogenesis are covered. It is clear to any observer of immunology that a detailed description of immune events would be far beyond the scope of this book, and it would hubris to think otherwise. For those well versed in this field, parts of this chapter may be somewhat superfluous.

The development of the immune system is an extraordinary product of evolution. Its goal is to recognize that which is different from self, so its initial role is to respond to foreign antigens with an innate immune response that is geared to rapidly clear the body of the foreign invader. 'Innate immunity' is restricted to the non-antigen-specific immune response involving phagocytic cells that engulf and destroy invaders, humoral factors such as the complement system and receptors on antigen-presenting cells such as phagocytes called 'toll-like receptors' that interact with the invaders' molecules. This activates the antigen-presenting cell to initiate the 'adaptive' immune response. Clearly the invader may return, and so the adaptive immune response is in place to respond. The adaptive immune response is antigen specific and deals with the invaders that escaped the innate immune mechanism or have returned. The adaptive immune response consists of both B and T cells, and portions of these populations acquire the properties of memory cells of the secondary immune response. This adaptive immune response connotes an immune memory, hence the development of a complex way in which high-affinity molecules and cell-surface markers can distinguish between the invader and self. A given of this concept is that self antigens are not attacked: that is, an immune tolerance exists. Part of our story deals with the immune system's appropriate response to outside invaders (such as *Toxoplasma*) and the other part deals with understanding (and trying to explain) the response to autoantigens. The dynamic is not as simple as outlined; in fact, it starts as an appropriate response to a foreign antigen and then changes to an abnormal response against the eye. Many mechanisms, such as molecular mimicry, have been proposed.

To achieve this complex but highly specific immune response requires multiple players. Some of these are reviewed in the first part of this chapter. In the second part findings and theories of disease mechanisms relevant to the ocular diseases discussed in later chapters are introduced.

Elements of the immune system

The immune system is the result of several cell types, including lymphocytes (T and B cells), macrophages, and polymorphonuclear cells. However, additional cells, such as dendritic cells in the skin and spleen and ocular resident cells in the eye, also should be included. These components add up to a complex immune circuitry or 'ballet,' which in the vast number of individuals responds in a way that is beneficial to the organism.

Macrophages/monocytes

Phagocytic cells originate in the bone marrow. The concept that phagocytosis is important for the immunologic defense of the organism was proposed by Metchnikoff at the end of the nineteenth century. The macrophage, which is relatively large (15 μm), has an abundant smooth and rough endoplasmic reticulum. Lysosomal granules and a well-developed Golgi apparatus are also found. Several functional, histochemical, and morphologic characteristics of these cells can be noted (**Table 1-1**). In addition to the phagocytic

*The author thanks Drs William Paul and Igal Gery for reviewing this chapter. The helpful parts of the chapter are due to their good and wise counsel. The parts that are less so are due to my own shortcomings. RBN

Table 1-1 Macrophage characteristics

Histochemical	Surface Antigens	Receptors	Functions
5′-Nucleotidase	OKM1	Fc	Phagocytosis
Esterase	Class II antigens	IgM	Pinocytosis
Alkaline phosphodiesterase		Lymphokine	Immune activation
Aminopeptidase		Lactoferrin	Secretory
Insulin			Microbicidal
		Cb3	Tumoricidal
		Fibrinogen	
		Lipoprotein	

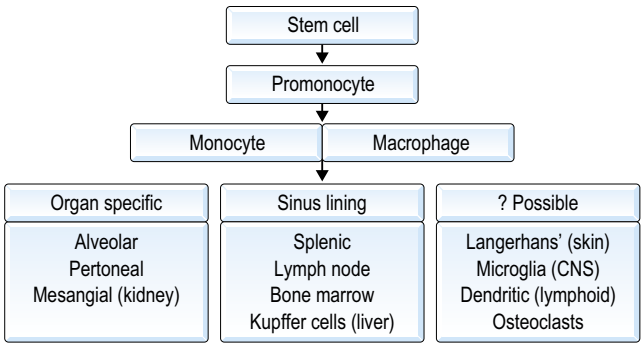

Figure 1-1. Macrophage differentiation.

