Neurobiology of Aging 52 (2017) 12–22

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Review

A review of human diseases caused or exacerbated by aberrant complement activation

Patrick L. McGeer*, Moonhee Lee, Edith G. McGeer

Kinsmen Laboratory of Neurological Research, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada

ARTICLE INFO

Article history:
Received 15 July 2016
Received in revised form 15 November 2016
Accepted 18 December 2016
Available online 27 December 2016

Keywords:
Complement
Membrane attack complex
Complement receptors
Complement-mediated diseases

ABSTRACT

Complement is the backbone of our innate immune system. It is of ancient evolutionary origin, being traced back to horseshoe crabs 350 million years ago. It consists today of more than 25 proteins which must work together like clockwork to distinguish friend from foe. Self-attack by the complement system can occur whenever it fails to do so. This failure has been reported to occur in an estimated 22 human diseases. A significant number of these are chronic degenerative neurological disorders. In some, there is overwhelming evidence that complement self-attack causes the disease. In many others, it is considered only to contribute to the overall pathology. Finding effective therapeutic agents should be a high priority for medical research. To date, the monoclonal antibody eculizumab is the only approved agent. Molecules under development include other monoclonal antibodies directed at C5, C3, and properdin, various aptamers to C3, and small molecules that are orally available.

1. Introduction

Complement is the backbone of our innate immune system. It operates in every tissue of the body. Despite its importance and elegance, it is the least understood of our self-protective mechanisms. It is of ancient evolutionary origin, being traced back as far as 350 million years ago in horseshoe crabs. It has since evolved so that in higher vertebrates today it consists of more than 25 proteins. The components must work together like clockwork to distinguish friend from foe. The system must be immediately available to deal with a foreign threat anywhere in the body. It must first recognize targets and opsonize them for phagocytosis by the body's professional phagocytes. When required, it must attack and destroy bacteria and viruses by assembling the membrane attack complex (MAC) to create holes in their protective membranes.

Given its complexity, it should not be surprising that abundant faults in the system should occur. Under such circumstances, the complement system may mistakenly attack host tissue in a process described as bystander lysis. Such attack is known to contribute to the pathology of a spectrum of human diseases. The complement system is therefore a 2-edged sword. Under normal circumstances, it is the body's most important protective mechanism. Under abnormal circumstances, it can be the cause, or the main contributor, to a large number of acute and chronic disorders. Finding agents that can prevent or compensate for abnormal complement activity should be a high priority for medical research.

The very existence of the complement system was discovered by chance. The initial discovery is attributed to Jules Bordet, a young Belgian scientist working at the Pasteur Institute in Paris. In 1896, he demonstrated that for serum to retain immunity against invading organisms, 2 components were required. They were a heat-stable component specific to the organism plus a heat-unstable and nonspecific component, which he named "annexin". Paul Ehrlich renamed the heat-labile material "complement" in the late 1890s. He chose the inappropriate name "complement" for the heat-labile component because, in the limited view at the time, it complemented the function of antibodies.

The name complement has persisted. It is unfortunate because it implies that complement is nothing more than an adjuvant to the adaptive immune system. That is far from the truth. Complement is the first source of self-defense. In evolution, it long preceded the adaptive immune system. The adaptive immune system is a development restricted to higher vertebrates. It clones antibodies against epitopes of foreign origin, but the action takes days to accomplish and cannot provide the instant protection provided by the complement system.

After Bordet, little was learned about the complement system until Hans Muller- Eberhard and his colleagues began pursuing its existence in the 1950's. They soon identified that C3 in serum was pivotal to antibody-mediated attack on pathogens. This mechanism

* Corresponding author at: Kinsmen Laboratory of Neurological Research, Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, British Columbia V6T 1Z3, Canada. Tel.: +1-604-822-7377; fax: +1-604-822-7086.
E-mail address: mcgeerpl@mail.ubc.ca (P.L. McGeer).

0197-4580/$ – see front matter © 2016 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.neurobiolaging.2016.12.017

was defined as the classical pathway since it was the first one to be discovered. During this same period, Louis Pillemer and colleagues discovered that another pathway existed which did not require antibody activation. It became known as the alternative pathway. It depended on properdin for activation (Hinz et al., 1956).

Both pathways involve a cascade of reactions. In pursuing these cascades, Muller-Eberhard soon determined that two entirely different complement functions were sequentially linked. The initial function involved opsonization to facilitate phagocytosis. The terminal function involved formation of the cytolytic MAC. He and his colleagues identified most of the proteins driving these cascades. They also identified many of the inhibiting proteins which control their level of activity. Nevertheless, their work was limited because it was confined to serum without realization that tissues are involved.

The next step came with the discovery that the senile plaques of Alzheimer disease (AD) were opsonized by complement (Eikelenboom and Stam, 1982, 1984; Eikelenboom et al., 1989; McGeer et al., 1989a), and that dystrophic neurites were being attacked by the MAC (McGeer et al., 1989b). At first it raised questions as to whether AD could be an autoimmune disease being driven by antibodies to senile plaques. However, no immunoglobulins could be identified in AD brain tissue. Moreover, the genes for C1q, C3, and C4 were expressed in brain and were upregulated more than 3-fold in AD (Walker and McGeer, 1992). Rogers et al. (1992) then demonstrated that C1q bound strongly to fibrillar amyloid beta protein (Abeta), indicating that the classical pathway did not require immunoglobulins for activation, but could be activated by any tissue component that C1q could recognize.

The discovery that complement was tissue based, and that it could be locally activated in minutes, opened the door for an understanding of its true physiological role. That role is to be the first line of defense, immediately recognizing invaders to any part of the body. It operates independently of the adaptive immune system which takes days to clone antibodies against pathogenic epitopes.

Fig. 1 is an outline of the complement system as it is understood today. It illustrates the classical and alternative activation pathways, also showing several of the inhibiting steps. In addition, it identifies the targets chosen for some of the therapeutic agents under development.

Much is yet to be learned about how complement operates at the local level. It still needs to be determined which cells are capable of producing the activating components and which cells produce the inhibiting factors. Any given cell may do both. It also needs to be understood how these factors interact with cells that promote or inhibit the ensuing inflammation. And it needs to be explored exactly how these factors become involved in the myriad of diseases where aberrant complement activation causes or contributes to the disease pathology.

2. Complement activators

2.1. Proteins associated with the classical pathway

2.1.1. C1q

C1q is the key protein which initiates the classical pathway. It is a complex molecule consisting of 6 heads, each with a triple helical structure designed for binding to specific targets. It has a molecular weight of approximately 400 kDa. It is best known for attaching to the Fc chain of IgG and IgM antibodies that have become activated by binding to their designated antigen. But the more important function is binding directly to a wide variety of other proteins. Such proteins occur on some bacteria and viruses. Direct binding provides an immediate source of self defense. However, a problem occurs if it binds to self proteins such as Abeta. This may help to phagocytose the protein, but if the process continues so that the MAC forms, lysis of host cells may occur. Thus, C1q is the factor which causes the complement system to be a 2-edged sword. Under normal circumstances it is helpful but under abnormal circumstances it can contribute to the pathology in many diseases. Therapy directed at preventing complement self-attack will most likely be effective in those conditions where MAC formation develops but opsonization remains unaffected. In conditions where there is a severe antigen-antibody reaction to self proteins, complement inhibitors may be overwhelmed by the process and therefore be ineffective.

C1q in its inactive state is complexed with two additional proteins named C1r and C1s. On activation, this tri-molecular complex dissociates. C1r, a beta globulin with a molecular weight of approximately 190 kDa, has the sole function of cleaving the thioester bond of C1s. C1s, an alpha globulin of only 87 kDa, then becomes an active serine protease. The classical complement cascade is initiated at this stage.

The C1s serine protease carries out the next step of cleaving C4 to produce C4a (a weak anaphylatoxin) and C4b. C4b can then bind covalently to form an amide or hydroxyl bond with a target close to the site of C1q binding. Bound C4b can then bind to C2 which is then cleaved to create the tissue bound protease C4b2a. This now has the capacity to bind and cleave C3, initiating the next stage of the cascade. The nomenclature is somewhat confusing since the numbering of the protein does not follow the cascade sequence. The problem is that C2 and C3 had been clearly identified and named before the discovery of C4.

C3 is the pivotal protein of both the classical and alternative pathways. It occurs in serum at the highest concentration of all the complement components. Cleavage of C3 completes the opsonization process of the classical, alternative, and lectin pathways. Presumably, it has a similarly high concentration in tissue as in serum although appropriate measurements have never been made. Bound C3 is cleaved into C3a, an anaphylatoxin, leaving behind the tissue-bound protease C4b2aC3b, which is named C5 convertase.

Entry into the terminal complex assembly may now take place. C5 convertase cleaves C5 into C5a and C5b. Both fragments go into solution and become independent of the convertase. C5a, the smaller fragment, is the most powerful of the anaphylatoxins. C5b is a hydrophobic molecule which seeks the lipid outer surface of living cells nearby. It may attach to such cells whether they are foreign or belong to the host. Attachment exposes a sequence on C5b which can bind C6. The complex C5b6 then exposes a further sequence which can bind C7. C5b67 in turn exposes yet another sequence which can bind C8. C5b678 sets the stage for the final step which is the binding of C9. C9 differs from its precursors in possessing a hydrophilic sequence in addition to the hydrophobic sequence needed for binding. Additional molecules of C9 are added to form C5b678C9(n). The hydrophilic sequences then form a pore which penetrates the inner lipid membrane. This causes lysis of cells. When the cells belong to the host, the phenomenon is termed bystander lysis.

