

Scleritis remains an enigmatic disease. Attempts to demonstrate a specific antigen associated with scleral vessel and tissue damage, or to reproduce suggested pathogenic mechanisms in experimental animal models, have not yielded consistent abnormalities [1]. As the sclera is avascular, nutrients come from the choroid and vascular plexi in Tenon's capsule and episclera, where there is an artery-to-artery anastomosis in which blood oscillates, rather than flowing rapidly. This predisposes to the development of vasculitis causing a spectrum of inflammatory conditions of varying intensity which, in the most severe form, necrotizing scleritis, may destroy all of the structural and cellular components of the sclera. The prevailing consensus view, however, based on the available evidence, is that disordered immune responses leading to vessel and tissue damage are central to the pathogenesis of scleritis. The histopathological and immunofluorescence detection of immune complex inflammatory microangiopathy in affected scleral biopsy specimens [2], the frequent association of scleritis with systemic autoimmune diseases associated with circulating immune complexes (rheumatoid arthritis, systemic lupus erythematosus, or polyarteritis nodosa) [2–4], the favorable response of scleritis to immunosuppressive agents [3, 4], and the absence of vascular perfusion in severe types of scleritis, as determined by anterior segment fluorescein angiography [5], all suggest that scleritis

represents an autoimmune process mediated by a localized immune complex microangiopathy or type III hypersensitivity reaction. The histopathological finding of a chronic granulomatous inflammation characterized predominantly by macrophages and T lymphocytes in scleritis biopsy specimens suggests that a cellular immunity dysfunction or type IV hypersensitivity reaction also may play a role [2].

The prevailing hypothesis, based on the aforementioned data and autoimmunity investigations, is that development of scleritis entails the interaction of genetically controlled mechanisms with environmental factors, such as infectious agents (e.g., virus) or trauma. Genetic predisposition, coupled with the triggering event, gives rise to an immune process that damages the vessels through immune complex deposition in vessel "walls" and subsequent complement activation (type III hypersensitivity). Persistent immunologic injury leads to granuloma formation (type IV hypersensitivity). In certain systemic vasculitic diseases, circulating immune complexes may deposit in episcleral and scleral perforating vessels, particularly if they have suffered a previous insult (mild infection, trauma), as well as in other vessels or tissues of the body.

This chapter reviews the immunological considerations of the sclera, emphasizing the issues of relevance regarding the pathogenic mechanisms of scleritis.

2.1 General Immune Response Considerations

To appreciate the pathophysiology of scleritis, it is necessary to understand how components of the immune response act and are controlled. An immune response is the result of a complex network of cellular interactions against a foreign agent or antigen that involves innate and adaptive components of the immune system [6].

The innate immune system consists of physical and chemical barriers, phagocytic cells, such as neutrophils, macrophages, and natural killer cells, and soluble factors, such as complement and lysozyme. The innate immune system acts as a first line of defense against foreign invaders. This natural, innate, or primitive immune response is not specific for a given antigen (does not need specific recognition), does not require central processing, and does not improve with repeated encounter (does not have cellular memory).

The adaptive immune system, consisting of cells such as T and B lymphocytes and soluble factors such as antibodies and cytokines, acts if the first defenses against antigen have not been sufficient to eliminate the foreign substance rapidly. The adaptive immune response is characterized by the relatively unique characteristics of specific recognition, central processing, cellular memory, and discrimination between self and nonself. Through evolution, humans have developed the ability to recognize myriads of foreign antigens through antigen-specific cells.

The adaptive immune response has three components: (1) the afferent arc, in which immunocompetent cells are exposed to an antigen, recognize the specific antigen, and become sensitized to that antigen; (2) central processing, in which immunocompetent cells participate in the differentiation and development of specific antibodies and mature effector cells; and (3) the efferent arc, in which an immune response is mounted against the specific antigens by the specific antibodies and the mature effector cells.

Innate and adaptive immune systems may interact at many levels. Antibodies (IgG and

IgM), produced by B lymphocytes and complement, help neutrophils and macrophages to recognize and interact with the antigen. Macrophages break down protein antigens, transport the antigen peptide fragments to lymph nodes, and “present” them in a specific, particular way on the macrophage cell membrane surface to lymphocytes, which then are “educated” about that particular antigen in such a way as to become reactive against it and to begin attempting to eliminate it. Macrophages also synthesize and secrete a variety of powerful biological molecules, including collagenase, lysozyme, interferon (α and β), interleukin 6, tumor necrosis factor, fibronectin, several growth and stimulating factors, arachidonic acid derivatives, and oxygen metabolites. Lymphocytes produce lymphokines, which stimulate neutrophils and macrophages to attack the antigen more effectively. The immune system also interacts with other systems, such as the clotting, fibrinolytic, and kinin systems, in the protection of the body from an antigen [2]. It is the combined responses of both natural and acquired immune systems that provide protection against harmful agents. These responses may be appropriate, in which case the individual is protected, or may be inappropriate, that is, either insufficient or excessive (hypersensitivity and autoimmune reactions), in which case the individual is harmed.

2.1.1 Components of the Adaptive Immune Response

The use of monoclonal antibodies that recognize selected cell surface glycoproteins has made it possible to characterize the cells involved in the immune response. The list of current (as of the Eighth International Workshop on Human Leukocyte Differentiation Antigens) clusters of differentiation (CD) and the cell types expressing these CD antigens is shown in Table 2.1. All these cells arise from pluripotential stem cells through two main lines of differentiation: (1) the lymphoid line, producing lymphocytes and (2) the myeloid line, producing monocytes/macrophages

Table 2.1 Components of the immune response detected by monoclonal antibodies

Antigen designation ^a	Cell specificity	Function
CD1	Thymocytes, Langerhans' cells	
CD2	T lymphocytes, some TPCs	Sheep erythrocyte receptor
CD3	T lymphocytes	Part of T-cell antigen receptor
CD4	T-helper-inducer lymphocytes, monocytes	MHC ^b class II immune recognition
CD5	T lymphocytes, B lymphocyte subset	
CD7	T lymphocytes, NK cells	Fc receptor IgM
CD8	T cytotoxic-suppressor lymphocytes, some TPCs	MHC class I immune recognition
CD9	Monocytes, platelets	
CD10	Pre-B lymphocytes, granulocytes	
CD11a	All leukocytes	α chain of LFA-1 (adhesion molecule)
CD11b	Monocytes, granulocytes, some TPCs ^b	α chain of complement receptor CR3
CD11c	NK, monocytes, granulocytes	
CDw12	Monocytes, granulocytes	
CD13	Monocytes and granulocytes	
CD14	Macrophages	
CD16	Granulocytes, TPCs, and macrophages	Fc receptor IgG (Fc γ RIII)
CD16b	Granulocytes	
CDw17	Monocytes, granulocytes, platelets	
CD18	All leukocytes	
CD19	B lymphocytes	
CD20	B lymphocytes	
CD21	B lymphocytes	Complement receptor CR2
CD22	B lymphocytes	
CD24	B lymphocytes, granulocytes	
CD25	Activated T lymphocytes, B lymphocytes, and macrophages	IL-2 receptor
CD26	B lymphocytes, macrophages	
CD28	T cytotoxic-suppressor lymphocyte subset	
CD29	All leukocytes	
CD31	B lymphocytes, monocytes, granulocytes, platelets	
CD32	B lymphocytes, macrophages, granulocytes	
CDw32	B lymphocytes, granulocytes, macrophages, platelets	Fc receptor IgG (Fc γ RII)
CD33	Monocytes and myeloid stem cells	
CD35	B lymphocytes, erythrocytes, monocytes, granulocytes, plasma cells	Complement receptor CR1
CD36	Monocytes, platelets	
CD40	B lymphocytes	
CD41	Megakaryocytes, platelets	Gp11b/111a
CD42	Megakaryocytes, platelets	Gp1b
CD43	T lymphocytes, monocytes, granulocytes	
CD44	All leukocytes	
CD45	All leukocytes	Leukocyte common Antigen
CD46	All leukocytes	
CD47	All leukocytes	
CD48	All leukocytes	

(continued)

Table 2.1 (continued)

Antigen designation ^a	Cell specificity	Function
CD51	All leukocytes	
CDw52	All leukocytes	
CD53	All leukocytes	
CD54	All leukocytes	
CD55	All leukocytes	
CD56	NK cells	
CD57	NK cells	
CD58	All leukocytes	
CD59	All leukocytes	
CDw60	Platelets	
CD61	Platelets	
CD63	Monocytes, platelets	
CD64	Monocytes	
CDw65	Monocytes, granulocytes	
CD68	Macrophages	
CD69	NK cells, macrophages	
CD71	Macrophages	
CD72	B lymphocytes	
CD74	B lymphocytes, monocytes	
CD77	B lymphocytes	
CDw78	B lymphocytes	

^aCD: cluster designation (based on the Eighth International Workshop on Human Leukocyte Differentiation Antigens, December 12–16, 2004, Adelaide, Australia)

^bTPC: third-population cells (natural killer and killer cells); NK, natural killer cell; MHC, major histocompatibility complex; IL-2, interleukin 2

and polymorphonuclear granulocytes (neutrophils, eosinophils, and basophils/mast cells). This myeloid line also gives rise to megakaryocytes, which eventually produce platelets [7].