characteristics already alluded to, these cells contain esterases and peroxidases, and bear membrane markers that are typical of their cell line (i.e., OKM1 antigen and F4/80). Other cell-surface markers are also present, such as class II antigens, Fc receptors (for antibody), and receptors for complement. These enzymes and cell markers help to identify this class of cells as well as their state of activation. The presence of esterase is a useful marker to distinguish macrophages from granulocytes and lymphocytes. Monocytes will leave the bloodstream because of either a predetermined maturational process or induced migration into an area as a result of chemotactic substances, often produced during inflammatory events. Once having taken up residence in various tissues, they become macrophages, which are frequently known by other names (**Fig. 1-1**). Dendritic cells, such as Langerhans' cells, are found in the skin and cornea, and play an important role in activating naive lymphocytes.

Macrophages play at least three major roles within the immune system. The first is to directly destroy foreign pathogens as well as clearing dying or diseased tissue. Killing of invading microbes is in part mediated by a burst of hydrogen peroxide (H_2O_2) activity by the activated macrophage. An example with ocular importance is the engulfment of the toxoplasmosis organism, with the macrophage often being a repository for this parasite if killing is inadequate. The second is to activate the immune system. Macrophages or other cells with similar characteristics are mandatory for antigen-specific activation of T lymphocytes. Internalizing and processing of the antigen by the macrophage are thought to be integral parts of this mechanism, and the macrophage (or dendritic cell) is often described as an antigen-presenting cell (APC). Other cells, such as B cells, can also serve this function. The macrophage and lymphocyte usually need to be in close contact with one another for this transfer to occur. Another requirement is for the cells to have in common a significant portion of their major histocompatibility complex (MHC), genes that express various cell-surface membranes essential for cellular communication and function. Thus this MHC stimulation leads to the initiation of an immune response, ultimately with both T and B cells potentially participating. Other cell-surface markers are needed for activation. This 'two-signal' theory has centered on other cell-surface antigens, such as the B7–CD28 complex. The engagement of B7 (on the macrophage side) with CD28 enhances the transcription of cytokine genes. Third, the macrophage is a potent secretory cell. Proteases can be released in abundance, which can degrade vessel surfaces and perivascular areas. Degradation products that result from these reactions are chemotactic and further enhance an immune response. Interleukin (IL)-1, a monokine with a molecular weight of 15 000 Da, is produced by the macrophage (as well as other cells) after interaction with exogenous pathogens or internal stimuli, such as immune complexes or T cells. IL-1 release directly affects T-cell growth and aids this cell in releasing its own secretory products. IL-1 is noted to act directly on the central nervous system, with a by-product being the induction of fever. Still other macrophage products stimulate fibroblast migration and division, all of which have potentially important consequences in the eye.

Macrophages produce IL-12 and IL-18 (once called interferon (IFN)-γ-inducing factor), IL-10, and transforming growth factor (TGF)-β. In a feedback mechanism, IFN-γ can activate macrophages, and the production of IL-12 by the macrophage plays an important role in T-cell activation. The role of macrophages in the eye still needs to be fully explored. One concept (in a disease not usually thought of as being immune driven) is that chronically activated macrophages congregate at the level of the retinal pigment epithelium (RPE), inducing the initial changes that lead to age-related macular degeneration.

Dendritic cells

Although macrophages play an important role, it is conjectured that dendritic cells are important macrophage-like cells in tissue. They are a subset of cells, perhaps of different lineage from macrophages, from which they can be distinguished by a lack of persistent adherence and by the bearing of an antigen, 33D1, on their surface, features that macrophages do not possess. The major role of dendritic cells is to serve as initiators of T-cell responses, for both CD4+ and CD8+ cells. Like macrophages, dendritic cells produce IL-12, an important activator of T-cell responsiveness. They are rich in MHC II intracellular compartments, an important factor in antigen presentation. The MHC class II compartments will move to the surface of the cell when the dendritic cell matures, stimulated by IFN-α and the CD40 ligand. Dendritic cells are special in that they inhabit tissues where foreign antigens may enter. Experiments with painting of the skin brought seminal observations. Antigens painted on the skin are 'brought' to the draining lymph nodes by the

dendritic cells of the skin (Langerhans' cells) where T-cell activation can occur. What is interesting is the migratory nature of these cells: they constantly carry important information to peripheral centers of the immune response. Whether dendritic APCs can activate T cells efficiently in the tissues themselves is an open question and is important to our understanding of immune responses in the eye. Dendritic cells are thought to be the APCs (or one of the major players) in corneal graft rejection. Thus the concept of removing dendritic cells from a graft has been proposed and used in experimental models. However, there is an opposing concept that peripheral immune tolerance, induced by antigens that foster programmed cell death (apoptosis), may depend on presentation of antigen bydendritic cells in the tissue.

