Chapter 23
Complement Systems and Allergy Diseases

Marianne Frieri

The Complement System

Pathways and Physiologic Activities

The complement system consists of more than 30 plasma and cell membrane proteins both first discovered classic (C_1–C_9), activated by antigen–antibody complexes, alternative pathway components (properdin, factors B and D), inhibitors (C_1, factor 1, etc.), microbial cell walls, and regulatory proteins (C_4 binding, factor H, S protein (Fig. 23.1)). Complement is part of the innate immune system and is an important effector mechanism of humoral immunity. The main physiologic activities are listed which illustrates host defense against infection, bridging innate and adaptive immunity. The removal of immune complexes and inflammatory products is performed by C1q and covalently bound fragments of C_3 and C_4. Initiators of activation pathways for the classical pathway include apoptotic cells, viruses, gram-negative bacteria, and C-reactive protein in addition to immune complexes. The early steps of complement activation and classical pathways are illustrated in Fig. 23.2. The mannose-binding lectin or collectin, homologous to C_1q, is initiated by organisms with terminal mannose groups, and decreased levels have been noted in children with recurrent infections. The late steps of complement activation and the membrane attack complex (MAC) are shown in Fig. 23.3.

M. Frieri, MD, PhD
North Shore Long Island Jewish Health Care System, State University of N.Y. @ Stony Brook, Nassau University Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554, USA
e-mail: mfrieri@numc.edu

M. Mahmoudi (ed.), *Allergy and Asthma*, DOI 10.1007/978-3-319-30835-7_23

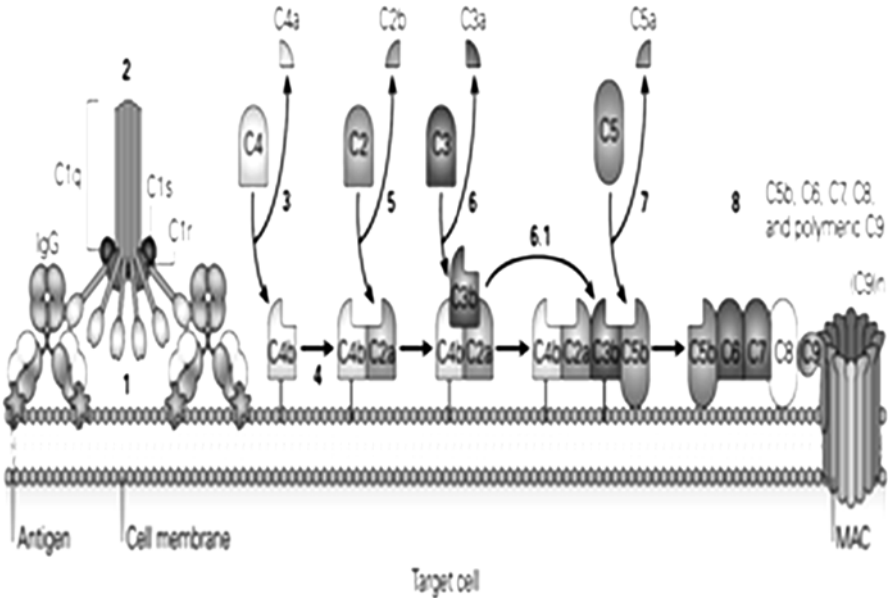

Fig. 23.1 Schematic representation of the classical complement cascade showing the initiation of the pathway by binding of the *C1q* component of *C1* binding to the *Fc* region of an *IgG* antibody molecule bound to an antigen on the surface of a target cell. The numbers in bold indicated the sequential steps which are involved in the activation of each of the components leading to the final lytic event carried out by the MAC. Some sources now use a revised nomenclature for the fragment of *C2*, in which *C2* is the small fragment diffuses away and *C2b* is the larger fragment that binds with *C4b* and acts in the convertase, *C4b2b* (Source: Immunology IV Text, Editor Bellanti, Berger)