2.1.1.1 Lymphocytes

Lymphocytes are mononuclear cells produced in primary lymphoid organs (thymus and adult bone marrow) that migrate secondarily into the secondary lymphoid tissues (lymph node, spleen, gut-associated lymphoid tissue, mammary-associated lymphoid tissue, and conjunctival-associated lymphoid tissue) and in blood. They compose approximately 30% of the total peripheral white blood cell count. Lymphocytes may be classified as T lymphocytes, B lymphocytes, and non-T, non-B (third population) lymphocytes.

T Lymphocytes

T lymphocytes, or thymus-derived cells, possess surface histocompatibility products (HLA-DR) and cell surface receptors for antigen (TCR-CD3), sheep erythrocytes (CD2), and the plant-derived mitogens (concanavalin A and phytohemagglutinin); they also possess CD5 and CD7 surface molecules. The T lymphocyte has an important role in recognition of foreign material, in specific effector responses, in helping B lymphocytes to synthesize antibody, in immunoregulatory functions, and in immunological memory. They also may participate in abnormal reactions, such as the type IV hypersensitivity or cell-mediated diseases. T lymphocytes can be further subdivided into subsets: T-helper lymphocytes (CD4) and T cytotoxic/suppressive lymphocytes (CD8) [8]. T-helper lymphocytes (CD4) participate in the

recognition of foreign material, proliferation, and generation of antibodies and other specialized T lymphocytes. On the other hand, CD8 T cytotoxic lymphocytes (CD8) are involved in cell killing, and T suppressor lymphocytes (CD8) are responsible for modulating immune responses, preventing uncontrolled host-damaging inflammatory responses.

CD4 lymphocytes may be subdivided into subsubsets. For example, there are two separate populations of CD4 lymphocytes (T-helper 1 and T-helper 2), based on the production of different lymphokines. T-helper 1 lymphocytes secrete interleukin 2 (IL-2) and interferon γ , but do not secrete IL-4 or IL-5; they can be cytolytic and can provide B lymphocyte help for IgG, IgM, and IgA synthesis, but not for IgE synthesis. T-helper 2 lymphocytes secrete IL-4 and IL-5, but not IL-2 or interferon γ ; they are not cytolytic and can provide B lymphocyte help for IgE, IgG, IgM, and IgA synthesis. Studies suggest that T-helper 1 lymphocytes participate in inflammatory reactions associated with delayed-type hypersensitivity reactions and low antibody production (e.g., contact dermatitis and *Mycobacterium tuberculosis* infection), whereas T-helper 2 lymphocytes participate in inflammatory reactions associated with persistent antibody production (e.g., allergic diseases, including vernal conjunctivitis) [9]. In recent years, an important role for a third subpopulation, T-helper 17 cells, has been identified in a wide range of autoimmune diseases and animal models [10–13].

CD8 lymphocytes also may be subdivided into subsubsets. For example, evidence exists that there are at least three subpopulations of T-suppressor lymphocytes.

B Lymphocytes

B lymphocytes, or bone marrow-derived cells [14, 15], possess on their surfaces immunoglobulin, class II histocompatibility glycoproteins (HLA-DR) and receptors for the Fc portion of antibody (CDw32) and for complement components, including CR1 (CD35) and CR2 (CD21). They also possess surface receptors for Epstein–Barr virus (EBV), for the plant mitogen known as pokeweed mitogen, for the purified protein derivative of

M. tuberculosis, and for lipopolysaccharide. B lymphocytes, assisted by T-helper lymphocytes, respond to specific antigenic stimulation by blastogenic transformation, antibody synthesis, and eventual evolution to end-stage plasma cells and memory cells. B lymphocytes are further subdivided into five separate classes synthesizing five different immunoglobulins: IgG, IgA, IgM, IgD, and IgE. In addition to the subsets depending on antibody class synthesis, B lymphocytes also differentiate into other subsets. There is a subpopulation of B lymphocytes characterized by the presence of the surface membrane glycoprotein CD5 (a surface glycoprotein ordinarily present on T lymphocytes) [16]; this subpopulation appears to be associated with autoantibody production [7, 17]. There is another subpopulation of B lymphocytes with suppressor activity.

Antibodies bind to antigens to form antigen–antibody complexes. These immune complexes, if not cleared by normal mechanisms, may result in vessel and surrounding tissue damage through activation of complement components and subsequent neutrophil and macrophage granule release.

Third-Population Lymphocytes or Null Lymphocytes

Third-population cells (TPCs), including natural killer (NK) cells and killer (K) cells, are lymphoid cells that do not carry the conventional cell surface glycoproteins characteristic of T or B lymphocytes, that is, helper T-cell receptors (TCRs) or immunoglobulin. Most TPC surface antigens detectable by monoclonal antibodies are shared with T lymphocytes and cells of the myelomonocytic series (Table 2.1). Natural killer cells are small, nonadherent, and have granules containing perforin, an enzyme responsible for cytotoxicity. NK cells compose an important component of the early, natural response part of the immune system; [18–20] without prior antigenic contact, NK cells spontaneously kill transformed (malignant) cells and virus-infected cells without major histocompatibility complex restriction. K cells do have surface receptors for the Fc portion of immunoglobulin. They participate in type II Gell and Coombs hypersensitivity reactions through the so-called antibody-dependent

cell-mediated cytotoxicity (ADCC) reaction. They also are involved in the removal of cellular antigens when the target cell is too large to be phagocytized.

2.1.1.2 Monocytes/Macrophages

Bone marrow-derived stem cells give rise to promonocytes, which subsequently differentiate into blood monocytes. Blood monocytes migrate into tissues to become macrophages. Aside from class II MHC glycoprotein on their cell surfaces (HLA-DR), monocytes/macrophages possess receptors for complement components, including CR1 (CD35) and CR3 (CD11b), as well as for the Fc portion of immunoglobulin G molecules (CD16), fibronectin, interferons (α , β , and γ), IL-1, tumor necrosis factor, and macrophage colony-stimulating factor. Monocytes/macrophages may be subdivided depending on two different functions, that is, phagocytosis and antigen presentation to lymphocytes.

Phagocytosis

The human blood monocyte possesses a horseshoe-shaped nucleus with faint azurophilic granules, ruffled membrane, a well-developed Golgi complex, and many intracytoplasmic lysosomes. Monocytes/macrophages are members of the natural immune system and they play a central role in host defense through phagocytosis. The phagocytic macrophages form a network, the reticuloendothelial system, found in many organs of the body. The reticuloendothelial system includes Kupffer cells in the liver, intraglomerular mesangial cells in the kidney, alveolar macrophages in the lung, microglial cells in the brain, spleen sinus cells, and lymph node sinus cells.

However, monocytes/macrophages can also participate in abnormal reactions. They can be attracted by complement components in type III hypersensitivity or immune complex-mediated diseases; furthermore, they can participate in granuloma formation as epithelioid cells (modified macrophages) or multinucleated giant cells (fusion of several epithelioid cells) in type IV hypersensitivity or cell-mediated diseases.