T cells

T cells are found in large numbers in the systemic circulation. Lymphocytes are broadly divided into two major categories, T cells and B cells (discussed later). These appellations are based on initial observations in chickens, in which a subgroup of lymphocytes homed to the thymus, where they underwent a maturational process leading to the heterogeneous population now recognized as 'thymus-dependent' or T cells. The thymus, the first lymphoid organ to develop, has essentially two compartments, the cortex and the medulla. Within the thymus are found epithelial cells, thymocytes (immature lymphocytes), occasional macrophages, and more mature lymphocytes. The highly cellular cortex is the center of mitoses, with large numbers of immature thymocytes and epithelial cells adhering to each other. As the thymocytes mature to T cells they migrate to the medulla and are ultimately released into the systemic circulation. Major alterations occur to the thymocyte during this maturational process. There is the activation of specific genes needed for only this portion of the lifecycle of the cells. In addition, lifelong characteristics are acquired. These include the development of specific receptors that recognize particular antigens, the acquisition of MHC restriction needed for proper immune interactions, and the acquisition of various T-cell functions, such as 'killing' and 'helping' other cells. These cells are activated by a complex of structures on their surface. The T-cell receptor (specific to the antigen that is being presented to the cell), the CD3 complex, and the antigen cradled in either an MHC class I or II cassette are needed. Other cofactors are also needed for very robust activation.

Some important qualities possessed by these cells are their immunologic recall or anamnestic capacity; this increases the number of specific cells as well as changing them into a 'memory' phenotype. They also have the capacity to produce cellular products called cytokines (**Table 1-2**). A T cell previously sensitized to a particular antigen can retain this immunologic memory (see below) essentially for its lifetime. With a repeat encounter, this memory response leads to an immune response that is more rapid and more pronounced than the first. Such an example is the positive skin response seen after purified protein derivative (PPD) testing.

The central role of the T cell in the immune system cannot be overemphasized. T cells function as pivotal modulators of the immune response, particularly by helping B-cell production of antibody and augmenting cell-mediated reactions through further recruitment of immunoreactive cells. T cells also may downregulate or prevent immune reactions through active suppression. In addition to these 'managerial' types of roles, some T-cell subsets are known to be cytotoxic and are recognized as belonging to the predominant cells in transplantation rejection crises. The accumulated evidence supports the importance of T cells in many aspects of the intraocular inflammatory process – from the propagation of disease to its subsequent downregulation.

Major subsets of T cells

The functions that have been briefly described are now thought to be carried out by at least three major subsets of T cells, with these cells identified either through functional studies or through monoclonal antibodies directed against antigens present on their surface. It was observed early on that T cells (as well as other cells) manifest myriad different molecules on their surface membranes, some of which are expressed uniquely at certain periods of cell activation or function. It was noted that certain monoclonal antibodies directed against these unique proteins bind to specific subsets of cells, thereby permitting a way to identify them (**Table 1-3**). The antibodies to the CD3 antigen (e.g., OKT3) are directed against an antigen found on all mature human T cells in the circulation; approximately 70–80% of lymphocytes in the systemic circulation bear this marker. Antibodies to the CD4 antigen (e.g., OKT4) define the helper subgroup of human T cells (about 60–80% of the total T cells). These cells are not cytotoxic but rather aid in the regulation of B-cell responses and in cell-mediated reactions. They are the major regulatory cells in the immune system. These CD4+ cells respond to antigens complexed to MHCs of the class II type. The CD4+ subgroup of cells is particularly susceptible to the human immunodeficiency virus (HIV) of the acquired immunodeficiency syndrome (AIDS), with the percentage of this subset decreasing dramatically as this disease progresses. Further, these helper cells are necessary components of the autoimmune response seen in the experimental models of ocular inflammatory disease induced with retinal antigens (see discussion of autoimmunity later in this chapter). There is a subset of CD4+ cells that also bear IL-2 receptors (CD25) on their surface. In rodents, and possibly also in humans, some T-regulatory cells may bear the CD25 receptor (see below).