2.2. Proteins associated with the alternative pathway

The alternative pathway was first identified by a study of properdin carried out by Louis Pillemer and colleagues in the 1950s. They found that an X-linked deficiency in properdin led to immunological deficiencies including erythrocyte vulnerability in paroxysmal nocturnal hemoglobinemia. Accordingly, it was originally named the properdin pathway. But the dominant protein in the pathway was found to be C3 and not properdin so the designation was dropped. When C3 dissociates into C3a and C3b, C3a become an anaphylatoxin, whereas the thioester of C3b can form covalent amide or hydroxyl bonds with cell surface proteins. That

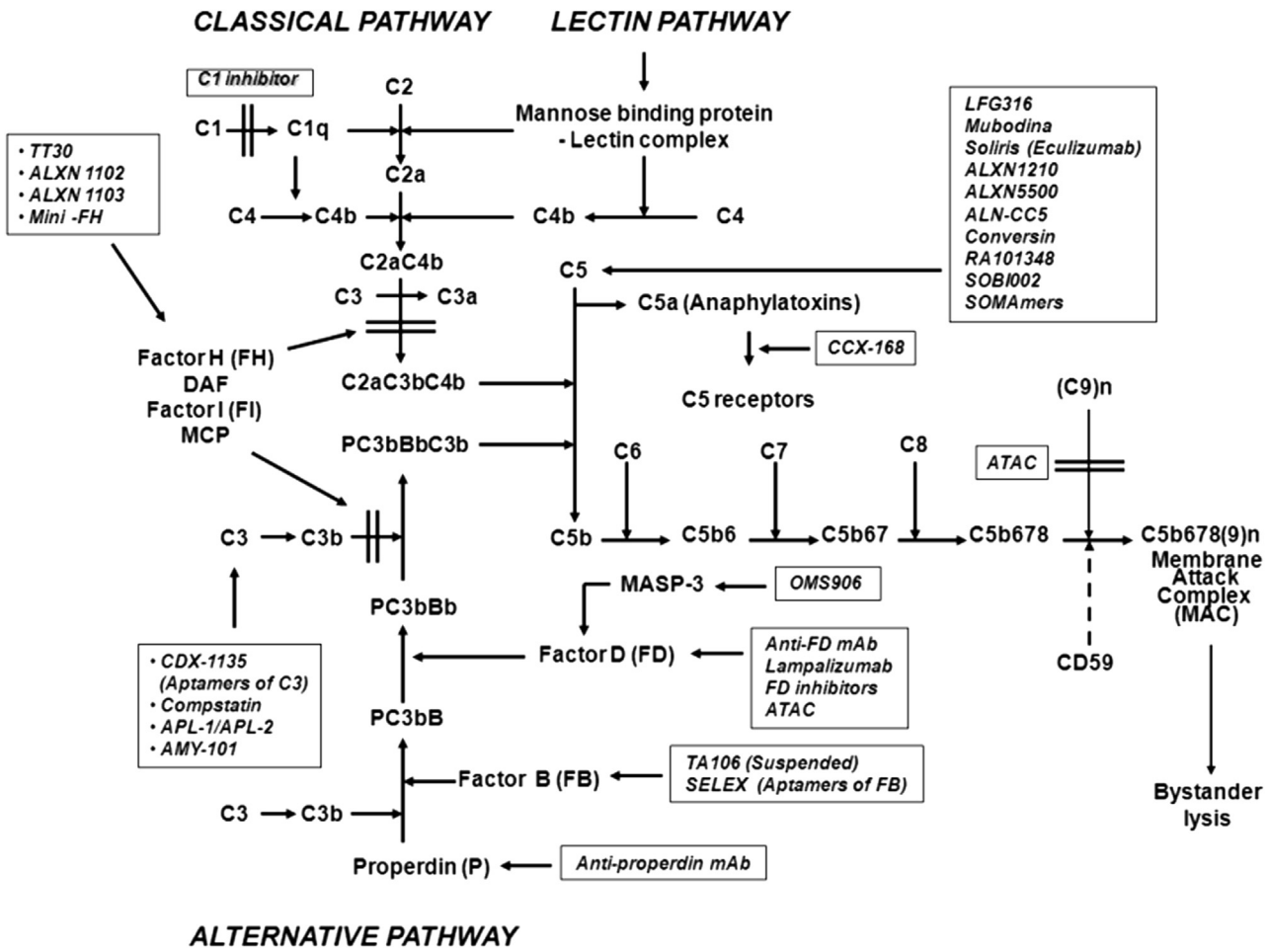

Fig. 1. Complement activating pathways. The activation steps of the classical and alternative pathways are shown. Double bars indicate the steps inhibited by some endogenous regulators. The boxed areas identify potential therapeutic agents under development and the steps that are targeted (Section 12.3).

process is facilitated by attachment to properdin. The complex PC3b then attaches to factor B to form PC3bB. The factor B moiety can then be cleaved by the serum protease factor D to produce the highly active complex PC3bBb. This is known as C3 convertase. It can now bind additional C3b molecules to form PC3bBb3b. The latter can cleave C5. Once C5b is formed, the alternative pathway proceeds in the same fashion as the classical pathway to form the MAC. Although it is generally believed that all of this is confined to serum and depends on the continuous hydrolysis of small amounts of C3, this is far from certain. The alternative pathway might be active in any tissue of the body. Insights into this possibility may be gained by knowledge of tissue-based disease entities that are induced by failure of inhibitors that are specific to the alternative pathway.

2.2.1. Proteins associated with the lectin pathway

The lectin pathway is a third mechanism for activating complement. It is actually a minor variation of the classical pathway. It is initiated by mannose binding protein attaching to carbohydrate moieties found on the surfaces of some bacteria. It proceeds identically to the classical pathway from the C2 stage onward.

2.2.2. Anaphylatoxins

The anaphylatoxins are the small fragments that form following enzymatic cleavage of C3, C4, and C5. C5a is the most active anaphylatoxin followed by C3a. C4a is very weak. The anaphylatoxins are highly soluble and diffuse away from the site of complement activation. Their primary purpose is to stimulate inflammation. They do so by attaching to the surface of phagocytes and other cells. These phagocytes then release inflammatory cytokines and other toxins to produce the inflammatory effect. Blocking of C5a has been a successful therapeutic strategy for certain complement-mediated diseases.

3. Complement receptors

3.1. Complement receptor 1 (CR1, CD35)

This protein is expressed by phagocytes. Included are resident cells of the monocyte phagocytic system, circulating neutrophils and dendritic cells. It is regarded as the main receptor to stimulate clearance of unwanted debris. It is designed to recognize materials that have been marked for phagocytosis.

3.2. Complement receptor 2 (CR2, CD21)

This protein is also known as the C3d receptor. It is particularly concentrated on circulating B-cells.

3.3. Complement receptor 3 (CR3, CD11b)

Complement receptor 3 (CR3, CD11b) is believed to be exclusively associated with leukocytes, particularly T-cells, where it is presumed to have a regulatory function.

3.4. Complement receptor 4

Complement receptor 4 (CR4, CD11C) has a distribution similar to CR3 with high homology in its structure. How it differs in function from CR3 is yet to be determined.

3.5. Complement receptor C3a

Complement receptor C3a recognizes the anaphylatoxins C3a and C4a.

3.6. Complement receptor C5a

Complement receptor C5a (C5aR, CD88) recognizes the anaphylatoxin C5a which is the most powerful of the group. It is distributed on neutrophils, monocytes, and other leukocytes, as well as numerous nonmyeloid cells. It is an inflammatory stimulant appropriate to its powerful anaphylatoxic function.

3.7. Lymphocyte function–associated protein

Lymphocyte function–associated protein is a combination of CD 11a and the beta 2 integrin CD 18. It is expressed on all leukocytes and promotes their binding to phagocytic targets.

3.8. Complement inhibitor proteins

Complement inhibitors act at successive stages of the classical and alternative pathways to keep the level of activity within physiological limits.

3.9. C1 inhibitor

C1 inhibitor is designed to arrest initiation of the classical pathway. It is a protease blocker of the serpin class. It irreversibly binds to C1r and C1s, thus inhibiting their activity. It circulates in serum, presumably due to production by the liver. The serum levels are approximately 2.5 micrograms/mL. It is unknown what other cells in the body can produce C1 inhibitor.

3.10. C4 binding protein

C4 binding protein inhibits C4 activation as well as C3b activity. It acts as a cofactor for factor I, another inhibitor of complement activation. It exists in serum at a level of 200 micrograms/mL.

3.11. Factor I

Factor I is a serine protease which acts in concert with C4 binding protein to prevent unregulated activation of C3. It is present in serum at a concentration of 34 micrograms/mL. Membrane cofactor protein, also known as CD46, has cofactor activity by acting as a receptor for inactivation (through cleavage) of complement components C3b and C4b by serum factor I.

3.12. Factor H

Factor H is a circulating protein of approximately 150 kDa. It is considered to be selective for the alternative pathway. Its principle function is to control the levels of alternative pathway regulation by inactivating C3b which has become bound and activated on target cells. It circulates at the relatively high level of 500 micrograms/mL which may indicate that it is a highly important self-protective molecule.

3.13. Decay accelerating factor

Decay accelerating factor (CD55, DAF) is a membrane-bound protein which protects host cells by inhibiting over activation of C4bC2a of the classical pathway and C3 convertase of the alternative pathway. It attaches to host cells indirectly, requiring initial binding to a cell surface–bound glycophosphatidyl inositol (GPI) anchor. It becomes inactive in X-linked diseases involving mutations in the gene responsible for producing N-acetylglucosaminyl phosphatidylinositol (GlcNAc-PI), the first intermediate in the biosynthetic pathway of the GPI anchor. The physiological deficiency occurs even though plentiful CD 55 is being produced.

3.14. Protectin

Protectin (CD59, or membrane inhibitor of reactive lysis, MIRL), like DAF, is bound to host cell surfaces through the GPI anchor. It inhibits C9 attachment to C5b678. As with DAF, a physiological deficiency occurs even though plentiful protectin is being produced.

4. Membrane cofactor protein

Membrane cofactor protein (CD 46) acts as a cofactor for Factor I.

4.1. Clusterin

Clusterin (S-protein, apolipoprotein J) is a circulating protein with multiple properties. It is believed to inhibit complement activation although the manner has not been defined.