Table 2.2 Secretory products of macrophages^a

<i>Enzymes</i>	<i>Coagulation factors</i>
Lysozyme	Factors X, IX, VII, V
Neutral proteases	Protein kinase
(collagenase and elastase)	Thromboplastin
Acid proteases (cathepsins)	Prothrombin
Acid lipases	Fibrinolysis inhibitor
Acid nucleases	
Acid phosphatases	<i>Components of</i>
Acid glycosidases	<i>complement cascade</i>
Acid sulfatases	C1, C4, C2, C3, C5
Arginase	Factors B and D
Plasminogen activator	Properdin
Lipoprotein lipase	C3b inactivator
Phospholipase A ₂	β IH
Cytolytic proteinase	
Angiotensin convertase	<i>Other proteins</i>
	Transcobalamin II
<i>Inhibitors of enzymes</i>	Transferrin
α_2 -Macroglobulin	Fibronectin
α_1 -Antiprotease	Interferons α and β
Lipocortin	Tumor necrosis factor α
α_1 -Antichymotrypsin	Interleukins 1 and 6
	Macrophage colony-
<i>Reactive oxygen</i>	stimulating factor
<i>intermediates</i>	Granulocyte-macrophage
O ₂ , H ₂ O ₂ , OH,	colony-stimulating factor
hypohalous acids	Haptoglobin
	Platelet-derived growth
<i>Lipids</i>	factor
PGE ₂ ^b	Transforming growth
PGF _{2α} ^b	factor β
Prostacyclin	Erythropoietin
Tromboxane A ₂	Thymosin B ₄
Leukotrienes B, C, D, and E	Apolipoprotein E
Mono-HETES ^b	Serum amyloid A
Di-HETES	Serum amyloid P
Platelet-activating factor	
	<i>Small molecules</i>
	Purines
	Pyrimidines

^aAdapted from references [21–23]

^bPGE₂ prostaglandin E₂, PGF_{2 α} prostaglandin F_{2 α} , HETES hydroxyeicosatetraenoic acids

Monocytes/macrophages secrete a variety of powerful biological molecules that are important (Table 2.2) [21–23]. Among these molecules, the enzymes, collagenase and elastase, participate in connective tissue degradation.

Antigen-Presenting Cells

Macrophages are the preeminent antigen-presenting cells. They phagocytose the antigen, partially degrade it, and transport the fragments

to the cell surface. The combination of these degraded fragments in close juxtaposition to class II MHC glycoproteins forms the recognition unit for the helper TCRs specific for the epitope of the antigen [24–26]. Antigen-presenting cells produce a variety of soluble factors during the presentation of the antigen to T-helper lymphocytes, including IL-1, which promotes the differentiation of both T and B lymphocytes.

Langerhans' cells are also important antigen-presenting cells [27], particularly for the eye. They are derived from bone marrow macrophage precursors and, like macrophages, they also possess a high density of class II MHC glycoproteins on their cell surfaces (HLA-DR), along with receptors for complement component (CR1/CD35) and the Fc portion of immunoglobulin G (CD16). Unlike macrophages, Langerhans' cells have a racket-shaped cytoplasmic granule (the Birbeck granule), are not phagocytic, and have the characteristic surface molecule CD1.

Other cells that do not arise from the monocyte/macrophage lineage may also be important in processing and presenting antigen; B lymphocytes, constitutively rich in class II MHC glycoproteins, are functionally important as antigen-presenting cells, particularly when the B lymphocyte is specific for the antigen being presented.

Cells other than macrophages, Langerhans' cells, or B lymphocytes can acquire the ability to "present" antigens through the induction of class II MHC glycoproteins on their cell surface under the influence of cytokines (interferon γ and tumor necrosis factor); these cells include connective tissue fibroblasts, corneal endothelial cells, or vascular endothelial cells [28, 29]. It has been suggested that such induction of expression of "inappropriate" class II MHC glycoproteins might contribute to the pathogenesis of a variety of autoimmune diseases [30].

2.1.1.3 Polymorphonuclear Granulocytes

Polymorphonuclear granulocytes are leukocytes that form part of the natural immune system. They play a central role in host defense through phagocytosis, but if they accumulate in excessive numbers, persist, and are activated in an uncon-

trolled manner the result may be deleterious to host tissues. As the name suggests, they contain a multilobed nucleus and many granules. Polymorphonuclear leukocytes are classified as neutrophils, basophils, or eosinophils, depending on the differential staining of their granules.

Neutrophils

Neutrophils represent over 90% of the circulating granulocytes. They possess surface receptors for the Fc portion of IgG (CD16) and for complement components, including C5a (important in chemotaxis), and CR1 (CD35) and CR3 (CD11b) (important in adhesion and phagocytosis). When appropriately stimulating by chemotactic agents (complement components, fibrinolytic and kinin system components, and products from other leukocytes, platelets, and certain bacteria), neutrophils move from blood to tissues through margination (adhesion through endothelial cells) and diapedesis (movement through the capillary wall). Neutrophils release the contents of their primary (azurophilic) granules (lysosomes) and secondary (specific) granules (Table 2.3) into an endocytic vacuole, resulting in phagocytosis of a microorganism or in tissue injury (type III hypersensitivity reactions or immune complex-mediated diseases) [31, 32]. Secondary granules release collagenase, which participates in connective tissue degradation. Aside from the products secreted by the granules, neutrophils also release lipids, such as an arachidonic acid derivatives as well as reactive oxygen derivatives [32].

Eosinophils

Eosinophils represent 3–5% of the circulating granulocytes. They possess surface receptors for the Fc portion of IgE (low affinity) and IgG (CD16) and for complement components. Eosinophils play a specialized role in allergic and parasitic conditions. Although less important, they also participate in type III hypersensitivity reactions or immune complex-mediated diseases following attraction to the inflammatory area by products from mast cells, basophils (eosinophil chemotactic factor of anaphylaxis, ECF-A), and complement. Eosinophils release the contents of

Table 2.3 Secretory products of neutrophils^a

Azurophil granules	Specific granules	Other granules
Myeloperoxidase	Alkaline phosphatase	Acid phosphatase
Acid phosphatase	Histaminase	Heparitinase
5'-Nucleotidase	Collagenase	β -Glucosaminidase
Lysozyme	Lysozyme	α -Mannosidase
Elastase	Vitamine B ₁₂ -binding proteins	Acid proteinase
Cathepsin G	Plasminogen activator	Elastase?
Cathepsin B	Lactoferrin	Gelatinase?
Cathepsin D	Receptors	Laminin receptor
Proteinase 3	Laminin	Glycosaminoglycans
Beta-Glycerophosphatase	C3bi	
Beta-Glucuronidase	fMet-Leu-Phe	
N-Acetyl- β -glucosaminidase	Cytochrome <i>b</i>	
α -Mannosidase	Flavoproteins	
Arylsulfatase		
α -Fucosidase		
Esterase		
Histonase		
Cationic proteins		
Defensins		
Bactericidal permeability-increasing (BPI) protein		
Glycosaminoglycans		
Azurophil-derived bactericidal factors (ADBFs)		

^aAdapted from references [31] and [32]

their granules to the outside of the cell after fusion of the intracellular granules with the plasma membrane (degranulation). Table 2.4 shows the known secretory products of eosinophils [32].

Basophils/Mast Cells

Basophils represent less than 0.2% of the circulating granulocytes. They possess surface receptors for the Fc portion of IgE (high affinity) and IgG (CD16) and for complement components, including C5a, CR1 (CD35), and CR3 (CD11b). The mast cell is often indistinguishable from the basophil in a number of properties. There are at least two classes of mast cells, distinguished on the basis of their neutral protease composition, T lymphocyte dependency, and ultrastructural characteristics (Table 2.5): [33–36] one consists of the mucosa-associated mast cells (MMCs), and the other includes connective tissue-associated mast cells (CTMCs). Basophils and mast cells play a specialized role in allergic reactions.

They also can participate in type III hypersensitivity or immune complex-mediated diseases. IgE antibody induced by the antigen binds to circulating basophils or to tissue mast cells, which then release histamine, platelet-activating factor, and other biological molecules when antigen binds to two adjacent IgE molecules on the mast cell surface (Table 2.6) [33]. Histamine and other vasoactive amines cause an increase in vascular permeability, allowing the immune complexes to become trapped in the vessel wall.