Antibodies to the CD8 antigen (i.e., OKT8) distinguish a population that includes cytotoxic T cells, making up about 20–30% of the total number of T cells. (In the older literature it was thought to harbor suppressor cells, but this is no longer thought to be the case). Antibodies directed against the CD8 antigen block class I histocompatibility-associated reactions.

Cytokines

Intercellular communication is in large part mediated by cytokines and chemokines (see below). Cytokines are produced by lymphocytes and macrophages, as well as by other cells. They are hormone-like proteins capable of amplifying an immune response as well as suppressing it. With the activation of a T lymphocyte, the production and release of various lymphokines will occur. One of the most important is IL-2, with a molecular weight of 15 000 Da in humans.

Table 1-2 Cytokines: An incomplete list

Type	Source	Target and Effect
Interferon-γ	T cells	Antiviral effects; promotes expression of MHC II Antigens on cell surfaces; increases MΦ tumor killing; inhibits some T-cell proliferation
Transforming growth factor-β	T cells, resident ocular cells	Suppresses generation of certain T cells; involved in ACAID and oral tolerance
Interleukin		
IL-1	Many nucleated cells, high levels in MΦ, keratinocyte, endothelial cells, some T and B cells	T- and B-cell proliferation; fibroblasts – proliferation, prostaglandin production; CNS – fever; bone and cartilage resorption; adhesion-molecule expression on endothelium
IL-2	Activated T cells	Activates T cells, B cells, MΦ, NK cells
IL-3	T cells	Affects hemopoietic lineage that is nonlymphoid eosinophil regulator; similar function to IL-5 GM-CSF
IL-4	T cells	Regulates many aspects of B-cell development, affects T cells, mast cells, and MΦ
IL-5	T cells, eosinophils	Affects hemopoietic lineage that is nonlymphoid, eosinophil regulator: similar function to IL-3 GM-CSF; induces B-cell differentiation into IgG- and IgM-secreting plasma cells
IL-6	MΦ T cells fibroblasts; endothelial cells, RPE	B cells – cofactor for Ig production; T cells – co-mitogen; proinflammatory in eye
IL-7	Stromal cells in bone marrow and thymus	Stimulates early B-cell progenitors; affects immature T cells
IL-8	NK cells, T cells	Chemoattractant of neutrophils, basophils, and some T cells; aids in neutrophils adhering to endothelium; induced by IL-1, TNF-α, and endotoxin
IL-9	T cells	Supports growth of helper T cells; may be enhancing factor for hematopoiesis in presence of other cytokines
IL-10	T cells, B cells, stimulated MΦ	Inhibits production of lymphokines by Th1 T cells
IL-11	Bone marrow stromal cells (fibroblasts)	Stimulates cells of myeloid, lymphoid, erythroid, and megakaryocytic lines; induces osteoclast formation; enhances erythrocytopoiesis, antigen-specific antibodies, acute-phase proteins, fever
IL-12	B cells, T cells	Induces IFN-γ synthesis: augments T-cell cytotoxic activity with IL-2; is chemotactic for NK cells and stimulates interaction with vascular endothelium; promotes lytic activity of NK cells; antitumor effects regulate proliferation of Th1 T cells but not Th2 or Th0
IL-13	T cells	Antiinflammatory activity as IL-4 and IL-10; down regulates IL-12 and IFN-α production and thus favors Th2 T-cell responses; inhibits proliferation of normal and leukemic human B-cell precursors; monocyte chemoattractant
IL-14	T cells	Induces B-cell proliferation, malignant B cells; inhibits immunoglobulin secretion
IL-15	Variety of cells	Stimulates proliferation of T cells; shares bioactivity of IL-2 and uses components of IL-2 receptor
IFN-α	Variety of cells	Antiviral
IFN-β	Variety of cells	Antiviral
IFN-γ	T and NK cells	Inflammation, activates MΦ
TGF-β	MΦ, lymphocytes	Depends on cell interaction
TNF-α	MΦ	Inflammation, tumor killing
TNF-β	T cells	Inflammation, tumor killing, enhanced phagocytosis

ACAID, anterior chamber-acquired immune deviation; CNS, central nervous system; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; MΦ, macrophage; NK, natural killer; RPE, retinal pigment epithelium; TFG, transforming growth factor; TNF, tumor necrosis factor.