Biologic Properties of Complement Fragments Related to Allergic Diseases

Complement cascade activation leads to generation of biologically active fragments (Table 23.1). The products of C_3 and C_5 are small polypeptide anaphylatoxins that have a variety of biologic properties; C_3a, C_4a, and C_5a release inflammatory mediators from mast cells, induce smooth muscle contraction, promote vascular permeability, and induce adhesion molecules on endothelial cells. C_3a can also lead to mucus secretion by goblet cells, and C_3a and C_3a des arg can modulate synthesis of tumor necrosis factor alpha (TNFα) and interleukin 1 beta (IL-1β) by mononuclear cells to focus the production of proinflammatory cytokines that contribute to the pathophysiology of asthmatic inflammation. Anaphylatoxic peptides can trigger a variety of responses which contribute to allergic and inflammatory reactions. Anaphylaxis is an immediate systemic reaction due to rapid, IgE-mediated release of potent mediators from tissue mast cells and peripheral blood basophils. Anaphylactoid reactions are immediate systemic reactions that mimic anaphylaxis,

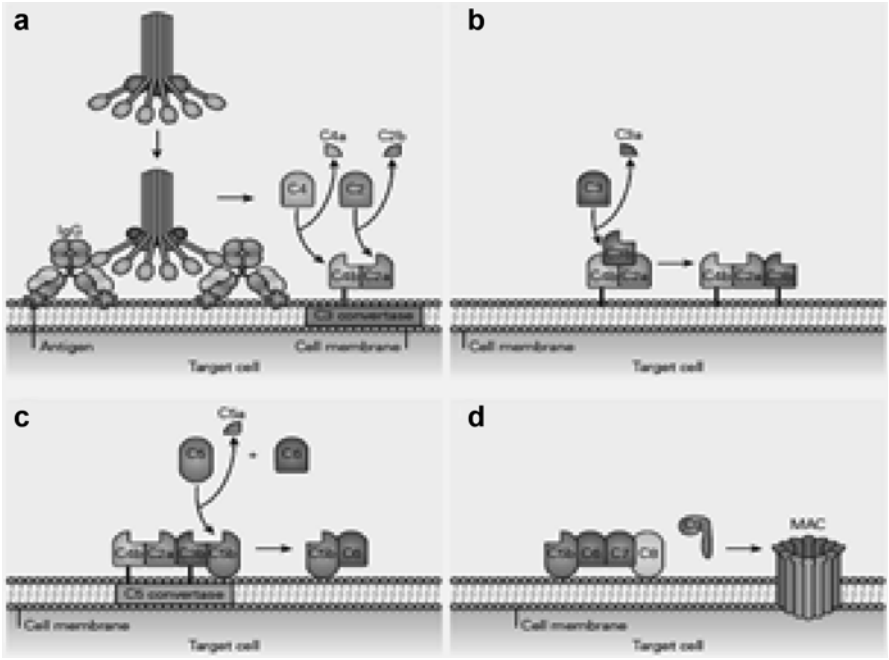

Fig. 23.2 Schematic representation of classical pathway activation. (**a**) Upon binding of *C1* to the Fc region of *IgG* or *IgM*, *C1r* and *C1s* are activated. *C1s* cleaves *C4* and *C2*, and the *C4b* binds covalently to the surface of a target cell and *C2a* subsequently binds to the *C4b* forming *C4b2a* complex, the *C3* convertase. (**b**) Following the binding of *C3* to the *C4b2a* complex, it is cleaved by the *C2a* component of the complex releasing *C3a*, which diffuses away, and *C3b*, which adheres to the *C4b2a* complex forming *C4b2a3b*, the *C5* convertase; note that *C4b2a* may deposit at a distance from the initial *C1* site and that many molecules of *C3b* may be deposited. Only a few will join with *C4b2a* to form the *C5* convertase. (**c**) Cleavage of *C5* by *C2a* releases *C5a* and allows *C5b* to bind with *C6*. The *C5b6* complex can insert into the plasma membrane; *C5b6* can also insert at a distance from the convertase that cleaved the *C5*. (**d**) *C7* and *C8* can bind with *C5b6*, forming a complex causing *C9* molecules to unfold, polymerize, and insert into the membrane, to a protein-linked pore (Source: Immunology IV Text, Editor Bellanti, Berger)

but are not caused by IgE-mediated immune responses. Mast cell and basophil mediators may play a role in anaphylaxis and anaphylactoid reactions through tryptase which may activate complement by cleavage of C3.

C_5a also plays an important role in recruiting phagocytic cells to sites of immune complex deposition in the lung leading to enhanced oxidative and lipoxygenase activity with leukotriene B_4 (LTβ4) production. LTβ4 and other leukotriene mediators are known to play important roles in asthma allergic rhinitis and cystic fibrosis. The presence of C_3a and C_5a in the lung can also induce respiratory distress through contraction of smooth muscle walls in bronchioles and pulmonary arteries. Animal studies have demonstrated the expression of C_3aR and C_5aR by cells in the lung suggesting a role for these receptors during lung inflammation both in sepsis and asthma (Table 23.2).