2.1.1.4 Platelets

Blood platelets, cells highly adapted for blood clotting, also are involved in the immune response to injury, reflecting their evolutionary heritage as myeloid (inflammatory) cells. They possess surface receptors for the Fc portion of IgG (CD16) and IgE (low affinity), for class I histocompatibility glycoproteins (HLA-A, -B, or -C), and for factor VIII. They also carry molecules, such as Gp11b/111a

Table 2.4 Secretory products of eosinophils^a

<i>Peptides and enzymes</i>
Lysosomal hydrolases
Arylsulfatase
β -Glucuronidase
Acid phosphatase
Alkaline phosphatase
β -Glycerophosphatase
Ribonuclease
Proteinases
Collagenase
Cathepsin
Histaminase
Peroxisomes
Major basic protein
Eosinophil cationic protein
Eosinophil peroxidases
Phospholipases
Lysophospholipases
<i>Lipids</i>
<i>Reactive oxygen intermediates</i>

^aAdapted from reference [32]

Table 2.5 Differences between mast cell subtypes^a

Property	Mucosal mast cell (MMC)	Connective tissue mast cell (CTMC)
Staining (Alcian blue/safranin)	Blue	Red–blue
Protease type	Tryptase	Tryptase and chymase
T lymphocyte dependency	Yes	No
Migration	Migratory	Nonmigratory
Life span	Short	Long
Half-life	<40 days	>6 months
Proteoglycan	Chondroitin sulfate	Heparin

^aAdapted from reference [33]

Table 2.6 Secretory products of mast cells and basophils^a

Histamine
Serotonin
Rat mast-cell protease I and II
Heparin
Chondroitin sulfate
β -Hexosaminidase
β -Glucuronidase
β -D-Galactosidase
Arylsulfatase
Eosinophil chemotactic factor of anaphylaxis (ECF-A)
Slow-reactive substance of anaphylaxis (SRS-A)
High-molecular-weight neutrophil chemotactic factor
Arachidonic acid derivatives
Platelet-activating factor

^aAdapted from reference [33]

Table 2.7 Secretory products of platelets^a

<i>Alfa granules</i>	<i>Dense granules</i>
Fibronectin	Serotonin
Fibrinogen	Adenosine diphosphate (ADP)
Plasminogen	<i>Others</i>
Thrombospondin	Arachidonic acid derivatives
von Willebrand's factor	
α_2 -Plasmin inhibitor	
Platelet-derived growth factor (PDGF)	
Platelet factor 4s (PF4)	
Transforming growth factor (TGF) α and β	
β -Lysin	
Permeability factor	
Factors D and H	
Decay-accelerating factor	

^aAdapted from reference [37]

(CDw41), which binds fibrinogen, and Gp1b (CDw42), which binds von Willebrand's factor.

Following endothelial injury, platelets adhere to and aggregate at the endothelial surface, releasing from their granules permeability-increasing molecules (Table 2.7) [37]. Endothelial injury may be caused by type III hypersensitivity or immune complex-mediated reactions. Platelet-activating factor released by basophils/mast

cells after antigen–IgE antibody complex formation induces platelets to aggregate and release their vasoactive amines. These amines separate endothelial cells and allow the immune complexes to enter the vessel wall. Once the immune complexes are deposited, they initiate an inflammatory reaction through activation of complement components and polymorphonuclear granulocyte lysosomal enzyme release.

2.1.2 Immunoregulation

The integrity of the immune response is crucially dependent of a complex series of interactions of the cells involved in the immune response and their secretory products (Tables 2.1–2.7). Obviously, these interactions must be tightly regulated. Abnormalities in this regulation lead to expression of inflammatory diseases.

2.1.2.1 Major Histocompatibility Complex

Immunological recognition, including interaction between antigen-presenting cells and lymphocytes, as well as between different lymphocytes, results in a complex network, the primary conductor of which is the array of highly polymorphic cell-surface glycoproteins called HLA alleles encoded in humans by the genetic material located on the short arm of chromosome 6, a region known as the major histocompatibility complex (MHC). This genetic material is divided into three distinct families, class I, II, and III MHC genes. Class I MHC genes encode the human leucocyte antigens HLA-A, HLA-B, and HLA-C, present on the surface of all nucleated cells. Class I antigens consist of one glycosylated polypeptide heavy chain with three globular domains, α_1 , α_2 , and α_3 , noncovalently associated by its α_3 domain with a nonglycosylated peptide light chain, a β_2 -microglobulin encoded outside of the MHC on chromosome 15. Class II MHC genes encode the human leucocyte antigens HLA-DP, HLA-DQ, and HLA-DR, present on the surface of a small number of cell types (macrophages, monocytes, Langerhans' cells, and T and B lymphocytes), but their synthesis and cell surface expression can be induced by interferon γ on various other cells, including connective tissue fibroblasts, corneal endothelial cells, and vascular endothelial cells [28, 29]. Class II antigens consist of two noncovalently associated polypeptide chains, the α chain and the β chain, both with two globular domains. Class III MHC genes encode three proteins of the complement system (C2, factor B, and C4). They have been mapped within a 0.7-cM region between HLA-B

and HLA-DR [38]. The tight linkage of these regions suggests that regulation of class I, II, and III MHC gene expression may occur concomitantly.

The surface MHC glycoproteins are essential for immune recognition of antigen and subsequent activation of the immune response. T-helper lymphocytes recognize antigen through the TCR in association with class II MHC glycoproteins on antigen-presenting cells. T-helper lymphocytes can cooperate with B lymphocytes in association with class II MHC glycoproteins to induce antibody production. They also can release lymphokines that help macrophages to attack antigen. Cytotoxic T lymphocytes, involved in viral infections and in tissue graft rejections, recognize viral antigens and foreign graft tissue antigens in association with class I MHC glycoproteins. The result of these specific interactions leads to the ultimate response, that is, resistance (strong immune response) or susceptibility (low or no reactivity) to the antigen [7].

In human beings, certain diseases are associated with unusual frequencies of one or more of these MHC glycoproteins, suggesting that having a particular HLA gene may affect the person's susceptibility to a disease, resistance to it, or both. HLA-B27 is present in 90% of patients with ankylosing spondylitis and in 80% of patients with reactive arthritis disease. HLA-DRw4 gene is present in 64% of patients with rheumatoid arthritis. Other HLA glycoproteins have been found in association with other disorders [7].

2.1.2.2 Humoral Mechanisms: Antibodies

The immune response may also be modulated by humoral mechanisms. Circulating antibodies can participate in immunoregulation by three mechanisms.

In the first mechanism, "antigen blocking," high concentrations of circulating antibody compete with receptors on B lymphocytes for circulating antigen, preventing activation of antigen-specific B lymphocytes.

In the second mechanism, "receptor cross-linking," antibody binds to Fc receptors and antigen receptors (antigen-binding region of the antibody) on B lymphocytes, usually resulting in

the prevention of B-lymphocyte activation; however, this mechanism can sometimes result in B-lymphocyte activation, particularly when the ratio of antigen to antibody is high. It appears that the early formed antibody induces B-lymphocyte activation and further antibody synthesis; once the antibody concentration exceeds the antigen concentration, B-lymphocyte activation is inhibited. Therefore, the ratio of antigen to antibody plays an important role in regulating the immune response.

In the third mechanism, “idiotypic regulation,” antibody binds to B-lymphocyte antigen receptors. *Idiotypic* refers to the antigen receptor present in the variable region of an immunoglobulin, and which is specific for a given antigen. Jerne [39] suggested that idiotypes produced in response to antigen stimulate production of anti-idiotypic antibodies that then regulate production of idiotypes. Anti-idiotypes stimulate production of anti-anti-idiotypes, which then regulate production of anti-idiotypes. Because anti-idiotypes resemble the original antigen, they can bind directly to the B-lymphocyte or T-lymphocyte antigen receptor and, depending on their concentration, they can either activate or inactivate B or T lymphocytes [39, 40].

2.1.2.3 Cellular Mechanisms

The immune response also may be modulated by cellular mechanisms. T-suppressor lymphocytes inhibit T-helper lymphocytes or B-lymphocyte activation. They can be antigen specific, idiosyncratic, and antigen nonspecific. T-contrasuppressor lymphocytes inhibit T-suppressor lymphocyte functions, allowing T-helper activation [41, 42]. T-lymphocyte lymphokines play an important role in regulating the components of the immune response.

Immunoregulation also may be accomplished by regulatory B lymphocytes and B-lymphocyte lymphokines. For example, B-lymphocyte-derived enhancing factor (BEF) inhibits T-suppressor lymphocyte activation, allowing B-lymphocyte functions, such as antibody synthesis. On the other hand, B-lymphocyte-derived suppressor factors (BSFs) inhibit B-lymphocyte activation.