The release of this lymphokine can stimulate lymphocyte growth and amplify or augment specific immune responses. Another lymphokine is IFN-γ, an important immunoregulator with the potent capacity to induce class II antigen expression on cells. TGF-β is a ubiquitous protein produced by many cells, including platelets and T cells; it appears to have the distinct ability to downregulate immune responses, and to play an important role in anterior chamber-acquired immune deviation (ACAID) and oral tolerance. The number of lymphokines that have been purified and for which effects have been described (see Table 1-2 for a partial list) continues to grow rapidly.

Table 1-3 Selected human leukocyte differentiation antigens (Incomplete list)

Cluster Designation	Main Cellular Distribution	Associated Functions
CD3	T cells, thymocytes	Signal transduction
CD4	Helper T cells	MHC class II coreceptor
CD8	Suppressor T cells, cytotoxic T cells	MHC class I receptor
CD11a	Leukocytes	LFA-1, adhesion molecule
CD11b	Granulocytes, MΦ	Mac-1 adhesion molecule
CD11c	Granulocytes, MΦ, T cells, B cells	α-Integrin, adhesion molecule
CD19	B cells	B-cell activation
CD20	B cells	B-cell activation
CD22	B cells	B-cell regulatory
CD25	T cells, B cells	α chain of IL-2 receptor (Tac) activation
CD28	T cells	Co-stimulatory T-cell marker
CD45	Leukocytes	Maturation
CD54	Endothelial, dendritic, and epithelial cells; activated T and B cells	ICAM-1, adhesion molecule; ligand of LFA-1 and Mac-1
CD56	NK cells	N-CAM, adhesion molecule
CD68	Macrophages	
CD69	NK cells, lymphocytes	Signal transmission receptor
CX3CR1	Monocytes	Chemoattractant
CXCR3	T cells	Cell maturation
CCR7	T cells	Migration to inflammation
CCR5	T cells	Chemokine receptor
CD8 – Co-receptor TRC during antigen stimulation with cytotoxic T-cells		

ICAM, intercellular adhesion molecule; IL, interleukin; LFA, lymphocyte function-associated molecule; MHC, major histocompatibility complex; N-CAM, neural cell adhesion molecule.

T-cell subsets

Helper T cells have been further subdivided, based on their functional characteristics, into several groups (**Fig. 1-2**). The first is the Th1 cell (**Fig. 1-3**). These cells show a cytokine profile of IFN-γ production. The cytokine profile of Th2 cells comprises IL-4, IL-5, IL-13 and perhaps TGF-β, and IL-10. In many animal models of human disease Th1 cells are associated with the initiation of disease, whereas Th2 cells are related to disease downregulation and allergy initiation, or are involved in parasitic diseases. But this story is still unclear. We know from experimental models of uveitis (see below), in which the autoaggressive cells that induce disease are the Th1 cells, that under certain conditions one can induce disease with Th2 cells (nature did not read the textbooks!). Indeed, yet another subset of cells that has been the center of great interest recently is that of the Th17 cell.[1] These cells produce proinflammatory cytokines including IL-17 (hence the name), IL-21 and 22. These cells develop in different environments depending on whether we look in the mouse or the human. In humans, IL-1, IL-6, and IL-23 appear to promote these cells. The cells play a role in host defense mechanisms against fungi and bacteria, and also in autoimmune disease. We have reported the presence of Th17 cells in the blood of sarcoidosis patients with uveitis.[2] Additionally, another human T-cell subset, NKT cells, also produce IL-17 and bear IL-23 receptors on their surface.[3]