4.2. Diseases associated with aberrant complement activation

Aberrant complement activation has been reported to occur in a spectrum of human diseases. A summary of these diseases is shown in Table 1 along with the key evidence and supportive documentation. In some diseases, there is overwhelming evidence that mutations are the cause. In other diseases, the evidence suggests that complement activation contributes to the pathology. At this stage, most of the evidence is preliminary and needs to be further explored (for reviews see Ehrnthaller et al. (2011) and Holers (2014)).

4.3. Age-related macular degeneration

An estimated 10 million people in the United States and 50 million people worldwide suffer from age-related macular degeneration (AMD). It is characterized by degeneration of retinal pigment epithelial (RBE) cells. MAC attack on RBE cells has been demonstrated by immunohistochemistry (Anderson et al., 2010). RBE cells are believed to afford protection to photoreceptor cells. Since photoreceptor cells are concentrated in the macula, AMD is the result. AMD occurs in a dry form and a more serious wet form. In the dry form, drusen deposits are typically found throughout the retina. Since this occurs in many people with normal vision, drusen by themselves are not considered to be a cause. The wet form is a complication of the dry form, where new blood vessels, originating in the choroid, penetrate the retina. This neovascularization has been reported to be associated with enhanced production of vascular endothelial growth factor. However, this is uncertain and the true stimulus for neovascular production is still unknown. Involvement of the complement system has been indicated by genetic studies showing that the risk of contracting AMD is increased by polymorphisms in genes encoding for Factor H (Haines et al., 2005); Factor B (Gold et al., 2006); and C3 (Yates et al., 2007).

Table 1
Complement-mediated diseases and key references

Disease	Type of evidence	Key references
Age-related macular degeneration	Genetic	Anderson et al., 2010
Atypical hemolytic uremia syndrome	Genetic	Kavanagh et al., 2007
Alzheimer disease	Epidemiological	McGeer et al., 2013
Amyotrophic lateral sclerosis	Immunohistochem	Kawamata et al., 1992
Atherosclerosis	Immunohistochem	Vlaicu et al., 1985
Diabetes	Serum antibodies	Radillo et al., 1996
Epilepsy	Upregulated C3mRNA	Bellander et al., 2001
Inflammatory bowel disease	Immunohistochem	Halstensen et al., 1991
Malaria infection	RBC IgG and C3bBb	Silver et al., 2010
Malignancies	Complement upregulation	Rutkowski et al., 2010
Multiple sclerosis	Immunohistochem	Schwab and McGeer, 2002
Neuromyelitis optica	Autoantibodies	Wingerchuk, 2007
Parkinson disease	Immunohistochem	Yamada et al., 1992
Paroxysmal nocturnal hemoglobinemia	Genetic	Luzzatto, 2006
Rheumatoid arthritis	Immunochem	Morgan et al., 1988
Schizophrenia	Genetic	Sekar et al., 2016
Skin diseases	Autoantibodies	Multiple authors
Traumatic brain injury	CSF complement	Stahel et al., 2001
Uveitis	Genetic	Thompson et al., 2013

These 3 proteins are all crucial to self-protection from MAC attack initiated by the alternative complement pathway. Since AMD is a tissue-based disorder, it may be the alternative pathway that can be operative in tissue as it is in serum. There is currently no approved treatment that will prevent or arrest progression of this disease.

4.4. Atypical hemolytic uremia syndrome (aHUS)

aHUS is a condition associated with mutations in one or more of a bewildering array of complement self-protective proteins. Approximately 30% are associated with various mutations in factor H; 10% with various mutations in membrane cofactor protein (MCP); and 2%–5% with various mutations in factor I (Kavanagh and Goodship, 2007). More recently, it has been discovered that recessive mutations in the gene encoding diacylglycerol kinase result in the onset under 1 year of age (LeMaire et al., 2013). In Japan, mutations in C3 and thrombomodulin have also been identified with aHUS (Fan et al., 2013). Mutations are considered to be predisposing rather than causative since penetrance can vary (Bresin et al., 2013; Kavanagh and Goodship, 2007).

The consequence of these mutations is a widespread occurrence of bystander lysis. Glomeruli of the kidney are particularly vulnerable. Erythrocytes and endothelial cells are also damaged. The syndrome is characterized by a low platelet count, kidney failure, and small vessel thrombosis. The latter is the major cause of death. The most serious cases die in infancy. Less serious cases may result in teenage kidney failure. Such cases can be temporarily treated with kidney dialysis but kidney transplants are eventually required to avoid death. Onset may occur later in life due to the delayed appearance of a mutation or due to its relative mildness. Such cases are more amenable to therapeutic intervention.

4.5. Alzheimer disease

Immunohistochemical investigation of complement proteins in postmortem brains of Alzheimer cases represented a breakthrough in our understanding of the role of the complement system in innate immunity. The opsonizing components of complement were found to be associated with extracellular Abeta deposits (Eikelenboom and Stam, 1982, 1984; Eikelenboom et al., 1989), whereas the terminal components were found to be associated with dystrophic neurites (McGeer et al., 1989b). Rogers et al. (1992) discovered why the complement system is so important in AD by identifying that C1q binds to Abeta and its N-terminal fragments. Thus, Abeta deposits directly activate the complement system, initiating all the inflammatory consequences which occur in AD (Yasojima et al., 1999). This finding was rediscovered some 27 years later as a breakthrough (Hong et al., 2016), indicating how easily key advances can be overlooked and lost. Terai et al. (1997) had first found that neurons in AD expressed proteins of the classical pathway.

Complement receptor 1 is the protein on phagocytes mainly responsible for recognizing the activated complement fragments. Certain isoforms of this protein greatly increase the risk of developing AD (Luo et al., 2014; Mahmoudi et al., 2015; Schmidt et al., 2014).

Since self-damage from the MAC is prominent in AD, it is logical to suppose that those taking anti-inflammatory agents should be relatively spared from the disease. An initial epidemiological study was carried out in which the prevalence of AD among rheumatoid arthritics over the age of 65 was compared with the prevalence of AD reported to occur in age-matched general populations. An apparent 6-fold sparing was noted (McGeer et al., 1990). This finding has now been verified in at least 17 epidemiological studies (reviewed by McGeer et al., 1996). There is one important caveat. NSAIDs need to be started well before AD is diagnosed. The earlier the commencement, the greater the sparing.

The necessity for prediagnostic commencement of NSAID consumption has since been revealed by biomarker studies. They establish that disease onset occurs a decade or more before clinical signs develop. This can be detected by a reduction of Abeta42 in the CSF at least 10, and possibly 20 years before clinical diagnosis. This is followed by an increase in tau species in the CSF. Progression can be measured by PET and MRI scanning, all of which become abnormal years before AD can be diagnosed clinically (Bateman et al., 2012; Villemagne et al., 2013).

The positive aspect is that the data reveal that a window of opportunity exists for effective prevention of AD. If anti-inflammatory therapy is started at the time when AD deposition first commences, then the buildup of Abeta can be aborted with consequent inhibition of cognitive decline.

5. Amyotrophic lateral sclerosis (ALS)

ALS is a universally fatal disorder. The cause is unknown. There is no approved treatment that will lengthen to any useful extent the time between diagnosis and death. There is strong evidence that complement is activated in this disorder and that neuronal processes are being attacked by the terminal complement components. Kawamata et al. (1992) found that complement receptors CR3 and CR4 were abundantly present in affected areas of the spinal cord, motor nuclei of the brain stem, and the primary motor cortex. Clusters of complement-activated oligodendroglia, as well as degenerating neurites positive for C3d and C4d, were detected in ALS-affected areas.

Mantovani et al. (2014) found the terminal complement activation products C5a and C5b-9 to be significantly elevated in ALS patient blood. Sta et al. (2011) found high levels of the mRNA and protein for C1q and C4, as well as the downstream components C3 and C5b-9, in the spinal cord and motor cortex of all ALS samples analyzed. More importantly, Bahia et al. (2016) found that C1q and the MAC were deposited on motor end plates of ALS intercostal

muscles, indicating that complement activation may precede endplate denervation.

In summary, these data indicate that a complement-driven immune reaction develops in ALS which may be the main factor in the fatal progression of neuronal loss.

5.1. Atherosclerosis

Atherosclerosis is the leading cause of death in all developed countries. Coronary artery disease and stroke account for 75%–80% of these deaths. For people between the ages of 60 and 80, 71% have significant cardiovascular disease, whereas the incidence rises to 85% for those over 80.

It has long been known that there is full activation of the complement cascade in atherosclerotic plaques (Niculescu et al., 1987; Torzewski et al., 1998; Vlaicu et al., 1985). Vlaicu et al. (1985) reported the C5b-9 complex to be present in aortic, femoral, and iliac plaques but absent in atherosclerosis free intima. Similarly, Niculescu et al. (1987) reported immunohistochemical detection of C5b-9 neoantigens, C3c, and C3d in early to advanced stages of atherosclerosis. Torzewski et al. (1998) found by immunohistochemical staining that the intima of early atherosclerotic plaques had colocalization of the terminal complement complex with C-reactive protein as the possible complement activator. Horvath et al. (2013) examined the extent of complement activation in patients with established coronary heart disease and reported that elevated C1rC1sC1inh levels were elevated in the plasma of cases but not in normal controls. Speidl et al. (2005) found that C5a predicted future cardiovascular events in patients with advanced atherosclerosis. Oksjoki et al. (2007) found a greater than 5-fold increase in receptors for C3a and C5a in human coronary plaques compared with normal arterial tissue. Yasojima et al. (2001) reported that the mRNAs for C1r, C1s, C7, and C8 were elevated in plaque tissue compared with adjacent normal arterial tissue.

These data provide a strong case for aberrant complement activation contributing to the pathogenesis of atherosclerosis.

5.2. Diabetes

Sundsmo et al. (1985) reported that serum levels of C3a, C4a, and C5a were elevated in newly diagnosed type 1 diabetes cases. Radillo et al. (1996) reported that sera from type 1 diabetes patients contained complement fixing antibodies. Binding of this serum was found to occur using purified islet cells, with cytotoxicity occurring when complement was activated. Similarly, Rowe et al. (2013) identified C-fixing islet cell antibodies in type 1 diabetic cases. These data indicate the possibility that aberrant complement activation plays a role in the development of type 1 diabetes.