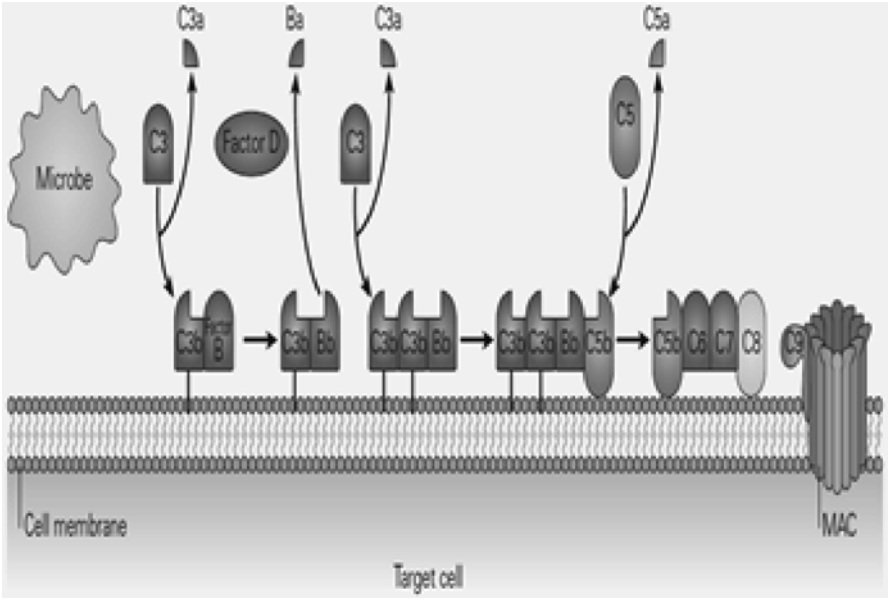

Fig. 23.3 Schematic representation of the alternative pathway showing the initiation of the pathway when *C3b*, which may be formed by one of the other pathways or by nonspecific proteolytic cleavage of *C3*, binds with Factor B, which is analogous to *C2*. When bound to *C3b*, B acquires a conformation that allows it to be cleaved of *C3*, binds with *Factor B*, which is analogous to *C2*. When bound to *C3b*, B acquires a conformation that allows it to be cleaved by the protease D following which the subsequent steps of the pathway are similar to those of the other two pathways (Source: Immunology IV Text, Editor Bellanti, Berger)

Table 23.1 Three main physiological activities of the complement system

Activity	Complement protein
Host defense Opsonization Chemotaxis and activation of leukocytes Lysis of bacteria and cells Interface between innate and adaptive immunity Augmentation of antibody responses Enhancement of immunologic memory	Covalently bound C3; C4 anaphylatoxins (C5a, C3a; C4a) receptors on leukocytes Membrane-attack complex (C5b–C9) C3b; C4b bound to immune complexes; AG; C3rc on B cells; APC C3b and C4b bound to immune complexes and to AG; C3rc on follicular dendritic cells
Disposal of waste Clearance of immune complexes from tissues Clearance of apoptotic cells	Clq; covalently bound fragments of C3 and C4 Clq; covalently bound fragments of C3 and C4

From Frieri
Modified from Walport

Cellular Receptors and Regulators

Receptors for complement components are expressed on many cells with important functions as listed in Table 23.3a. However, unlike most cellular receptors, some of the complement receptors also act as control molecules and interact with the molecule they bind to allow for further degradation of the bound fragment. Various inhibitors and regulators of complement activation and actions are listed in Table 23.3b. C_5a also acts as potent chemoattractant for LFA integrins (CD11a/CD18) to enhance leukocyte movement into tissues at the site of infection. There are four cell membrane receptors for bound C_3 or CR1, CR2, Cr3, and Cr4 that are within two gene families. CR1 or CD35 is found on mononuclear cells, neutrophils, mast cells, basophils, eosinophils, B and T lymphocytes, and kidney podocytes. It functions in phagocytosis and clearance of immune complexes. CR2 or CD35 expressed on B cell and follicular dendritic cells in addition to immature epithelial cells is utilized by Epstein–Barr viruses (EBVs) as a cellular receptor to promote cell entry.