One concept is that Th1 cells may initiate an immune response but the Th17 cells are involved in more chronic activity. Anti-IL-17 will almost certainly be an area of intense investigation in the coming years. An interesting question is whether Th1 cells and IL-17 are distinct cells, or are they rather a function of the immune environment, so that under certain circumstances they produce IL-17 and under others a Th1 repertoire? One still cannot answer that question in the human setting, but under experimental conditions it has been seen that Th17 cells may switch to a Th1 character, but that Th1 cells maintain that phenotype and do not change.[4] Also under experimental conditions in animals, when comparing these cells the nature of the intraocular inflammatory response was seen to be different. Th17 did not induce a

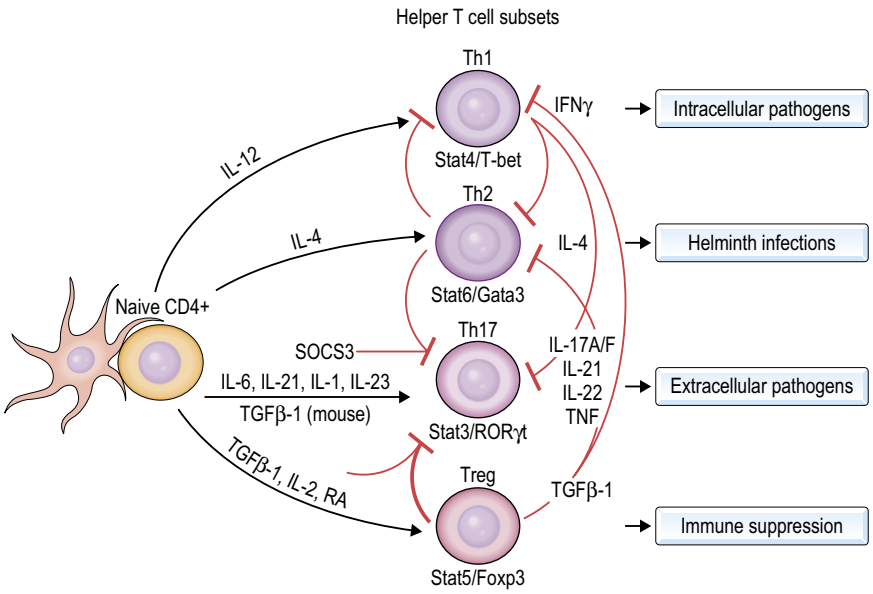

Figure 1-2. Helper T-cell subsets now recognized. *(From: Zhi Chen, O'Shea JJ. Th17 cells: a new fate for differentiating helper T cells. Immunol Res 2008; 41: 87, with permission.)*

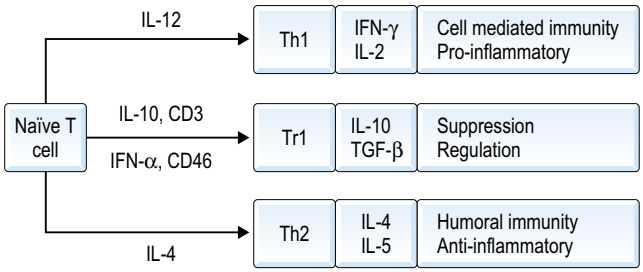

Figure 1-3. Development of three types of T cell participating in the immune response. Other T-cell types also exist, but are not shown. *(With kind permission from Springer Science & Business Media: From Th17 cells: a new fate for differentiating helper T cells. Zhi Chen – John J. O'Shea. Immunol Res (2008) 41:87–102.)*

large lymphoid expansion and splenomegaly, as did Th1 cells; Th1 cells infiltrating the eye dissipate rapidly, whereas IL-17 cells remain; and markers on the surface of these infiltrating cells are different.[5]

IL-22 is part of the IL-17 group of cytokines produced during an inflammatory response.[6] Albeit made by lymphocytes, its receptors are present on epithelial cells. Thus it has been suggested that one of it major roles is to be the cross-talk lymphokine between resident tissue cells and infiltrating inflammatory cells, particularly T cells. This pro-inflammatory cytokine is found in the synovia of patients with rheumatoid arthritis and is upregulated in both Crohn's disease and ulcerative colitis.[7,8]