5.3. Epilepsy

Bellander et al. (2001) reported that patients having frontal or temporal lobe resection due to intractable intracranial hypertension after traumatic head injury, had an increase in complement components C1q, C3b, C3d, and C5b-9 in the immediate vicinity of the lesion. They also found, by in situ hybridization, an upregulation of C3-mRNA, indicative of local synthesis. They concluded that complement activation contributes to the development of secondary brain damage.

Aronica et al. (2007) investigated human temporal lobe epilepsy and found astroglial, microglial, and neuronal expression of C1q, C3c, and C3d in regions of neuronal loss. They found that C5b-9 was predominantly detected in microglial cells. They concluded that persistent complement activation could contribute to an inflammatory response which would destabilize neuronal networks. These data indicate a possible involvement of aberrant complement activation in chronic epilepsy cases.

6. Irritable bowel syndrome: Crohn's disease, ulcerative colitis

Potter et al. (1979) reported upregulation of C1q metabolism in patients with ulcerative colitis and Crohn's disease. They concluded that the activation of the classical pathway plays a role in the pathogenesis of these disease entities. Ahrenstedt et al. (1990) found that enhanced local production of complement components in the small intestines of patients with Crohn's disease. Halstensen and Brandtzaeg (1991) identified neoepitopes of C3b on ethanol-fixed mucosal specimens of these same disease entities. Zimmerman-Nielsen et al. (2005) reported complement activation to be upregulated in the plasma during these diseases, and it was downregulated by prednisolone treatment. Pagoldh et al. (2014) examined fecal matter and found a correlation between complement C3 levels and bowel movements. They concluded that their results were predictive of a need for colectomy. In summary, these results provide evidence that complement activation plays a significant role in exacerbating the pathology of ulcerative colitis and Crohn's disease.

6.1. Malaria infection

Malaria is a prevalent disease in Africa and south East Asia, resulting in an estimated 650,000 deaths per year. The infective agent, plasmodium falciparum, is transmitted by mosquitoes. It produces enhanced complement activation in humans and susceptible animals. IgG and C3bBb complexes have been identified on erythrocytes of infected humans, indicating damage caused by the activation of both the classical and alternative pathways (Silver et al., 2010).

Fernandez-Arias et al. (2013) reported that the levels of complement receptor 1 on peripheral monocytes/macrophages and B-cells is significantly decreased in patients infected with malaria, indicating an impaired clearance of immune complexes. Robson et al. (1988) noted that a human malaria parasite expresses a highly conserved sequence found in thrombospondin and properdin.

Patel et al. (2008) found that C5 deficiency, and C5a or C5a receptor blockade protects against cerebral malaria. Biryukov and Stoute (2014) present evidence of the critical role of C5a and the MAC in the pathogenesis of malaria. They conclude that these observations justify the testing of complement inhibitors as adjunctive treatment for severe malaria.

Dasari et al. (2014) report that the digestive vacuole of plasmodium falciparum, which is released into the bloodstream on rupture of each parasitized red blood cell, activates the alternative complement pathway. They analyzed brain tissue by immunohistochemistry from patients who had died from malaria. They identified C3d and the assembled C5b-9 complex in all the sections and conclude that this activation may promote the development of anemia in patients with severe malaria.

6.2. Malignancies

Successful methods for treating most forms of cancer are desperately needed. The complement system is one possible target for therapy. It has been wrongly assumed that the body's immune system will recognize tumors as foreign cells and make use of the complement system to try and eliminate them. Some leading investigators have explored the counterintuitive concept that malignant cells use the complement system to gain an advantage over

normal cells. According to this concept, malignant cells first develop enhanced protection against complement attack. They then secrete factors that enhance their growth, stimulate their blood supply, and melt the surrounding matrix so they can escape into the circulation and establish mitotic sites. Under these circumstances complement inhibitors could act as oncogenic inhibitors. Reviews on the subject have been compiled by Rutkowski et al. (2010) and Pio et al. (2013).

The complement system has been reported to be activated in malignancies such as B cell lymphomas (McConnell et al., 1978), breast cancer (Niculescu et al., 1992), and human neuroblastoma cell lines (Gasque et al., 1996). However, there is no direct evidence to support the contention that suppressing complement activation can eliminate nascent tumors.

Nitta et al. (2013) reported enhancement of cancer cell motility and invasiveness by anaphylatoxin C5a because of aberrant expression of CD88, the C5a receptor. Similarly, Nitta et al. (2014) reported that cancer cells release C5a via a serine protease to enhance invasiveness. Lu and Hu (2014) reported that C5a stimulated the proliferation of breast cancer cells via Akt-dependent RGC-32 gene activation. In summary, complement inhibitors may be therapeutic candidates in a variety of malignancies.

7. Multiple sclerosis

Multiple sclerosis (MS) is a progressive demyelinating neurodegenerative disorder for which no preventive therapy or method of arrest currently exists. Sanders et al. (1986) were the first to implicate complement activation in the pathogenesis. They detected sC5b-9 in the CSF of MS and acute phase Guillian-Barre syndrome cases. Aeinehband et al. (2015) found C3 levels to be elevated in the CSF, and that this elevation correlated with the degree of disability. In concert with this finding Morgan et al. (1984) found a significant decrease in the levels of C9 in MS cases. Their interpretation was consumption of C9 due to the formation of the MAC. Compston et al. (1989) found granular deposits of C9 and MAC in capillary endothelial cells predominantly within plaques and adjacent white matter in MS cases. Schwab and McGeer (2002) reported C4d immunoreactive oligodendrocytes in MS cases as well as C1q-C9 immunoreactive fibers in large MS lesions, indicating involvement of complement activation. Michailidou et al. (2015) found complement C1q-C3-associated synaptic changes in MS hippocampus. Taken together, these data provide strong evidence of complement activation contributing to the pathogenesis of MS, indicating the prospect of effective therapy being provided by complement inhibitors.

7.1. Neuromyelitis optica

Neuromyelitis optica is a severe disease involving inflammatory attack and demyelination in the spinal cord (myelitis) and the optic nerve (optica). The disease is episodic, with residual effects being characteristic. Severe attacks can be fatal. Weakness of the limbs and loss of bladder control are typical of the spinal cord demyelination. Loss of vision is characteristic of the optic nerve demyelination. The principle reason is believed to be development of auto antibodies against aquaporin-4 by B-cells. For reviews see Wingerchuk (2007) and Argyriou and Makris (2008). The antibodies target astrocytes. Thus it can be described as an astrocytopathic disease (Uzawa et al., 2014).

CSF levels of C5a and sC5b-9 were reported to be elevated in neuromyelitis optica indicating the activation of the MAC in the CNS (Kuroda et al., 2013; Wang et al., 2014a). Serum antibody levels of several complement components have also been reported to be affected, with the suggestion that inhibiting the alternative pathway of complement would be an effective therapeutic strategy (Nytrova et al., 2014; Veszeli et al., 2014). Support for this concept has been indicated by a small open label trial of eculizumab in which no relapses were recorded over a 12-month period (Pittock et al., 2013).

8. Parkinson disease

Parkinson disease is the second most common neurogedenerative disorder after AD. The etiology is unknown. It involves progressive loss of substantia nigra neurons. This tiny area of brain has only about 500,000 neurons. Motor symptoms do not develop until at least two-thirds of these have been destroyed, so there is a broad window of opportunity to intervene with effective therapeutic agents. Yamada et al. (1992) were the first to demonstrate involvement of the complement system by demonstrating immunohistochemically that extra neuronal Lewy bodies and dendritic spheroid bodies were immunopositive for C3d, C4d, C7, and C9. McGeer and McGeer (2004) then showed that there was a marked elevation in the mRNA levels for complement in regions affected by Parkinson disease. Depboylu et al. (2011) indicated a possible involvement of C1q in the clearance of extracellular melanin.

9. Paroxysmal nocturnal hemoglobinemia

Paroxysmal nocturnal hemoglobinemia (PNH) was the first disease demonstrated to be linked to pathological complement activation. As described previously, Pillemer et al originally found that an X-linked deficiency in properdin was associated with the erythrocyte vulnerability in PNH. However, the reason was not properly understood until investigators discovered that PNH patients develop stem cell clones in their marrow that have a deletion of GPI-anchored proteins (GPI-APs; Takeda et al., 1993). Genetic studies have identified the cause to be somatic mutations in the gene phosphatidylinositol glycan class A (Luzzatto, 2006). The gene encodes enzymes catalyzing the first step of GPI-anchor-biosynthesis, in which there is a transfer of N-acetylglucosamine to phosphatidylinositol in hematopoietic stem cells (Luzzatto, 2006). The proteins which fail to become anchored, and are therefore non-functional, include decay accelerating factor (DAF, CD55), an inhibitor alternative pathway C3 convertase, and protectin (CD59), an inhibitor of MAC formation. As the PNH name implies, these episodes occur in paroxysms, usually at night. The consequences are hemoglobinemia, hemoglobinuria, and, much more seriously, thromboembolism. The reason for this latter complication is unclear, but it is the major source of morbidity and mortality. The peripheral blood of PNH patients is a variable mixture of normal and mutated erythrocytes. The higher the proportion of mutated erythrocytes, the greater the chance of a hemolytic episode and a consequent thrombotic event (Moyo et al., 2004).

A breakthrough in treatment came with the development of eculizumab (Soliris). It is a humanized monoclonal antibody which binds to serum C5 (Kelly et al., 2011). Consequently, the MAC cannot form on PNH erythrocytes. It was found to be a successful long-term treatment for the disorder (Hillmen et al., 2006). PNH patient survival was found to be similar to an age- and sex-matched control group who did not suffer from this disease (Kelly et al., 2011). This compared with previous clinical experience where approximately 50% of the patients died as a result of the disease. Nevertheless, the treatment is not totally effective since blockage at the C5 level is unable to compensate for the earlier defect at the C3 convertase level. This defect is caused by a failure of DAF to protect PNH erythrocytes. New strategies have been proposed by Risitano (2013).