Clinical Associations

Clinical effects of hereditary complement deficiencies related to infection, glomerulonephritis, angioedema, hemolysis, and systemic lupus erythematous (SLE) have been reported by Walport in articles on Complement. First and second of two parts

Table 23.2 Initiators of activation pathways

Pathway	Initiators
Classical	Immune complexes; apoptotic cells; certain viruses and gram-negative bacteria; CRP bound to ligand
Mannose-binding lectin	Microbes with terminal mannose groups
Alternative	Many bacteria, fungi, viruses, and tumor cells

Source: Frieri
Modified from Walport
CRP C reactive protein

Table 23.3a Major mechanisms of regulation of complement activation and function

Mechanism	Examples
Inhibition of active proteases	C1 inhibitor (C1NH)
Dissociation of convertases	DAF, CR1
Stabilization of convertases	Properdin (P)
Cleavage of active convertase subunits	Factor I
Promoters of cleavage by factor I	Factor H, C4 binding protein, CR1, membrane cofactor protein
Binding of lipophilic intermediates	S-protein (vitronectin), C8 binding protein (aka homologous restriction factor, HRF), protectin (CD59)

Source: Berger, Bellanti

Table 23.3b Regulatory proteins

Name(s)	Abbreviation or symbol	Family	Function
C1 inhibitor (C1 esterase inhibitor)	C1 INH	Serpin	Inhibits C1r, C1s, MASPs, noncomplement proteases
C4 binding protein	C4bp	RCA[a]	Binds to C4, inhibits classical pathway
Factor H (b-1-H)	H	RCA	Binds to C3b, inhibits alternative pathway
Properdin	P		Stabilizes alternative pathway convertases
C3b/C4b inactivator (Factor I)	I		Cleaves C4b and C3b
Decay accelerating factor	DAF, CD55	RCA	Destabilizes all convertases
Complement receptor type I	CR1, CD35	RCA	Binds to C3b, destabilizes convertases, and acts as cofactor for cleavage by I
Membrane cofactor protein	MCP, CD46	RCA	Cofactor for cleavage of C4b and C3 by I
S protein (vitronectin)			Inhibits insertion of C5b67
C8 binding protein (homologous restriction factor)			Inhibits addition and action of C8
Protectin (membrane inhibitor of reactive lysis)	CD59		Inhibits binding and polymerization of C9

Source: Berger, Bellanti
[a]*RCA* regulators of complement activation

N Engl J Med. 2001 Apr 5;344(14):1058–66 and *N Engl J Med.* 2001 Apr 12; 344(15):1140–4. Complement is part of the innate immune system and underlies one of the main effector mechanisms of antibody-mediated immunity. It has three overarching physiologic activities defending against pyogenic bacterial infection, bridging innate and adaptive immunity, and disposing of immune complexes and the products of inflammatory injury. In this review, each of these activities will be placed in a clinical context. The pathways leading to the cleavage of C3 are triggered enzyme cascades, analogous to the coagulation, fibrinolysis, and kinin pathways. The terminal complement pathway, leading to the formation of the membrane attack complex, is a unique system that builds up a lipophilic complex in cell membranes from several plasma proteins.

SLE can be associated with allergic disease such as urticaria and can masquerade as atopy.

Complement deficiency can lead to increased susceptibility to pyogenic infections such as *Haemophilus influenzae* and *Streptococcus pneumoniae*, abnormality of function of the mannose-binding lectin, defective regulation of C_3 associated with membranoproliferative glomerulonephritis, or compromise of the lytic activity increasing neisserial infections. C_{3b} and iC_{3b} which are covalently bound cleavage

Table 23.4a Clinical effects of hereditary complement deficiencies

Complement deficiency	Consequence of complement activation
C3	Loss of major complement opsonin; failure to activate membrane-attack complex pathway
C3, properdin	Failure to form membrane-attack complex
C3 membrane attack complex proteins	Loss of regulation of C1 and failure to activate kallikrein
C1 inhibitor	Failure to prevent membrane attack complexes on autologous cells
CD59	
C1q, C1r; C1s; C4,C2	Failure to activate the classical pathway
Factor H and factor I	Failure to regulate the activation of C3; severe secondary C3 deficiency