T-regulatory cells

It is clear that just as the immune system needs cells to initiate a response it needs cells to suppress or modify an immune response. One of the ways that need is met is with T-regulatory (Tr) cells.[9,10] It is hypothesized that these derive from a naive T cell under the influence of cytokines different from those of either Th1 or Th2 cells (see Fig. 1-3). T regs can be found in the thymus (u T regs) or in the peripheral circulation which can be induced (i T regs). Of interest is a report by Kemper and co-workers[11] of stimulating CD4+ cells with CD3 and CD46 (a complement regulator) and inducing Tr cells, that is, producing large amounts of IL-10, moderate amounts of TGF-β, and little IL-2. The literature is replete with information about different types of Tr cell and they have been reported in several organs, such as the gut, where peripheral immune tolerance needs to be induced.[12] Certain characteristics of many of these cells have been described (**Table 1-4**), and the underlying feature is their ability to produce IL-10 and TGF-β. They are capable of downregulating both CD4- and CD8-mediated inflammatory responses, requiring cell-to-cell contact. There are probably many types because nature usually provides redundancies. Of great interest are those that bear CD25 (the IL-2 receptor) on their cell surface. Much interest has centered on cells that have large numbers of these receptors on their surface ('bright cells'), with work suggesting that they are indeed 'negative regulatory' cells – that is, suppressor cells that can modify an immune response. Although the evidence is much clearer in mouse models, this area still is unfolding in human immunology, and it is not clear what the best markers for these cells are. Such an example is forkhead/winged helix transcription factor, or FoxP3,[13] thought to be a reliable marker in mice for the development and function of naturally occurring T-regulatory cells, but its expression has been seen in T-effector cells (cells that induce inflammation) and so its value has been called into question, at least in humans.[14] When we evaluated the T cells of patients with ocular inflammatory disease, we found that the FoxP3 marker varied tremendously between patients and was not a very good indicator of poor T-regulatory function.[15]

Table 1-4 Cytokine repertoire of various CD4+ T cells

Cytokine	Tr1	Th0	Th1	Th2	Th17
IL-2	±	3+	3+	±	
IFN-γ	2+	2+	3+	±	
IL-4	–	2+	±	3+	
IL-5	2+	2+	±	3+	
IL-10	3+	1+	1+	2+	
TGF-β	3+	2+	2+	2+	
IL-17					3+
IL-22					2+

Based on findings in Roncarolo MG, Bacchetta R, Bordignon C, et al. Type 1 T regulatory cells. Immunol Rev 2001; 181: 68–71.

An interesting observation is the increase in a subset of NK cells (so called CD56 'bright') after daclizumab therapy was noted; this subset makes large amounts of IL-10.[16] The implication of this increase in this cell population is that a regulatory cell is to be found there. The increase is seen when patients' disease is well controlled, and it has also been seen in multiple sclerosis patients receiving daclizumab therapy.

T-cell receptor

Much interest has centered on the T-cell receptor (TCR) (**Fig. 1-4**). T cells need to produce the TCR on their cell surface to recognize the MHC; this is part of the system that permits information transmitted to it by peptides presented on the APC. This complex interaction involves the MHC antigen on the APC surface, the peptide, either the CD4 or the CD8 antigen, and the TCR. The TCR is similar in structure to an immunoglobulin, having both an α and a β chain. The more distal ends of these chains are variable, and the hypervariable regions are termed V (variable) and J (joining) on the α chain and V, and D (diversity) regions on the β chain. Compared with the number of immunoglobulin genes, there are fewer V genes and more J genes in the TCR repertoire. It is logically assumed that the peptide, which has a special shape and therefore fits specifically in a lock-and-key fashion into the groove between the MHC and the TCR, would be the 'cement' of this union. In general that would be true, but 'superantigens,' which can bind to the sides of these molecules, can also bring them together and, under the right circumstances, initiate cellular responses. These superantigens are glycoproteins and can be bacterial products such as enterotoxins or viral products. It has been suggested that of all the possible combinations of gene arrangements that could possibly produce the variable region believed to cradle the peptide, certain genes within a family seem to be noted more frequently in autoimmune disease. One such group is the Vα family, with Vβ8.2 receiving much attention. A very small number of cells have a TCR made up not of α and β chains but rather γ and δ