10. Rheumatoid arthritis

A plethora of papers have been published on the activation of complement in rheumatoid arthritis. Only the most representative of these are cited in this review. Ruddy et al. (1975) first drew

attention to the phenomenon by reporting depressed synovial fluid levels of properdin and factor B consistent with alternative pathway activation. Perrin et al. (1977) then found an increase in the breakdown products C3d, C4d, and Ba, confirming that the activation did occur. Morgan et al. (1988) recorded an increase in the MAC, indicative of the destructive nature of this activation. Rus et al. (1990) confirmed this finding by showing intense immunoreactivity for C5b-9 in synovial membranes obtained during meniscectomy. Olmez et al. (1991) and Brodeur et al. (1991) also found high levels of C3 activation products and the MAC in synovial fluid of rheumatoid arthritic patients. Nakagawa et al. (1999) showed that C1s was activated in the degenerating articular cartilage of rheumatoid arthritic patients indicating that the classical pathway was also involved. Wouters et al. (2006) measured C1q-C4 levels in the plasma of active rheumatoid arthritis compared with inactive cases. Active cases had considerably higher levels, suggesting these indicators of classical complement activation might be used as biomarkers. Okroj et al. (2007) provided a comprehensive summary of the field.

11. Schizophrenia

Sekar et al. (2016) reported that variations in complement C4 affected the risk of schizophrenia. They found that alleles of C4 generated widely varying levels of *C4A* and *C4B* in brain, with high *C4A* levels being particularly associated with schizophrenia.

12. Skin diseases: allergies, burns, pemphigus, psoriasis

Skin is the first and major method of distinguishing friend from foe. It protects all the deeper layers of the body. It also differs from other organs by continuously replacing itself. It is equipped with a powerful immune system to ward-off the ever present challenges of the external environment. Complement is a vital component of that immune protection. As with other organs, aberrant complement activity can damage host skin. Therefore, agents that can appropriately inhibit aberrant complement activation will have important therapeutic benefits in skin disorders where self-damage occurs.

Pemphigus is one example. In this potentially fatal disorder, there is an autoimmune attack against desmoglien, the adhesive protein which forms the attachment of adjacent epidermal cells. The classical and alternative pathways are both activated, with consequent formation of the membrane attack complex (Kawana et al., 1989).

Psoriasis is a common skin condition which is characterized by an immune response. Rosenberg et al. (1990) first reported complement activation in psoriasis. Takematsu and Tagami (1992) found high levels of sC5b-9 in the stratum corneum of psoriatic skin. This may result from a deficiency in psoriatic arthritic patients of membrane-bound CD59, the protective agent against self-attack by the MAC (Triolo et al., 2003).

Dermatitis herpetiformis is a condition which is characterized by an extremely itchy rash. The lesions are characterized by depositions of IgA accompanied by C3, Factor P, and Factor B, indicating activation of the alternative pathway of complement (Seah et al., 1973). Dahl et al. (1985) found granular deposits of polymerized C9 at sites of IgA deposition in dermal papillae.

Burn wounds are characterized by persistent inflammation. Wan et al. (1998) did a longitudinal study of complement components in burn patients. They found sharp increases in C3d on or before day 7 with fluctuations in C3, C3d, and Factor Ba persisting for about a year. Van de Goot et al. (2009) found C3d and C-reactive protein to be elevated for at least 46 days after injury. These data indicate that damage caused by persistent complement activation in burn patients could be ameliorated by complement inhibitors.

12.1. Traumatic brain injury

Stahel et al. (2001) measured sC5b-9 by ELISA in the ventricular CSF of patients with severe traumatic brain injury for up to 10 days after trauma. They found dramatically increased levels of the MAC. They were up to 1800 fold higher than in control CSF. Bellander et al. (2001) examined brain tissue that had been removed at operation due to intractable intracranial hypertension after traumatic brain injury. The operations were performed 2–82 hours after contusion. They found increased immunoreactivity for C1q, C3b, C3d, and the MAC in the immediate vicinity of the penumbra. They concluded that complement activation with formation of the MAC was a mediator in the development of secondary brain damage. These studies indicate that prompt administration of an effective MAC inhibitor will have an important ameliorative effect in traumatic brain injury. Brennan et al. (2012) have provided a review of the field.

12.2. Uveitis

Vergani et al. (1986) initially found that C3d levels were found in the plasma of 11 of 15 patients with idiopathic uveitis. They concluded that the activation of complement, possibly triggered by uveal deposition of immune complexes, played an important role in the pathogenesis. Thompson et al. (2013) much later found an association of factor H tyrosine 402 histidine genotype in sarcoid-related uveitis. Wang et al. (2014b) then found a protective association between Factor I and uveitis in Chinese, depending on gender and HLA-B27 status.

12.3. Approaches to therapy

Given the number of diseases where aberrant complement activation is involved in the pathology, considerable effort to develop new therapeutic agents should be expected. The success of eculizumab in the treatment of PNH has spurred particular interest in monoclonal antibodies. LFG316 (Novartis) and Mubodina (Adienne) are competitors directed at inhibiting C5. Also under development are a number of aptamers (binding ligands) to C5 such as the SOMAmers of SomeLogic. TT30 (Alexion) is a fusion protein directed at an earlier step in the alternative complement pathway (Fridkis-Harell et al., 2011; Risitano et al., 2012). It recognizes human complement receptor type 2 (CR2/CD21). Compstatin, a cyclic tridecapeptide, is a highly potent and selective C3 inhibitor. It is thought to have considerable therapeutic potential, as do a number of analogs that are in the various stages of development. Also there are a number of aptamers against C3 that are being investigated despite the failure of the Celldex candidate CDX-1135. A disadvantage of C3 as a target is that C3 is by far the most abundant serum complement protein, being several times higher than C5. Properdin and Factors B and D are more promising targets (Formeris et al., 2010). Their relatively low level of expression makes blocking a less onerous challenge. Novelmed is developing a monoclonal antibody against the N-terminus of properdin. SOMAmers is developing SELEX, as an aptamer for Factor B.

Perhaps the most inviting target is Factor D because of its very low serum concentration (Barnum et al., 1984). Roche is evaluating lampalizumab, a monoclonal antibody, which binds to Factor D. Aurin Biotech is developing the aurin tricarboxylic acid complex as an orally available material which strongly binds to Factor D and C9 (Lee et al., 2012, 2013). These compounds are an indicator of the intense activity that is taking place in this very promising field.

13. Conclusions

Complement is the body's first line of defense against foreign invaders. It is an extremely sophisticated system, consisting of more than 25 proteins that must work in concert to be effective. Despite more than a century of investigative activity, there is still much to be learned about the fundamentals of the system. During this period, numerous diseases have been identified in which complement activation is the cause or is contributing to the pathology. There is an urgent medical need to develop therapeutic agents that can be effective in treating these conditions. Eculizumab, a monoclonal antibody against C5, is the only agent that has so far been approved for use. It can be anticipated that this important field will become much more active in the future.

Disclosure statement

The authors are shareholders in Aurin Biotech Inc.

Acknowledgements

The research was supported by the donations from individual British Columbians. The authors are founders and shareholders in Aurin Biotechnology which is developing ATAC as a possible treatment for aberrant complement disorders.

References

Aeinehband, S., Lindblom, R.P., Al Nimer, F., Vijayaraghavan, S., Sandholm, K., Khademi, M., Olsson, T., Nilsson, B., Ekdahl, K.N., Darreh-Shori, T., Piehl, F., 2015. Complement component C3 and butyrylcholinesterase activity are associated with neurodegeneration and clinical disability in multiple sclerosis. PLoS One 10, e0122048.

Ahrenstedt, O., Knutson, L., Nilsson, B., Nilsson-Ekdahl, K., Odlind, B., Hallgren, R., 1990. Enhanced local production of complement components in the small intestines of patients with Crohn's disease. N. Engl. J. Med. 322, 1345–1349.

Anderson, D.H., Radeke, M.J., Gallo, N.B., Chapin, E.A., Johnson, P.T., Curletti, C.R., Hancox, L.S., Hu, J., Ebright, J.N., Malek, G., Hauser, M.A., Rickman, C.B., Bok, D., Hageman, G.S., Johnson, L.V., 2010. The pivotal role of the complement system in aging and age-related macular degeneration: hypothesis revisited. Prog. Ret. Eye Res. 29, 95–112.

Argyriou, A.A., Makris, N., 2008. Neuromyelitis optica: a distinct demyelinating disease of the central nervous system. Acta Neurol. Scand. 118, 209–217.

Aronica, E., Boer, K., van Vliet, E.A., Redeker, S., Baayen, J.C., Spliet, W.G., van Rijen, P.C., Troost, D., da Silva, F.H., Wadman, W.J., Gorter, J.A., 2007. Complement activation in experimental and human temporal lobe epilepsy. Neurobiol. Dis. 26, 497–511.

Bahia El Idrissi, N., Bosch, S., Ramaglia, V., Aronica, E., Baas, F., Troost, D., 2016. Complement activation at the motor end-plates in amyotrophic lateral sclerosis. J. Neuroinflammation 13, 72.

Barnum, S.R., Niemann, M.A., Kearney, J.F., Volanakis, J.E., 1984. Quantitation of complement Factor D in human serum by a solid-phase radioimmunoassay. J. Immunol. Methods 67, 307–309.

Bateman, R.J., Xiong, C., Benziger, T.L.S., Fagan, A.M., Goate, A., Fox, N.C., Marcus, D.S., Cairns, N.J., Xie, X., Blazey, T.M., Holtzman, D.M., Santacruz, A., Buckles, V., Oliver, A., Moulder, K., Aisen, P.S., Ghetti, B., Klunk, W.E., McDade, E., Martins, R.N., Masters, C.L., Mayeux, R., Ringman, J.M., Rossor, M.N., Schofield, P.R., Sperling, R.A., Salloway, S., Morris, J.C. Dominantly Inherited Alzheimer Network, 2012. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. New Engl. J. Med. 367, 793–804.