Source: Frieri
Modified from Walport

Table 23.4b Clinical effects of hereditary complement deficiencies

Complement deficiency	Clinical association
C3	Pyrogenic bacterial infections, may have a distinctive rash; membranoproliferative GN
C3, properdin	Neisserial infection
C3 membrane attack complex proteins	Angioedema
C1 inhibitor	
CD59	Hemolysis, thrombosis
C1q, C1r; C1s; Cls; C4; C2	SLE
Factor H and factor I	Hemolytic uremic syndrome
	Membranoproliferative glomerulonephritis

Source: Frieri
Modified from Walport

fragments of C_3 are the most significant opsonins for bacterial host defense. Mannose-binding lectin as previously mentioned is low in recurrent infections but also involved in tissue inflammation and necrosis. The mechanism of entry used by various organisms involving complement is discussed in Walport's article as three pathways of activation of the complement system: the classical, mannose-binding lectin, and alternative pathways (Tables 23.4a and 23.4b).

Three types of complement deficiency can cause increased susceptibility to pyogenic infections: a deficiency of the opsonic activities of the complement system, which causes a general susceptibility to pyogenic organisms; any deficiency that compromises the lytic activity of complement, which can increase the susceptibility to neisserial infections; and deficient function of the mannose-binding lectin pathway.

EBV uses glycoprotein 350/20, measles and picornaviruses employ hemagglutinin and capsid, and *M. tuberculosis* uses C3 fragments.

Hereditary angioedema (HAE), an autosomal dominant disease, is a deficiency of the C_1 inhibitor with loss of regulation and failure to activate kallikrein. This disorder can lead to severe illness when it involves the intestinal submucosa or obstruction of the upper airway leading to death by suffocation. Symptoms usually

Table 23.5 Proteins of the complement system and entry in to human cells

Microorganisms	Mechanism of entry into host cell
Epstein-Barr virus	Glycoprotein 350/220
Measles	Hemagglutinin
Picornaviruses	Capsid
Mycobacterium tuberculosis	C3 fragments

Source: Frieri
Modified from Walport

begin in adolescence, and edema of the gastrointestinal tract results in severe colicky abdominal pain, nausea, and vomiting. Urticaria is not part of the syndrome, and swelling can be triggered by trauma, psychological stress with increased frequency with angiotensin inhibitors. Over 100 mutations in the C_1-INH gene have been described. Type 1 HAE is due to a mutation which prevents the transcription of the abnormal allele, whereas type 2 variant is due to a point mutation in the gene abolishing its activity as a serine protease inhibitor. Patients with the type 2 variant have normal or elevated antigenic levels but synthesize a dysfunctional protein with reduced or absent C_1-INH function.

A third type in women has clinical findings but normal C_1-INH levels and function. Acquired angioedema in older patients with lymphoproliferative or monoclonal gammopathies has consumption of C_1q. Laboratory features of HAE are decreased C_1-INH, C_2, and C4 levels.

A review by Khan was performed of historical and current literature of HAE. HAE I and II are related to insufficient production of C1-esterase inhibitor (C1-INH) or production of a dysfunctional C1-INH protein, respectively. HAE III is not related to C1-INH deficiency and the pathogenesis is unknown. Bradykinin appears to be the main mediator responsible for angioedema in patients with C1-INH deficiencies. Angioedema of the extremities, face, and upper airway along with gastrointestinal angioedema is the most common clinical feature in HAE. The laboratory tests that are most commonly used in the diagnosis of HAE include C4 and C1-INH concentration and C1-INH function. Advances in our understanding of the pathogenesis of HAE have led to several advances in the therapy of this disease. Despite our more thorough understanding of the genetics and pathophysiology of HAE, many questions remain unanswered.

Table 23.5 summarizes the complement profiles of the major forms of recurrent angioedema. As can be appreciated from this table, it is relatively easy to distinguish HAE with normal C1-INH from HAE due to C1-INH deficiency. The major challenge is distinguishing HAE with normal C1-INH from unknown or sporadic angioedema.

Treatment with infusion of C_1 inhibitor can be lifesaving for HAE as listed in Walport's article. Patients with complement deficiencies are also associated with various rheumatic diseases such as SLE, anaphylactoid purpura, dermatomyositis, and vasculitis (Table 23.6).

Paroxysmal nocturnal hemoglobinuria is a rare disease characterized by intravascular hemolysis, hemoglobinuria, and venous thrombosis due to the absence of decay accelerating factor (CD55) and inhibitor of the MAC (CD59).