2.1.2.4 Summary

Antigen is presented to T-helper lymphocytes (class II MHC) and B lymphocytes (class II MHC) by antigen-presenting cells (class II MHC), which stimulates them (recognition of “nonself” through class II MHC cell surface glycoproteins). Once activated, T-helper lymphocytes help specific B lymphocytes to produce antibodies. Antibody production is regulated by blocking or cross-linking. T-helper lymphocytes and B lymphocytes are regulated by anti-idiotypes, T-suppressor lymphocytes (also stimulated by antigen), and T- and B-lymphocyte-derived lymphokines.

2.1.3 Abnormalities of the Immune Response

2.1.3.1 Hypersensitivity Reactions

If the immune response of an organism to an antigen is excessive or inappropriate, tissue damage may occur. Gell, Coombs, and Lackmann [43] described four types of tissue-damaging hypersensitivity reactions: (1) type I or anaphylactic, (2) type II or cytotoxic, (3) type III or immune complex mediated, and (4) type IV or cell mediated (delayed). Because only type III and type IV hypersensitivity reactions are thought to play a primary role in the pathogenesis of scleral inflammation [2], we focus our general review on them.

Type III Hypersensitivity Reactions

Type III hypersensitivity reactions are mediated by immune complexes. The antibody reacts with the antigen whether within the circulation (circulating immune complexes) or at extravascular sites, where antigen may have been deposited (in situ immune complexes). The resulting immune complex activates the complement cascade, which attracts neutrophils and macrophages that release proteolytic enzymes capable of causing tissue damage. Tissue damage appears as areas of fibrinoid necrosis. The distribution of tissue injury is determined by the sites of deposition of the immune complexes (vessels, renal glomeruli, joints). Two general types of antigen may cause

immune complex deposition: (1) exogenous, such as bacteria, virus, parasites, fungi, or drugs and (2) endogenous or “self” components, such as nuclear antigens, immunoglobulins, or tumor antigens (resulting in autoimmunity; this is discussed in Sect. 2.1.3.2).

Immune complex-mediated disease may be generalized, if immune complexes are formed in the circulation and are deposited in many organs, or localized, if the complexes are formed and deposited locally (local Arthus reaction) to particular organs, such as the kidney (glomerulonephritis), joints (arthritis), or the small blood vessels of the skin (purpura).

Systemic Immune Complex Disease

The classic condition ascribed to systemic immune complex disease is acute serum sickness. Rabbits given a single intravenous injection of bovine serum albumin (BSA) developed necrotizing arteritis and glomerulonephritis, similar to the lesions seen in humans with polyarteritis nodosa (PAN) [44, 45]. These lesions appear at 10–14 days, the period when circulating immune complexes are being formed in slight antigen excess.

The process is initiated by the introduction of antigen into the circulation and its interaction with immunocompetent cells, resulting approximately 5 days later in the formation of antibodies. Antibodies react with the antigen still present in the circulation to form antigen–antibody complexes. Antigen–antibody complexes formed in the circulation are deposited in various tissues. The factors that determine whether immune complex formation will result in tissue deposition and disease are diverse, and include the following.

1. *Immune complex size*: The size of an immune complex is determined by the ratio of antigen to antibody. Large immune complexes (great antibody excess) are readily phagocytized by the reticuloendothelial system and small immune complexes (great antigen excess) are too small to localize in tissues. The most pathogenic complexes are of intermediate size (formed in slight antigen or antibody excess) because of their longevity in the circulation [46].

2. *Antigen and antibody valences*: Monovalent and oligovalent antigens bind only one or a few antibody molecules and form small immune complexes, whereas multivalent antigens bind and cross-link many antibody molecules and form large, lattice-like structures [47].
3. *Reticuloendothelial system function*: Because the reticuloendothelial system normally phagocytizes the circulating immune complexes, its dysfunction increases the persistence of immune complexes in circulation and tissue deposition.
4. *Local characteristics of vessels*: The focal distribution of vasculitic lesions in animals and humans can be explained partially by structural and hemodynamic differences among various blood vessels and by the tendency of immune complexes to deposit at the branch points of the vessels [48, 49].

Local vasoactive factors increase vascular permeability, which allows immune complexes to leave the circulation and deposit within or outside the vessel wall [50, 51]. The increased vascular permeability results from the action of vasoactive amines derived from platelets (platelet-activating factor) and IgE (serotonin and histamine). These amines induce contraction of vascular endothelial cells, disrupting their close apposition and producing interendothelial gaps through which immune complexes travel, becoming trapped in the basement membrane or depositing in the tissues.

Once immune complexes are deposited in or outside the vessel wall, complement components are activated, some of which (1) are chemotactic factors for neutrophils and eosinophils and mononuclear leukocytes (C3a, C5a, and C5b67), (2) increase vascular permeability and cause contraction of smooth muscle (C3a and C5a), or (3) cause cell membrane damage (membrane attack complex, C5 through C9). Antibodies IgG₁, IgG₂, IgG₃, and IgM all activate the classic complement pathway efficiently, whereas IgG₄, IgA, and aggregates of IgE interact with the complement system via the alternative pathway. During the active phase of the disease, consumption of complement components decreases the serum levels.

Neutrophils attracted by complement components cause vessel and surrounding tissue damage through the release of the lysosomal enzymes, reactive oxygen metabolites, and proinflammatory substances, such as platelet-activating factor, leukotrienes, and prostaglandins. Platelets may adhere to locally damaged endothelium and aggregate, obstruct blood vessels, and release more inflammatory mediators, augmenting vessel and tissue necrosis. The reaction spirals into an amplification cascade, causing damage to vessel walls and other surrounding tissues. The resultant pathological lesion is termed vasculitis if it occurs in blood vessels, glomerulonephritis if it occurs in renal glomeruli, arthritis if it occurs in joints, and so on. The immune complexes can be seen by immunofluorescence microscopy as deposits of immunoglobulin and complement.

A chronic form of serum sickness or immune complex disease results from repeated or prolonged exposure to an antigen. This occurs in systemic vasculitic diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and polyarteritis nodosa. However, although immunoglobulins and complement as part of immune complexes can be seen by immunofluorescence techniques, the inciting antigens are unknown.

Local Immune Complex Disease (Arthus Reaction)

The classic condition ascribed to local immune complex disease is the Arthus reaction [52]. In this model, necrotizing vasculitis is seen at the site of locally injected antigen in animals preimmunized (having circulating antibodies) with the same antigen. Vessel damage occurs because of the reaction of preformed antibody with locally injected antigen in vessel walls. As the antigen diffuses into the vascular wall, large immune complexes are formed because of the excess of antibodies, which precipitate locally and trigger the inflammatory reaction discussed earlier. The Arthus reaction develops over a few hours and reaches a peak 4–10 h after injection; the area discloses edema, hemorrhage, and occasionally ulceration as a result of inflammatory reaction, rupture of the vessel wall, or thrombosis of the vessel lumen. The immune complexes precipi-

tated in the vessel walls, usually capillaries and postcapillary venules, can be seen by light microscopy as neutrophilic infiltration of the vessel wall and by immunofluorescence microscopy as deposits of immunoglobulin and complement.

Type IV Hypersensitivity Reactions

Type IV hypersensitivity reactions are also known as delayed hypersensitivity reactions because they require more than 12 h after the antigenic challenge to develop. They are mediated by cells (T lymphocytes) and not by antibodies. After antigen presentation by the antigen-presenting cells, T lymphocytes proliferate and release lymphokines, which may cause direct cytotoxicity or stimulate neutrophils and macrophages to produce tissue damage [7]. Four kinds of type IV hypersensitivity can be distinguished: (1) Jones-Mote, (2) contact, (3) tuberculin, and (4) granulomatous. The first three reactions develop between 24 and 72 h after antigen challenge, whereas the fourth type requires at least 14 days [7].

Granulomatous hypersensitivity causes many of the pathological hallmarks of diseases, such as tuberculosis, schistosomiasis, or scleral inflammation. Persistence of microbiological agents (*M. tuberculosis*, viruses, parasites, and fungi), foreign body deposition (talc), or immune complexes provides the long-term stimulus for the inflammatory response to produce granulomas [53]. Histologically, granulomas are composed of macrophages and epithelioid cells (modified macrophage) with variable numbers of neutrophils, eosinophils, lymphocytes, and plasma cells. Also seen in this type of reaction is the multinucleated giant cell (Langhans' giant cell), which is derived from fusion of several epithelioid cells; this cell is believed to be an end stage of differentiation of the monocyte/macrophage line [54].