Bellander, B.M., Singhrao, S.K., Ohlsson, M., Mattsson, P., Svensson, M., 2001. Complement activation in human brain after traumatic brain injury. J. Neurotrauma 18, 1295–1311.

Biryukov, S., Stoute, J.A., 2014. Complement activation in malaria: friend or foe? Trends Mol. Med. 20, 293–301.

Brennan, F.H., Anderson, A.J., Taylor, S.M., Woodruff, T.M., Ruitenberg, M.J., 2012. Complement activation in the injured central nervous system: another dual-edged sword? J. Neuroinflamation 9, 137.

Bresin, E., Rurali, E., Caprioli, J., Sanchez-Corral, P., Fremeaux-Bacchi, V., Rodriguez de Cordoba, S., Pinto, S., Goodship, T.H., Alberti, M., Ribes, D., Valoti, E., Remuzzi, G., Noris, M. European Working Party on Complement Genetics in Renal Diseases, 2013. Combined complement gene mutations in atypical hemolytic uremic syndrome influence clinical genotype. J. Am. Soc. Nephrol. 24, 475–486.

Brodeur, J.P., Ruddy, S., Schwartz, L.B., Moxley, G., 1991. Synovial fluid levels of complement SC5b-9 and fragment Bb are elevated in patients with rheumatoid arthritis. Arthritis Rheum. 34, 1531–1537.

Compston, D.A., Morgan, B.P., Campbell, A.K., Wilkins, P., Cole, G., Thomas, N.D., Jasani, B., 1989. Immunocytochemical localization of the terminal complement complex in multiple sclerosis. Neuropathol. Appl. Neurobiol. 15, 307–316.

Dahl, M.V., Falk, R.J., Carpenter, R., Michael, A.F., 1985. Membrane attack complex of complement in dermatitis herpetiformis. Arch. Dermatol. 121, 70–72.

Dasari, P., Fries, A., Heber, S.D., Salama, A., Blau, I.W., Lingelbach, K., Bhakdi, S.C., Udomsangpetch, R., Torzewski, M., Reiss, K., Bhakdi, S., 2014. Malaria anemia: digestive vacuole of Plasmodium falciparum mediates complement deposition in bystander cells to provoke hemophagocytosis. Med. Microbiol. Immunol. 203, 383–393.

Depboylu, C., Schäfer, M.K., Arias-Carrión, O., Oertel, W.H., Weihe, E., Höglinger, G.U., 2011. Possible involvement of complement factor C1q in the clearance of extracellular neuromelanin from the substantia nigra in Parkinson disease. J. Neuropathol. Exp. Neurol. 70, 125–132.

Ehrnthaller, C., Ignatius, I., Gebhart, F., Huber-Lang, I., 2011. New insights of an old defense system: structure, function, and clinical relevance of the complement system. Mol. Med. 17, 317–329.

Eikelenboom, P., Hack, C.E., Rozemuller, J.M., Stam, F.C., 1989. Virchows Arch. B Cell Pathol. Incl. Mol. Pathol. 56, 259–262.

Eikelenboom, P., Stam, F.C., 1982. Immunoglobulins and complement factors in senile plaques. An immunoperoxidase study. Acta Neuropathol. 57, 239–242.

Eikelenboom, P., Stam, F.C., 1984. An immunohistochemical study on cerebral vascular and senile plaque amyloid in Alzheimer's dementia. Virchows Arch. B Cell Pathol. Incl. Mol. Pathol. 47, 17–25.

Fan, X., Yoshida, Y., Honda, S., Matsumoto, M., Sawada, Y., Hattori, M., Hisanaga, S., Hiwa, R., Nakamura, F., Tomomori, M., Miyagawa, S., Fujimaru, R., Yamada, H., Sawai, T., Ikeda, Y., Iwata, N., Uemura, O., Matsukuma, E., Aizawa, Y., Harada, H., Wada, H., Ishikawa, E., Ashida, A., Nangaku, M., Miyata, T., Fujimura, Y., 2013. Analysis of genetic and predisposing factors in Japanese patients with atypical hemolytic uremic syndrome. Mol. Immunol. 54, 238–246.

Fernandez-Arias, C., Lopez, J.P., Hernandez-Perez, J.N., Bautista-Ojeda, M.D., Branch, O., Rodriguez, A., 2013. Malaria inhibits surface expression of complement receptor 1 in monocytes/macrophages, causing decreased immune complex internalization. J. Immunol. 190, 3363–3372.

Formeris, F., Ricklin, D., Wu, J., Tzekou, A., Wallace, R.S., Lambris, J.D., Gros, P., 2010. Structures of C3b in complex with Factors B and D give insight into complement convertase formation. Science 330, 1816–1820.

Fridkis-Harell, M., Storek, M., Mazsaroff, I., Risitano, A.M., Lundberg, A.S., Horvath, C.J., Holers, V.M., 2011. Design and development of TT30, a novel C3d-targeted C3/C5 convertase inhibitor for treatment of human complement alternative pathway-mediated diseases. Blood 118, 4705–4713.

Gasque, P., Chan, P., Mauger, C., Schouft, M.T., Singhrao, S., Dierich, M.P., Morgan, B.P., Fontaine, M., 1996. Identification and characterization of complement C3 receptors on human astrocytes. J. Immunol. 156, 2247–2255.

Gold, B., Merriam, J.E., Zernant, J., Hancox, L.S., Taiber, A.J., Gehrs, K., Cramer, K., Neel, J., Bergeron, J., Barile, G.R., Smith, R.T., AMD Genetics Clinical Study Group, Hageman, G.S., Dean, M., Allikmets, R., 2006. Variation in factor B (*BF*) and complement component 2 (*C2*) genes is associated with age-related macular degeneration. Nat. Genet. 38, 458–462.

Haines, J.L., Hauser, M.A., Schmidt, S., Scott, W.K., Olson, L.M., Gallins, P., Spencer, K.L., Kwan, S.Y., Noureddine, M., Gilbert, J.R., Schnetz-Boutaud, N., Agarwal, A., Postel, E.A., Pericak-Vance, M.A., 2005. Complement factor H variant increases the risk of age-related macular degeneration. Science 308, 419–421.

Halstensen, T.S., Brandtzaeg, P., 1991. Local complement activation in inflammatory bowel disease. Immunol. Res. 10, 485–492.

Hillmen, P., Young, N.S., Schubert, J., Brodsky, R.A., Socié, G., Muus, P., Röth, A., Szer, J., Elebute, M.O., Nakamura, R., Browne, P., Risitano, A.M., Hill, A., Schrezenmeier, H., Fu, C.L., Maciejewski, J., Rollins, S.A., Mojcik, C.F., Rother, R.P., Luzzatto, L., 2006. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N. Engl. J. Med. 355, 1233–1243.

Hinz Jr., C.F., Jordan Jr., W.S., Pillemer, L., 1956. The properdin system and immunity. IV. The hemolysis of erythrocytes from patients with paroxysmal nocturnal hemoglobinuria. J. Clin. Invest. 35, 453.

Holers, V.M., 2014. Complement and its receptors: new insights into human disease. Annu. Rev. Immunol. 32, 433–459.

Hong, S., Beja-Glasser, V.F., Nfonoyin, B.M., Frouin, A., Li, S., Ramakrishnan, S., Merry, K.M., Shi, Q., Rosenthal, A., Barres, B.A., Lemere, C.A., Selkoe, D.J., Stevens, B., 2016. Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science 352, 712–716.

Horváth, Z., Csuka, D., Vargova, K., Kovács, A., Molnár, A.Á., Gulácsi-Bárdos, P., Leé, S., Varga, L., Kiss, R.G., Préda, I., Füst, G., 2013. Elevated C1rC1sC1inh levels independently predict atherosclerotic coronary heart disease. Mol. Immunol. 54, 8–13.

Kavanagh, D., Goodship, T.H., 2007. Update on evaluating complement in hemolytic uremic syndrome. Curr. Opin. Nephrol. Hypertens. 16, 565–571.

Kawamata, T., Akiyama, H., Yamada, T., McGeer, P.L., 1992. Immunological reactions in amyotrophic lateral sclerosis brain and spinal cord tissue. Am. J. Pathol. 140, 691–707.

Kawana, S., Geoghegan, W.D., Jordon, R.E., Nishiyama, S., 1989. Deposition of the membrane attack complex of complement in pemphigus vulgaris and pemphigus foliaceus skin. J. Inves. Dermatol. 92, 588–592.