Table 23.6 Angioedema laboratory characteristics

	C1-INH level	C1-INH function	C4 level	C3 level	C1q level
HAE type I	*<50 %*	*<50 %*	*Low*	*Normal*	*Normal*
HAE type II	Normal	<50 %	Low	Normal	Normal
HAE with normal C1-INH	Normal	Normal	Normal	Normal	Normal
Acquired C1-INH I/II	Low	Low	<50 %	Normal/low	Low
ACE inhibitor	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

These characteristics can help to differentiate between types of HAE as well as distinguish between HAE and other forms of angioedema (such as ACE inhibitor-associated angioedema)
Modified from Khan

Hemolytic uremic syndrome is due to factor H and I deficiency. Total deficiency of C_3 and factor H mutations is associated with membranoproliferative glomerulonephritis. These patients have a complement consuming antibody called nephritic factor also found in partial lipodystrophy as listed in Walport's article. Apoptosis has been linked with autoimmune diseases associated with complement deficiencies. C_1q can bind to cells undergoing apoptosis with facilitation of elimination. Clearance of apoptotic cells has occurred through reactivity with collectin receptors or phagocytic cells that interact with C_1q and mannose-binding lectin.

Immunomodulation of Autoimmunity with Intravenous Immune Globulin and Mechanisms of Immunomodulation

The mode of action of immune globulin involves modulation of the expression and function of Fc receptors with complement activation and the cytokine network. The immunoregulatory effects of immune globulin which involve complement include blockade of Fc receptors on macrophages and other cell inhibitions of the Fcγ receptor IIB. The effect on inflammation includes the decrease of complement-mediated damage and immune complex-mediated inflammation, induction of anti-inflammatory cytokines, inhibition of endothelial cell activation, neutralization of bacterial toxins, and reduction in requirements of corticosteroids. The effects on B cells and antibody production, T cells and cell growth illustrated in immunomodulatory mechanisms, and agents for the treatment of autoimmune diseases include antigen-specific tolerance using intravenous or mucosal antigen application, altered peptides, or vaccines. In addition to immunoglobulin treatment, immunomodulation may also involve a change in the cytokine balance, administration of agents that suppress regulatory cytokines such as IL-10 and TGFß which can occur in allergen immunotherapy, and administration of agents that antagonize, TNFα or stem cell transplantation.

Table 23.7 Autoimmune/inflammatory diseases benefiting from immune globulin

Idiopathic thrombocytopenic purpura
Guillain–Barre' syndrome
Chronic demyelinating polyradiculoneuropathy
Myasthenia gravis
Multifocal motor neuropathy
Corticosteroid-resistant dermatomyositis
Kawasaki's disease
Prevention of graft-versus-host disease
Antineutrophil cytoplasmic vasculitis
Autoimmune uveitis
Multiple sclerosis

Modified from Kazatchkine

Table 23.8 Immunoregulatory effects of immune globulin

B cells and production of antibodies
Control of bone marrow B-cell lines
Negative signaling via Fc-y receptors
Selective downregulation and upregulation of antibody production
Neutralization by anti-idiotypes of circulating autoantibodies
T cells
Regulation of CD4-T-cell cytokine production
Neutralization of T-cell superantigens
Cells proliferation
Lymphocyte proliferation inhibition
Control of cell death

Modified from Kazatchkine and Kaven

Various autoimmune and inflammatory diseases benefiting from immune globulin and the immunomodulatory effects of immune globulin on B and T cells are illustrated in Walport's article (Tables 23.7 and 23.8).

Autoimmune Urticaria

Patients with SLE also can present with chronic urticaria, and a subpopulation of patients with chronic urticaria also possess IgG antibody directed to the α-subunit of high-affinity type I IgE receptor. IgG can activate basophils, which is dependent on or augmented by complement. SLE, a prototype of immune complex disease, and other autoimmune diseases are caused by a breakdown of tolerance and other factors. Factors that influence the pathogenesis of T-cell-mediated autoimmune diseases are due to genetic susceptibility, activation of autoreactive T cells or infiltration of target organs by T cells, and damage to target organs by T-cell effector molecules or other cell populations. Breakdown to tolerance can occur in SLE, autoimmune diabetes, and multiple sclerosis.