2.1.3.2 Autoimmunity

Autoimmunity is an immune response directed against endogenous structures of an organism (autoantigens or self-antigens); the organism escapes from the normal state of tolerance to its own tissue antigens to the abnormal state of responding to self as nonself [55]. The immune

response characterized by tissue damage may be exerted by immunoglobulins (autoantibodies) and/or by T lymphocytes. Both types II and type III hypersensitivity reactions have been implicated.

A growing number of diseases have been attributed to autoimmunity, although for many of them the evidence is not firm. Examples of these diseases range from highly organ-specific diseases, such as pernicious anemia, insulin-dependent diabetes mellitus, or Hashimoto's thyroiditis to multisystem disorders, such as lupus erythematosus or rheumatoid arthritis (Table 2.8). At least three requirements should be met before autoimmunity can be ascribed to a disease: (1) the presence of an immune reaction, (2) clinical or experimental evidence that the immune reaction is not secondary to tissue damage but is of primary pathogenetic significance, and (3) the absence of another well-defined cause of the disease.

Mechanisms of Autoimmunity

Susceptibility to autoimmunity or loss of self-tolerance is genetically controlled by genes within the MHC. A variety of infectious agents, including bacteria, mycoplasmas, and particularly viruses, have been implicated in triggering autoimmunity. The development of an autoimmune disease probably entails the interaction of genetically controlled mechanisms with environmental factors, such as infectious agents [56]. Several general mechanisms for autoimmunity have been postulated.

1. *Newly induced class II MHC expression:* acrophages Langerhans cells, monocytes, and T and B lymphocytes are the only cells that constitutively express class II MHC glycoproteins. Other cells, such as connective tissue fibroblasts or vascular endothelial cells, may be induced to express class II glycoproteins under inflammatory stimulation (interferon γ). It has been suggested that such aberrant expression of class II MHC glycoproteins could trigger an autoimmune response [30].
2. *Modification of a self-molecule:* If a self-molecule is complexed with a new carrier

Table 2.8 Autoimmune diseases

<i>Organ-specific probable</i>	<i>Nonorgan specific probable</i>
Hashimoto's thyroiditis	Systemic lupus erythematosus
Grave's disease	Rheumatoid arthritis
Primary myxedema	Sjögren's syndrome
Thyrotoxicosis	Reactive arthritis
Pernicious anemia	
Autoimmune encephalomyelitis	<i>Possible</i>
Addison's disease	Polyarteritis nodosa
Goodpasture's syndrome	Polymyositis-dermatomyositis
Autoimmune thrombocytopenia	Systemic sclerosis
Autoimmune hemolytic anemia	Mixed connective tissue disease
Myastenia gravis	
Insulin-dependent diabetes mellitus	
Pemphigus vulgaris	
Pemphigoid	
<i>Possible</i>	
Primary biliary cirrhosis	
Chronic active hepatitis	
Ulcerative colitis	
Noninfectious uveitis	
Noninfectious scleritis	

(infectious agent or drug), the carrier part of the complex may be recognized by T lymphocytes as nonself; T lymphocytes help B lymphocytes, resulting in autoantibody production. Another mechanism for self-molecule modification is through partial degradation (e.g., by an infectious agent); the degraded self-molecule (collagen, gamma globulin) may disclose new antigenic determinants that trigger an autoimmune response.

3. *Antigen mimicry:* Infectious agents may share regions of amino acid sequence with self-molecules; the immune response elicited by the infectious agent also may damage the self-molecule.
4. *Allelic variation MHC genes:* An antigen (e.g., an infectious agent) when presented in association with a particular allelic form of HLA glycoprotein ("susceptible") may mimic an autoantigen, eliciting an autoimmune response.
5. *Polyclonal B-lymphocyte activation:* Autoreactive B lymphocytes may be activated (antigen nonspecific) by B-lymphocyte mitogens, such as infectious agents or their

products, leading to polyclonal activation. Some of the nonspecific immunoglobulins produced may react with self-molecules, resulting in autoantibody production. For example, bacterial lipopolysaccharide may induce mouse B lymphocytes to form autoantibodies in vitro; some viruses (EBV) are non-specific, polyclonal B-lymphocyte mitogens (human B lymphocytes have surface receptors for EBV) and may thus induce the production of autoantibodies.

6. *Idiotypic networks:* Abnormalities in the immune response involving the idiotypic network may lead to the production of antibodies (idiotypic) against self-molecules. Anti-idiotypic antibodies against the idiotypic (e.g., antithyroid-stimulating hormone [TSH]) resemble the original antigen (e.g., TSH) and may react with the antigen receptor on specialized cells (e.g., TSH receptors on thyroid cells in Graves' disease) [57].
7. *Abnormalities of immunoregulatory T cells:* The normal immune system has the capacity to produce a small amount of autoantibodies without the production of autoimmune reactions; T-suppressor lymphocytes normally control this autoantibody production (through preventing T lymphocyte's help to B lymphocytes). Loss of T-suppressor lymphocyte function (e.g., following viral infection) may allow the production of large amounts of autoantibodies, leading to autoimmunity.

nents and eventual scar formation. Lymphocyte-derived chemotactic factor released from T lymphocytes, platelet-derived growth factor released from platelets, and leukotriene B₄ released from leukocytes have been shown to provide chemotactic signals for fibroblasts [58–61]. The C5-derived fragment from serum complement activation by the classic or alternative pathways can also provide chemotactic signals for fibroblasts [62]. Collagen, elastin, and fibronectin, as well as some of their degradation products, can be chemoattractants for fibroblasts [63–65].

Fibroblast functions, such as collagen, collagenase, and hyaluronic acid production, can be modulated by components of the immune response. Type I collagen production is stimulated by a lymphokine, the collagen production factor, and by a monokine, interleukin 1, but it is inhibited by another lymphokine, interferon γ [66–70]. Collagenase and hyaluronic acid productions are stimulated by interleukin 1 [67, 68, 71].

Fibroblasts have been found to synthesize several complement components [72–74]. C1q, the recognition unit of the classical pathway, and collagen have structural similarities because the genes for each share part of their coding region [75, 76]. Complement synthesis by fibroblasts can be regulated by several components of the immune response, including interleukin 1, tumor necrosis factor, and interferon γ [77–79].

Fibroblasts have been shown to express class I HLA glycoproteins constitutively [80–82], but under certain inflammatory stimuli, including that of interferon γ , they can also express class II HLA glycoproteins [83–85]. Class II HLA expression may allow fibroblasts to be involved in the initiation and perpetuation of an immune inflammatory response.

Following stimulation by interleukin 1, fibroblasts may synthesize and secrete prostaglandins, such as PGE₂ [86]. Prostaglandin E₂ production provides a regulatory signal in modulating the intensity of the inflammation during the immune response.

2.2 Connective Tissue and the Immune Response

2.2.1 Fibroblast Functions and the Immune Response

When connective tissue sustains an inflammatory (immunological, mechanical, or chemical) injury, fibroblasts migrate to the involved area to repair the damage. Specific chemoattractants have been identified that direct their migration for subsequent synthesis of new matrix compo-

2.3 The Sclera and the Immune Response: Scleritis

2.3.1 Immune Characteristics of the Sclera

The sclera is composed of fibroblasts, proteoglycans, collagen, elastin, and glycoproteins. Although the sclera does not have its own capillary network, its nutrition derives from the overlying episclera and underlying choroid. The sclera contains immunoglobulins, albumin, and the classic and alternative pathway components of complement [87, 88]. Complement present in the sclera may be activated by immune complexes through the classical pathway or by microorganisms through the alternative pathway. Inflammatory functions of activated complement include increased vascular permeability, mast cell degranulation, opsonization of immune complexes and microorganisms, neutrophil chemotaxis, and cytolysis [7]. IgG, IgA, albumin, and complement components C4, C2, C3, C5, C6, and C7 levels are higher in the posterior than in the anterior sclera, probably because of a greater adjacent vascular supply from the choroid [88]. Conversely, levels of C1, the recognition unit of the classic complement pathway, are higher in the anterior than in the posterior sclera. The preferential activation of complement by immune complexes anteriorly may explain, at least in part, why anterior scleritis is more common than posterior scleritis [88]. Because the diffusion of C1, the largest complement component (M_r 647,000), into the sclera may be restricted, local production may help to explain its presence. Scleral fibroblasts constitutively produce C1 [89]. After exposure to an inflammatory stimulus such as human interferon γ , scleral fibroblasts increase production of C1 and are induced to secrete new C2 and C4. No other complement components (C3, C5, C6, and C7) are secreted by scleral fibroblasts [89].