Kelly, R.J., Hill, A., Arnold, L.M., Brooksbank, G.L., Richards, S.J., Cullen, M., Mitchell, L.D., Cohen, D.R., Gregory, W.M., Hillmen, P., 2011. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. Blood 117, 6786–6792.
Kuroda, H., Fujihara, K., Takano, R., Takai, Y., Takahashi, T., Misu, T., Nakashima, I., Sato, S., Itoyama, Y., Aoki, M., 2013. Increase of complement fragment C5a in cerebrospinal fluid during exacerbation of neuromyelitis optica. J. Neuroimmunol 254, 178–182.
Lee, M., Guo, J.-P., McGeer, E.G., McGeer, P.L., 2013. Aurin tricarboxylic acid self-protects by inhibiting aberrant complement activation at the C3 convertase and C9 binding stages. Neurobiol. Aging 34, 1451–1461.
Lee, M., Guo, J.-P., Schwab, C., McGeer, E.G., McGeer, P.L., 2012. Selective inhibition of the membrane attack complex of complement by low molecular weight components of the aurin tricarboxylic acid synthetic complex. Neurobiol. Aging 33, 2237–2246.
Lemaire, M., Fremmeaux-Bacchi, V., Schaefer, E., Choi, M., Tang, W.H., Le Quintrec, M., Fakhouri, F., Taque, S., Nobili, F., Martinez, F., Ji, W., Overton, J.D., Mane, S.M., Nürnberg, G., Altmüller, J., Thiele, H., Morin, D., Deschenes, G., Baudouin, V., Llanas, B., Collard, L., Majid, M.A., Simkova, E., Nürnberg, P., Rioux-Leclerc, N., Moeckel, G.W., Gubler, M.C., Hwa, J., Loirat, C., Lifton, R.P., 2013. Recessive mutations in DGKE cause atypical hemolytic-uremic syndrome. Nat. Genet. 45, 531–536.
Lu, Y., Hu, X.B., 2014. C5a stimulates the proliferation of breast cancer cells via the Akt-dependent RGC-32 gene activation. Oncol. Rep. 32, 2813–2817.
Luo, J., Li, S., Qin, X., Song, L., Peng, Q., Chen, S., Xie, Y., Xie, L., Li, T., He, Y., Deng, Y., Wang, J., Zeng, Z., 2014. Meta-analysis of the association between CR 1 polymorphisms and risk of late-onset Alzheimer's disease. Neurosci. Lett. 578, 165–170.
Luzzatto, L., 2006. Paroxysmal nocturnal hemoglobinuria: an acquired X-linked genetic disease with somatic-cell mosaicism. Curr. Opin. Genet. Dev. 16, 317–322.
Mahmoudi, R., Kisserli, A., Novella, J.L., 2015. Alzheimer's disease is associated with low density of the long CR 1 isoform. Neurobiol. Aging 36, 1766.e5–1766.e12.
Mantovani, S., Gordon, R., Macmaw, J.K., Pfluger, C.M., Henderson, R.D., Noakes, P.G., McCombe, P.A., Woodruff, T.M., 2014. Elevation of the terminal complement activation products C5a and C5b-9 in ALS patient blood. J. Neuroimmunol. 276, 213–218.
McConnell, J., Klein, G., Lint, T.F., Lachmann, P.J., 1978. Activation of the alternative complement pathway by human B-cell lymphoma lines is associated with Epstein-Barr virus transformation of the cells. Eur. J. Immunol. 8, 453–458.
McGeer, P.L., Akiyama, H., Itagaki, S., McGeer, E.G., 1989a. Immune system response in Alzheimer's disease. Can. J. Neurol. Sci. 16, 516–527.
McGeer, P.L., Akiyama, H., Itagaki, S., McGeer, E.G., 1989b. Activation of the classical complement pathway in brain tissue of Alzheimer patients. Neurosci. Lett. 107, 341–346.
McGeer, P.L., McGeer, E.G., 2004. Inflammation and neurodegeneration in Parkinson's disease. Parkinsonism Relat. Disord. 10 (Suppl 1), S3–S7.
McGeer, P.L., McGeer, E.G., 2013. The amyloid cascade-inflammatory hypothesis of Alzheimer disease. Acta Neuropathol. 126, 479–497.
McGeer, P.L., Rogers, J., McGeer, E.G., Sibley, J., 1990. Does anti-inflammatory treatment protect against Alzheimer disease? Lancet 335, 1037.
McGeer, P.L., Schulzer, M., McGeer, E.G., 1996. Arthritis and antiinflammatory agents as negative risk factors for Alzheimer disease: a review of seventeen epidemiological studies. Neurology 47, 425–432.
Michailidou, I., Willems, J.G., Kooi, E.J., van Eden, C., Gold, S.M., Geurts, J.J., Baas, F., Huitinga, I., Ramaglia, V., 2015. Complement C1q-C3-associated synaptic changes in multiple sclerosis hippocampus. Ann. Neurol. 77, 1007–1026.
Morgan, B.P., Campbell, A.K., Compston, D.A., 1984. Terminal component of complement (C9) in cerebrospinal fluid of patients with multiple sclerosis. Lancet 2, 251–254.
Morgan, B.P., Daniels, R.H., Williams, B.D., 1988. Measurement of terminal complement complexes in rheumatoid arthritis. Clin. Exp. Immunol. 73, 473–478.
Moyo, V.M., Mukhina, G.L., Garrett, E.S., Brodsky, R.A., 2004. Natural history of paroxysmal nocturnal hemoglobinuria using modern diagnostic assays Brit. J. Haematol. 166, 133–138.
Nakagawa, K., Sakiyama, H., Tsuchida, T., Yamaguchi, K., Toyoguchi, T., Masuda, R., Moriya, H., 1999. Complement C1s activation in degenerating articular cartilage of rheumatoid arthritis patient: immunohistochemical studies with an active form specific antibody. Ann. Rheum. Dis. 58, 175–181.
Niculescu, F., Rus, H.G., Retegan, M., Vlaicu, R., 1992. Persistent complement activation on tumor cells in breast cancer. Am J Pathol. 140, 1039–1043.
Niculescu, F., Rus, H.G., Vlaicu, R., 1987. Activation of the human terminal complement pathway in atherosclerosis. Clin. Immunol. 45, 147–155.
Nitta, H., Murakami, Y., Wada, Y., Baba, H., Imamura, T., 2014. Cancer cells release anaphylatoxin C5a from C5 by serine protease to enhance invasiveness. Oncol. Rep. 32, 1715–1719.
Nitta, H., Wada, Y., Kawano, Y., Murakami, Y., Irie, A., Taniguchi, K., Kikuchi, K., Yamada, G., Suzuki, K., Honda, J., Wilson-Morifuji, M., Araki, N., Eto, M., Baba, H., Imamura, T., 2013. Enhancement of human cancer cell motility and invasiveness by anaphylatoxin C5a via aberrantly expressed C5a receptor (CD88). Clin. Cancer Res. 19, 2004–2013.
Nytrova, P., Pollukova, E., Kemlink, D., Woodhall, M., Horakova, D., Waters, P., Havrdova, E., Zivorova, D., Vincent, A., Trendelenburg, M., 2014. Complement activation in patients with neuromyelitis optica. J. Neuroimmunol 274, 185–191.
Okroj, M., Heinegard, D., Holmdahl, B., Blom, A.M., 2007. Rheumatoid arthritis and the complement system. Ann. Med. 1, 1–14.
Oksjoki, R., Laine, P., Helske, S., Vehmaan-Kreula, P., Mäyränpää, M.I., Gasque, P., Kovanen, P.T., Pentikäinen, M.O., 2007. Receptors for the anaphylatoxins C3a and C5a are expressed in human atherosclerotic coronary plaques. Atherosclerosis 195, 90–99.
Olmez, U., Garred, P., Mollnes, T.E., Harboe, M., Berntzen, H.B., Munthe, E., 1991. C3 activation products, C3 containing immune complexes, the terminal complement complex and native C9 in patients with rheumatoid arthritis. Scand. J. Rheumatol. 20, 183–189.
Pagoldh, M., Lange, S., Jennische, E., Almer, S., Bostrom, E.A., Eriksson, A., 2014. Faecal analysis and plasma complement factor C3 levels at admission for an acute attack of ulcerative colitis are predictive for the need for colectomy. Eur. J. Gastroenterol. Hepatol. 26, 295–300.
Patel, S.N., Berghout, J., Lovegrove, F.E., Ayi, K., Conroy, A., Serghides, L., Min-oo, G., Gowda, D.C., Sarma, J.V., Rittirsch, D., Ward, P.A., Liles, W.C., Gros, P., Kain, K.C., 2008. C5 deficiency and C5a or C5aR blockade protects against cerebral malaria. J. Exp. Med. 205, 1133–1143.
Perrin, L.H., Nydegger, U.E., Zubler, R.H., Lambert, P.H., Miescher, P.A., 1977. Correlation between levels of breakdown products of C3, C4 and properdin factor B in synovial fluids from patients with rheumatoid arthritis. Arthritis Rheum. 20, 647–652.
Pio, R., Ajona, D., Lambris, J.D., 2013. Complement inhibition in cancer therapy. Semin. Immunol. 25, 54–64.
Pittock, S.J., Lennon, V.A., McKeon, A., Mandrekar, J., Weinshenker, B.G., Lucchinetti, C.F., O'Toole, O., Wingerchuk, D.M., 2013. Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study. Lancet Neurol. 12, 554–562.
Potter, B.J., Hodgson, H.J., Mee, A.S., Jewell, D.P., 1979. C1q in ulcerative colitis and Crohn's disease. Gut 20, 1012–1019.
Radillo, O., Nocera, A., Leprini, A., Barocci, S., Mollnes, T.E., Pocecco, M., Pausa, M., Valente, U., Betterle, C., Tedesco, F., 1996. Complement-fixing islet cell antibodies in type-1 diabetes can trigger the assembly of the terminal complement complex on human islet cells and are potentially cytotoxic. Clin. Immunol. Immunopathol 79, 217–223.
Risitano, A.M., 2013. Paroxysmal nocturnal hemoglobinuria and the complement system: recent insights and anticomplement strategies. Adv. Exp. Med. 735, 155–172.
Risitano, A.M., Notaro, R., Pascariello, C., Sica, M., del Vecchio, L., Horvath, C.J., Fridkis-Hareli, M., Selleri, C., Lindorfer, M.A., Taylor, R.P., Luzzatto, L., Holers, V.M., 2012. The complement receptor 2/factor H fusion protein TT30 protects paroxysmal nocturnal hemoglobinuria erythrocytes from complement-mediated hemolysis and C3 fragment opsonization. Blood 119, 6307–6316.
Robson, K.J.H., Hall, J.R.S., Jennings, M.W., Harris, T.J.R., Marsh, K., Newbold, C.I., Tate, V.E., Weatherall, D.J., 1988. A highly conserved amino-acid sequence in thrombospondin, properdin and in proteins from sporozoites and blood stages of a human malaria parasite. Nature 335, 79–82.
Rogers, J., Cooper, N.R., Webster, S., Schultz, J., McGeer, P.L., Styren, S.D., Civin, W.H., Brachova, L., Bradt, B., Ward, P., 1992. Complement activation by b-amyloid in Alzheimer disease. Proc. Natl. Acad. Sci. U. S. A. 89, 10016–10020.
Rosenberg, E.W., Noah, P.W., Wyatt, R.J., Jones, R.M., Kolb, W.P., 1990. Complement activation in psoriasis. Clin. Exp. Dermatol. 15, 16–20.
Rowe, P., Wasserfall, C., Croker, B., Campbell-Thompson, M., Pugliese, A., Atkinson, M., Schatz, D., 2013. Increased complement activation in human type 1 diabetes pancreatica. Diabetes Care 36, 3815–3817.
Ruddy, S., Fearon, D.T., Austen, K.F., 1975. Depressed synovial fluid levels of properdin and properdin factor B in patients with rheumatoid arthritis. Arthritis Rheum. 18, 289–295.
Rus, V., Malide, D., Boloşiu, H.D., Parasca, I., Duţu, A.L., 1990. Levels of SC5b-9 complement complex in plasma and synovial fluid of patients with rheumatoid arthritis. Med. Intern. 28, 305–310.
Rutkowski, M.J., Sughrue, M.E., Kane, A.J., Mills, S.A., Parsa, A.T., 2010. Cancer and the complement cascade. Mol. Cancer Res. 11, 1453–1465.
Sanders, M.E., Koski, C.L., Robbins, D., Shin, M.L., Frank, M.M., Joiner, K.A., 1986. Activated terminal complement in cerebrospinal fluid in Guillain-Barre syndrome and multiple sclerosis. J. Immunol. 136, 4456–4459.
Schmidt, C., Wolff, M., von Ahsen, N., Lange, K., Friede, T., Zerr, I., 2014. CR1 is potentially associated with rate of decline in sporadic Alzheimer's disease. J. Clin. Neurosci. 21, 1705–1708.
Schwab, C., McGeer, P.L., 2002. Complement activated C4d immunoreactive oligodendrocytes delineate early plaques in multiple sclerosis. Exp. Neurol. 174, 81–88.
Seah, P.P., Fry, L., Mazageri, M.R., Mowbray, J.F., Hoffbrand, A.V., Holborrow, E.J., 1973. Alternate-pathway complement fixation by IgA in the skin in dermatitis herpetiformis. Lancet 7822, 175–177.
Sekar, A., Bialis, A.R., deRivera, H., Davis, A., Hammond, T.R., Kamitaki, N., Tooley, K., Presumey, J., Baum, M., Van Doren, V., Genovese, G., Rose, S.A., Handsaker, R.E., Schizophrenia Working Group of the Psychiatric Genomics Consortium, Daly, M.J., Carroll, M.C., Stevens, B., McCarroll, S.A., 2016. Schizophrenia risk from complex variation of complement component 4. Nature 530, 177–183.
Silver, K.L., Higgins, S.J., McDonald, C.R., Kain, K.C., 2010. Complement driven innate immune response to malaria: fuelling severe malarial diseases. Cell Microbiol. 12, 1036–1045.
Speidl, W.S., Exner, M., Amighi, J., Kastl, S.P., Zorn, G., Maurer, G., Wagner, O., Huber, K., Minar, E., Wojta, J., Schillinger, M., 2005. Complement component C5a