Evidenced-Based Medicine

Complement Therapeutics in Clinical Practice

Treatment of patients with congenital complement deficiencies focuses on the underlying problems of infection and autoimmunity. Recombinant complement components for a completely deficient patient are possible, and blood transfusion to replace missing components has been tried with some success in two SLE patients with C2 deficiency and several patients with factor H deficiency. Renal transplantation might be a viable therapy specifically for atypical HUS patients with an MCP mutation.

The success of animal studies led to clinical trials, with sCR1 being used for treatment of acute respiratory distress syndrome, myocardial infarction, and lung transplantation and post-cardiopulmonary bypass syndrome and anti-C5 mAb in multicentered trials for myocardial infarction, post-cardiopulmonary bypass syndrome, rheumatoid arthritis, membranous nephropathy, and lupus nephritis.

The complement system as part of innate immunity provides an important effector system for host defense, clearance of immune complexes, and regulation or acquired immune reactions. The future of complement therapy may include targeted gene therapy or replacement with recombinant proteins for patients with complement deficiencies.

Therapeutic complement inhibitor approaches have been considered for treatment of bulbous pemphigus, rejection of transplanted tissues, Alzheimer's disease since plaques contain high levels of classical and alternative pathway components as well as MAC components and immune-based fetal loss. As listed in an article by Tichaczek-Goska D on deficiencies and excessive human complement system activation in disorders of multifarious etiology in Adv Clin Exp Med. 2012 Jan–Feb;21(1):105–14 who described, selected diseases and syndromes are associated with excessive complement activation HIV and a great many other serious medical conditions. Other disorders that interface importantly with the complement system besides SLE include rheumatoid arthritis and related arthritides including cryoglobulinemia.

Complement also can be an important factor in tissue necrosis after ischemia. In addition, myocardial infarction and stroke are associated with complement activation in the area of tissue infarction. Complement participates in internal homeostasis by removing damaged, neoplastic, or infected cells. Thus, complement science is no longer thought to be just protein pathways involved in esoteric diseases but can be related to both autoimmune and cerebrovascular and myocardial disease. Deficiencies of the C3 and other complement components contribute to the emergence of recurrent bacterial, viral, and fungal infections and autoimmune diseases such as rheumatoid arthritis. The excessive activation of complement proteins is often discovered to be the reason for many diseases that include Alzheimer's syndrome, schizophrenia, atypical hemolytic uremic syndrome, angioedema, macular degeneration, and Crohn's disease that was also described by Tichaczek-Goska D etiology in *Adv Clin Exp Med*. 2012 Jan–Feb;21(1):105–14.

Bibliography

1. Bellanti J, Chapter 4, Complement Author: Melvin Berger, I Care Press, 2012;101–129.
2. Walport MJ. Complement, first and second of two parts. N Engl J Med. 2001;344:1140–4; 1058–1066.
3. Frieri M. Complement mediated diseases. Allergy Asthma Proc. 2002;23:319–24.
4. Frank MM. Complement disorders and hereditary angioedema. J Allergy Clin Immunol. 2010;125(2, Suppl 2):S262–71.
5. Frieri M. Asthma concepts in the new millennium-update in asthma pathophysiology. Allergy Asthma Proc. 2005;26:83–8.
6. Greenberger PA, Lieberman PJ. Idiopathic anaphylaxis. J Allergy Clin Immunol Pract. 2014;2(3):243–50.
7. Frieri M. Identification of masqueraders of autoimmune disease in the office. Allergy Asthma Proc. 2003;24(6):421–9.
8. Wen L, Atkinson JP, Giclas PC. Clinical and laboratory evaluation of complement deficiency. J Allergy Clin Immunol. 2004;113:585–93.
9. Kikuchi Y, Kaplan AP. Mechanisms of autoimmune activating basophils in chronic urticaria. J Allergy Clin Immunol. 2001;107:1056–62.
10. Kannradt T, Mitchison NA. Tolerance and autoimmunity. N Engl J Med. 2001;344:655–64.
11. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. N Engl J Med. 2001;345:747–55.
12. Khan D. Hereditary angioedema: historical aspects, classification, pathophysiology, clinical presentation, and laboratory diagnosis. Allergy Asthma Proc. 2011;32(1):1–10.
13. Tichaczek-Goska D. Deficiencies and excessive human complement system activation in disorders of multifarious etiology. Adv Clin Exp Med. 2012;21(1):105–14.
14. Berger M. Complement. In: Bellanti JA, editor. Immunology IV. Clinical applications in health and disease. Bethesda: I Care Press; 2012. p. 101–29.