Scleral fibroblasts constitutively express class I HLA glycoproteins (HLA-A, -B, and -C) but can be induced to express class II HLA glycopro-

teins (HLA-DR, -DP, and -DQ) under exposure to an inflammatory stimulus, such as interferon γ [89]. HLA-DR expression in human scleral specimens has been found to be high in patients with scleritis [2]. These findings suggest that scleral fibroblasts have the ability to participate in immunological diseases. Aberrant expression of HLA-DR was proposed by Botazzo et al. [30] to play a pivotal role in the initiation and perpetuation of the immune response leading to autoimmune disorders.

Immune complexes may be important in the pathogenesis of scleritis associated with autoimmune diseases [7, 90]. Activation of C1, already present in the sclera, by immune complexes may play a role in some types of scleral inflammation.

Normal human sclera has few or no macrophages, Langerhans' cells, neutrophils, or lymphocytes. After scleral inflammation, there is a marked increase in T-helper lymphocytes with a high T helper-to-T suppressor ratio. These findings suggest that T lymphocytes, as part of cell-mediated immune responses, also play a role in some forms of scleritis [2].

2.3.2 The Susceptible Host: Immunogenetics

Immunogenetic susceptibility has been found to be important in the development of some of the systemic vasculitic disorders associated with scleritis. For example, in the connective tissue disease most frequently associated with scleritis, rheumatoid arthritis, the class II MHC locus is associated with susceptibility to rheumatoid joint disease. A majority of patients with rheumatoid arthritis carry HLA-DR4, HLA-DR1, or both [91]. HLA-DR4 can be divided into five subtypes: Dw4, Dw10, Dw13, Dw14, and Dw15. Only Dw4 and Dw14, present in 50 and 35% of the patients, respectively, promote, independently of each other, susceptibility to rheumatoid arthritis [92, 93]. No immunogenetic studies have been performed in patients with scleritis.

2.3.3 Etiology

Scleral inflammation can often be associated with systemic vasculitic diseases, including the connective tissue vascular diseases, polyarteritis nodosa, and granulomatosis with polyangiitis (Wegener). The antigen(s) responsible for scleritis associated with systemic vasculitic diseases in an immunogenetically susceptible individual remains unidentified [94, 95]. It is possible that scleritis associated with systemic vasculitic diseases shares the same causative factors of these disorders. It is also possible, indeed likely, that any of these disorders is triggered by more than one etiological factor. For example, current research on rheumatoid arthritis etiology is focused on exogenous infectious agents, such as viruses or mycobacteria, and endogenous substances, such as connective tissue molecules. Exogenous infectious agents are hypothesized as causative factors because of data showing that a persistent but only weakly cytotoxic virus may generate an immune reaction that becomes self-sustaining. Endogenous substances are considered as possible triggers because of data showing that certain individuals immunogenetically disposed to develop rheumatoid arthritis have abnormal lymphocytes that allow a chronic persistent arthritis to develop in response to connective tissue molecules, such as proteoglycans or collagen. Another possibility involves components of the two theories already mentioned: an infection in a susceptible individual could result in production of antibodies that cross-react with connective tissue molecules in the joints.

2.3.3.1 Exogenous Agents

Viruses

To date, no virus has been proved to cause rheumatoid arthritis, but because of the capacity of viruses to alter immune responses they remain prime candidates for the initiation or propagation of this disease [96]. Viral or subviral components or new virus-induced antigens expressed on the infected cell surface (either virus material or a combination of infected cell and virus material) may act as neoantigens and invoke an immune response [97]. A virus can also invoke

an immune response by unmasking a substructure present in the infected cell, by secondary derepression of a gene encoding an infected cell membrane antigen [98, 99]. Other possible mechanisms have been implicated in the production of autoimmunity triggered by viruses (see Sect. "Mechanisms of Autoimmunity").

Many viruses have been proposed as etiological factors for rheumatoid arthritis [100, 101]. Rubella virus, cytomegalovirus, herpes virus type 1, human T-cell lymphotropic virus type I, EBV, and parvovirus are some examples, but only the two latter have received sustained scientific support.

1. *EBV*: Eighty percent of patients with rheumatoid arthritis have circulating antibodies in high titers directed against antigens specific for EBV [102]. The EBV receptor on the B lymphocyte, the target cell, is identical to complement receptor type 2 (CR2), which binds C3d, C3bi, and, with less affinity, C3b. EBV infection of B cells results in polyclonal activation and overproduction of autoantibodies, including rheumatoid factor [103]. Patients with rheumatoid arthritis shed more EBV in throat washings than do control subjects [104]. Support for the hypothesis that EBV does not cause rheumatoid arthritis comes from reports in which increased antibody titers against EBV were not found in early rheumatoid arthritis [105]. However, there has been found an identical amino acid sequence between the viral glycoprotein gp110 and the "susceptibility regions" HLA-Dw4, -Dw14, and -DR1 [106]. Patients with serologic evidence of a previous EBV infection have serum antibodies that recognize the same peptides from both gp110 and HLA-Dw4 [106, 107]. Tolerance of self-antigens in these patients could affect the immune response to EBV, leading to a continuous infection that would be manifested as rheumatoid arthritis. EBV antibody titers in patients with scleritis have not been reported.
2. *Parvoviruses*: Parvoviruses are small DNA viruses that cause disease in humans and animals, such as the Aleutian mink. Parvoviruses can integrate their own DNA into human chromosomes, perhaps leading to expression of

antigens that generate an immune response. Two patients with early rheumatoid arthritis have been reported to have had a recent infection with parvovirus B19; [108] two other patients with acute infection with parvovirus B19 were found to be transiently positive for rheumatoid factor and to develop arthritis [109]. After 6 months, the rheumatoid factor reverted to negative and the arthritic symptoms disappeared. No data on parvovirus infections in patients with scleritis have been reported.

The ideal viral pathogen that could cause rheumatoid arthritis or scleritis should be ubiquitous, persistent, and have the capability to alter immune responses in the genetically susceptible individual. It is possible that these characteristics might be distributed among two or more viruses that would work in series or parallel.

Mycobacteria

Mycobacteria express heat-shock proteins on their cell surfaces in response to various kinds of stress. Heat-shock proteins are the arthritogenic factors of adjuvant arthritis in rats [110]. Patients with rheumatoid arthritis have elevated serum levels of IgG and IgA to heat-shock proteins from mycobacteria [111] and synovial fluid proliferation of lymphocytes with CD3-associated T-cell receptor (the lymphocytes that proliferate in response to mycobacterial antigens) [112]. Lymphocytic proliferation in response to mycobacterial antigens could be perpetuated by heat-shock proteins on synovial cells and therefore participate in the genesis of rheumatoid arthritis. No data on mycobacterial infections in patients with scleritis have been reported, nor are there reports of studies on antibodies to heat-shock proteins.

2.3.3.2 Endogenous Substances

There is no doubt that autoimmunity has an important role in the development of rheumatoid arthritis, but data supporting autoimmunity as the initial cause of the disease are less firm [113]. The connective tissue molecules, proteoglycans and collagen, are the endogenous proteins most often implicated in this hypothesis, perhaps

related to common developmental characteristics between collagen and sclera [114]. Proteoglycans and collagen may provoke cell-mediated and humoral immune responses in experimental rheumatoid arthritis [115, 116]. They also may be involved in the generation of autoimmune mechanisms in rheumatoid arthritis in humans [117–123].

Glycosaminoglycans

Glycosaminoglycans have been shown to be antigenic in rheumatoid arthritis [122, 123]. Cell-mediated and humoral immune responses can derange the molecular structure of glycosaminoglycan. The degraded components can be recognized by the immune cells of the host as a foreign material and create a vicious circle of chronic inflammation.