predicts future cardiovascular events in patients with advanced atherosclerosis. Eur. Heart J. 26, 2294–2299.
Sta, M., Sylva-Steenland, R.M., Casula, M., deJong, L.M., Troost, D., Aronica, E., Baas, F., 2011. Innate and adaptive immunity in amyotrophic lateral sclerosis: evidence of complement activation Neurobiol. Aging 42, 211–220.
Stahel, P.F., Morganti-Kossmann, M.C., Perez, D., Redaelli, C., Gloor, B., Trentz, O., Kossmann, T., 2001. Intrathecal levels of complement-derived soluble membrane attack complex (sC5b-9) correlate with blood-brain barrier dysfunction in patients with traumatic brain injury. J. Neurotrauma 18, 773–781.
Sundsmo, J.S., Papin, R.A., Wood, L., Hirani, S., Waldeck, N., Buckingham, B., Kershnar, A., Ascher, M., Charles, M.A., 1985. Complement activation in type 1 human diabetes. Clin. Immunol. Immunopathol 35, 211–225.
Takeda, J., Miyata, T., Kawagoe, K., Iida, Y., Endo, Y., Fujita, T., Takahashi, M., Kitani, T., Kinoshita, T., 1993. Deficiency of the GPI anchor caused by a somatic mutation in the PIG-A gene in paroxysmal nocturnal hemoglobinuria. Cell 73, 703–711.
Takematsu, H., Tagami, H., 1992. Generation of terminal complement complexes in psoriatic lesioned skin. Dermatology 185, 246–250.
Terai, K., McGeer, E.G., McGeer, P.L., 1997. Neurons express proteins of the classical complement pathway in Alzheimer disease. Brain Res. 769, 385–390.
Thompson, I.A., Liu, B., Sen, H.N., Jiao, X., Katamay, R., Li, Z., Hu, M., Hejtmancik, F., Nussenblatt, R.B., 2013. Association of complement factor H tyrosine 402 histidine genotype with posterior involvement in sarcoid-related uveitis. Am. J. Ophthalmol. 155, 1068–1074.
Torzewski, J., Torzewski, M., Bowyer, D.E., Fröhlich, M., Koenig, W., Waltenberger, J., Fitzsimmons, C., Hombach, V., 1998. C-reactive protein frequently colocalizes with the terminal complement complex in the intima of early atherosclerotic lesions of human coronary arteries. Arterioscler. Thromb. Vasc. Biol. 18, 1386–1392.
Triolo, G., Accardo-Palumbo, A., Sallì, L., Ciccia, F., Ferrante, A., Tedesco, L., Sallì, S., Giardina, E., Pappalardo, A., Licata, G., 2003. Impaired expression of erythrocyte glycol-phosphotidylinosotol-anchored membrane CD59 in patients with psoriatic arthritis. Relation to terminal complement pathway activation. Clin. Exp. Rheumatol. 21, 225–228.
Uzawa, A., Mori, M., Kuwabara, S., 2014. Neuromyelitis optica: concept. Immunology and treatment. J. Clin. Neurosci. 21, 12–21.
Van de Goot, E., Krijnen, P.A., Begieneman, M.P., Ulrich, M.M., Middelkoop, E., Niessen, H.W., 2009. Acute inflammation is persistent in burn wounds: a pivotal role for complement and C-reactive protein. J. Burn Care Res. 30, 274–280.
Vergani, S., Di Mauro, E., Davies, E.T., Spinelli, D., Mieli-Vergani, G., Vergani, D., 1986. Complement activation in uveitis. Br. J. Ophthalmol. 70, 60–63.
Veszeli, N., Fust, G., Csuka, D., Trauninger, A., Bors, L., Rozsa, C., Nagy, Z., Jobbágy, Z., Eizler, K., Prohászka, Z., Varga, L., Illes, Z., 2014. A systematic analysis of the complement pathways in patients with neuromyelitis optica indicates alteration but no activation during remission. Mol. Immunol. 57, 200–209.
Villemagne, V.L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K.A., Salvado, O., Szoeke, C., Macaulay, S.L., Martins, R., Maruff, P., Ames, D., Rowe, C.C., Masters, C.L. Australian Imaging Biomarkers and Lifestyle (AIBL) Research Group, 2013. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol. 13, 70044–70049.
Vlaicu, R., Niculescu, F., Rus, H.G., Cristea, A., 1985. Immunohistochemical localization of the terminal C5b-9 complement complex in human aortic fibrous plaque. Atherosclerosis 57, 163–177.
Walker, D.G., McGeer, P.L., 1992. Complement gene expression in human brains: comparison between normal and Alzheimer disease cases. Mol. Brain Res. 14, 109–116.
Wan, K.C., Lewis, W.H., Leung, P.C., Chien, P., Hung, L.K., 1998. A longitudinal study of C3, C3d, and factor Ba in burn patients in Hong Kong Chinese. Burns 24, 241–244.
Wang, H., Wang, K., Wang, C., Qiu, W., Lu, Z., Hu, X., 2014a. Increased soluble C5b-9 in CSF of neuromyelitis optica. Scand. J. Immunol. 79, 127–130.
Wang, Y., Huang, X.F., Yang, M.M., Cai, W.J., Zheng, M.Q., Mao, G., Pang, C.P., Jin, Z.B., 2014b. CFI-rs 7356506 is a genetic protective factor for acute anterior uveitis in Chinese patients. B. J. Ophthalmol. 98, 1592–1596.
Wingerchuk, D.M., 2007. Neuromyelitis optica: new findings on pathogenesis. Int. Rev. Neurobiol. 79, 665–688.
Wouters, D., Voskuyl, A.E., Molenaar, E.T., Dijkmans, B.A., Hack, C.E., 2006. Evaluation of classical complement pathway activation in rheumatoid arthritis: measurement of C1q-C4 complexes as novel activation products. Arthritis Rheum. 54, 1143–1150.
Yamada, T., McGeer, P.L., McGeer, E.G., 1992. Lewy bodies in Parkinson's disease are recognized by antibodies to complement proteins. Acta Neuropathol. 84, 100–104.
Yasojima, K., Schwab, C., McGeer, E.G., McGeer, P.L., 1999. Upregulated production and activation of the complement system in Alzheimer disease brain. Am. J. Pathol. 154, 927–936.
Yasojima, K., Schwab, C., McGeer, E.G., McGeer, P.L., 2001. Complement components, but not the complement regulators C1 inhibitor and CD59, are upregulated in atherosclerotic plaques. Arterioscler. Thromb. Vasc. Biol. 21, 1214–1219.
Yates, J.R., Sepp, T., Matharu, B.K., Khan, J.C., Thurlby, D.A., Shahid, H., Clayton, D.G., Hayward, C., Morgan, J., Wright, A.F., Armbrecht, A.M., Dhillon, B., Deary, I.J., Redmond, E., Bird, A.C., Moore, A.T. Genetic Factors in AMD Study Group, 2007. Complement C3 variant and the risk of age-related macular degeneration. N. Engl. J. Med. 357, 553–561.
Zimmerman-Nielsen, E., Gronbaek, H., Dahlerup, J.F., Baatrup, G., Thorlacius-Ussing, O., 2005. Complement activation capacity in plasma before and during high-dose prednisolone treatment and tapering in exacerbations of Crohn's disease and ulcerative colitis. BMC Gastroenterol. 22, 531.