Immunological cross-reactivity of glycosaminoglycans between sclera and other organs suggests that autoimmunity to these molecules might participate in scleral inflammation [124–126]. Dermatan sulfate, isolated from bovine sclera and bovine cartilage, can, according to the size, be divided into large and small dermatan sulfates. The small dermatan sulfates of both sclera and cartilage tissues have closely related core proteins and display immunological cross-reactivity [126]. Immunological and histochemical studies have revealed that these small proteoglycans are bound to collagen type I [127, 128]. Small dermatan sulfates have the ability to inhibit fibrillogenesis of both collagen type I and type II through the core protein of the proteoglycan structure [129, 130]. No data on glycosaminoglycan-induced scleritis in animals or antibodies to glycosaminoglycans in patients with scleritis have been reported.

Collagen

Collagen has also been shown to be antigenic in rheumatoid arthritis [131–135]. Collagen type II-induced arthritis in animals and cellular and humoral sensitivity to collagen type II in humans with rheumatoid arthritis have supported the possibility of collagen autoimmunity as potential etiologic factor; however, there are data showing that antibodies against collagen type II do not

precede the clinical onset of rheumatoid arthritis [136]. Most of the more recent studies in humans conclude that rheumatoid arthritis is not caused by the development of autoantibodies to collagen type II, but that the activated immune system in rheumatoid arthritis develops clonal proliferation of B cells expressing antibody against epitopes of collagen type II normally masked by the native helical conformation of collagen and its coating with proteoglycan and other noncollagenous glycoproteins. Anticollagen antibodies against the degraded, fragmented collagen type II can amplify the immune response, resulting in synovitis and centripetal polarization of destructive arthritis [137].

We investigated whether or not immunization with collagen type I or type III participates in the pathogenesis of scleritis. Outbred female Wistar-Lewis rats (150–225 g, 7–10-week old) were injected intradermally in 8–10 sites (small blebs) on the back with native collagen type I or type III (1 mg/ml). Native collagen type I and III, previously dissolved in 0.1 M acetic acid, were emulsified with equal volumes of Freund's incomplete adjuvant. Rats were boosted intraperitoneally 1 week following the first immunization and then once a week for 8 weeks. Daily clinical ocular evaluation did not show any area of scleritis. Histopathology studies on sclera following sacrifice and bilateral enucleation of the animals, ranging up to 6 months after primary immunization, did not reveal inflammatory changes. These data suggest that autoimmunity to collagen is not an etiological factor in the pathogenesis of scleritis.

We also investigated whether or not patients with scleritis, particularly necrotizing scleritis, have antibodies to collagen type I. Sera from patients with necrotizing scleritis were examined by enzyme-linked immunoabsorbent assay (ELISA) for antibodies to native collagen type I. No differences in anticollagen type I antibodies were found between sera from patients with necrotizing scleritis and sera from normal individuals. These data suggest that autoimmunity to collagen type I is not an etiologic factor in the pathogenesis of scleritis.

2.3.4 Pathogenesis

The immunopathologic findings of vessel thrombosis and inflammatory infiltration of the vessel walls in scleritis associated with autoimmune diseases suggest that immune complex-mediated vasculitis plays a pivotal role in some types of scleral inflammation [2]. Immune complexes, either circulating or formed in the sclera itself, may localize in the episcleral vasculature and scleral-perforating vessels [1]. The mechanism of selective localization in the vessel walls is not clear, but the ratio of antigen to antibody in a complex may be important [138].

Scleral fibroblasts under inflammatory conditions increase production of the complement component C1, which can be activated by immune complexes through the classic pathway [89]. Complement components increase vascular permeability and generate chemotactic factors for neutrophils (e.g., C3a, C5a). Further activation of complement can lead to assembly of the membrane attack complex (C56789), thus effecting cellular damage. Neutrophils release their lysosomal enzymes, reactive oxygen metabolites, and proinflammatory substances, such as platelet-activating factor, leukotrienes, and prostaglandins. Platelets may adhere to locally damaged endothelium and aggregate, obstruct blood vessels, and release more inflammatory mediators, augmenting vessel and tissue necrosis [139, 140].

Scleral fibroblasts under inflammatory conditions express class II HLA glycoproteins which allow them to participate in the afferent arm of the immune response as cells presenting antigen to T-helper lymphocytes [2, 89]. At the molecular level, class II HLA glycoproteins, antigen, and TCR form a trimolecular complex that results in activation of the T-helper lymphocytes [141]. T-helper lymphocytes, as part of the efferent arm of the immune response, react to the antigen through the action of lymphokines in combination with the same class II HLA glycoproteins.

Scleral fibroblasts as well as other inflammatory cells and lymphokines have the potential to produce matrix-degrading enzymes, such as

collagenase, elastase, proteoglycanase, and glycoproteinases, under inflammatory conditions [142–146]. The components of the degraded matrix released may be recognized by the immune cells of the host as foreign material and trigger a vicious circle of chronic inflammation in which a truly autoimmune component against sclera eventually participates.

Immune complex-mediated vasculitis and cell-mediated immune responses may interact as part of the immune network activated in scleral inflammation [147]. It is not clear whether immune complexes act to trigger the cell-mediated immune response, whether T-lymphocyte activation by an unknown antigen results in B-lymphocyte activation and production of antibodies that can form immune complexes, or whether both these phenomena occur simultaneously. Whichever the case is, both mechanisms are important in the pathogenesis of some forms of scleritis [2].

Systemic vasculitic diseases associated with scleritis are frequently associated with circulating immune complexes as well as immune complex deposition in vessel walls in many organs, including the eye [2, 139, 148–157]. Immune complexes are capable of activating the complement cascade [139, 140, 158]. T-helper lymphocyte activation by antigen bound to class II HLA glycoproteins on antigen-presenting cells in an immunogenetically susceptible individual also participates in the pathogenesis of these diseases [91, 149–162].

Hembry and coworkers [163] produced an animal model of necrotizing scleritis following an Arthus reaction (local immune complex disease). Necrotizing scleritis was seen at the site of scleral injection with ovalbumin in rabbits previously sensitized over a prolonged period with the same antigen by intradermal injection.

We investigated whether or not scleritis can result from circulating immune complexes eventually deposited in the sclera. New Zealand White rabbits underwent right internal carotid artery dissection for catheterization with a permanent cannula. In vitro preformed immune complexes in varying degrees of antigen (ovalbumin) or antibody (anti-ovalbumin antibodies obtained in

rabbits after intracardiac injection 7 days following intraperitoneal immunization with ovalbumin) excess were injected once a day for 7 days. Daily clinical ocular evaluation did not show any area of scleritis. Histopathology studies on sclera, following sacrifice and bilateral enucleation of animals 7 days after first intravascular injection, did not reveal inflammatory changes. Further investigations with this model are needed because the factors that govern the deposition of immune complexes in vessel walls are diverse (immune complex size, antigen and antibody valences, reticuloendothelial system function, local characteristics of vessels, etc.) and the duration of immune complex supply required to produce scleritis is undoubtedly quite long. Both the quantity and quality of the host immune response seem to be responsible for the variable vasculitic manifestations of immune complex disease in animal models and humans [164, 165].

2.4 Summary

The sclera has the ability to participate in immunological diseases. The normal sclera contains immunoglobulins, albumin, and many of the classic and alternative pathway components of complement, and has few or no macrophages, Langerhans' cells, neutrophils, or lymphocytes.

Under inflammatory conditions, scleral fibroblasts express class II HLA glycoproteins, increase production of the recognition unit of the classic complement pathway, C1, and are induced to secrete new C2 and C4 complement components. Inflammatory functions of activated complement include increased vascular permeability, mast cell degranulation, opsonization of immune complexes and microorganisms, neutrophil chemotaxis, and cytolysis.

Under inflammatory conditions, the sclera shows immune complex vessel deposition and a marked increase of macrophages and T lymphocytes, with a high T-helper lymphocyte-to-T-suppressor lymphocyte ratio.

The development of scleritis probably entails the interaction of genetically controlled mechanisms with environmental factors, such as

infectious agents (e.g., viruses, mycobacteria) or trauma. This interaction gives rise to an autoimmune process that damages the vessels through immune complex vessel deposition, subsequent complement activation, and neutrophil enzyme release (type III hypersensitivity). Persistent immunological injury leads to a chronic granulomatous response (type IV hypersensitivity) mediated by macrophages, epithelioid cells, multinucleated giant cells, and lymphocytes.

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