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Function and regulation of the complement system in cardiovascular diseases

Riina Oksjoki[1], Petri T. Kovanen[1], Seppo Meri[2], Markku O. Pentikainen[1]

[1]Wihuri Research Institute, Helsinki, Finland; [2]Department of Bacteriology and Immunology, University of Helsinki, Helsinki, Finland

TABLE OF CONTENTS

1. Abstract
2. Introduction to the complement system
2.1. Activation of the complement system
2.2. Regulation of the complement system
2.3. Effector mechanisms
3. Complement in cardiovascular diseases
3.1. Atherosclerosis
3.2. Arterial aneurysms
3.3. Ischemia-reperfusion injury
3.4. Heart failure
4. Perspectives
5. Acknowledgements
6. References

1. ABSTRACT

The complement system plays a central role in innate immunity and also regulates adaptive immunity. The complement system has been demonstrated to contribute to various diseases, including cardiovascular diseases. Complement is extensively activated in atherosclerotic lesions, in arterial aneurysms, and in the myocardium of ischemic and failing hearts. Accumulating evidence shows that limitation of excessive complement activation under these conditions may hold therapeutic value. On the other hand, defects in the classical complement pathway predispose to vasculitis and atherosclerosis, possibly due to ineffective clearance of apoptotic/necrotic cells and abnormal processing of immune complexes. Here, we describe complement activation and regulation in cardiovascular diseases and discuss the evidence derived mainly from experimental animals suggesting that modulation of complement activation may alter the course of these disorders.

2. INTRODUCTION TO THE COMPLEMENT SYSTEM

The complement system is composed of approximately 30 plasma and cell membrane proteins that interact with each other to constitute a cascade of activation steps. The complement system plays a central role in innate immunity and also regulates various responses of adaptive immunity. Complement activation is essential to the host's immune defense, but its uncontrolled or inappropriately targeted activation leads to various diseases such as glomerulonephritis, hemolytic uremic syndrome, paroxysmal nocturnal hemolytic anemia, and angioedema and also plays a role in a variety of other diseases such as rheumatoid arthritis, psoriasis, dermatomyositis, pemphigoid, sepsis, acute pancreatitis, and cardiovascular diseases. The aim of this review is to discuss the potential of the complement system to contribute to the pathogenesis of cardiovascular diseases and the possible therapeutic value of modulating complement activation.

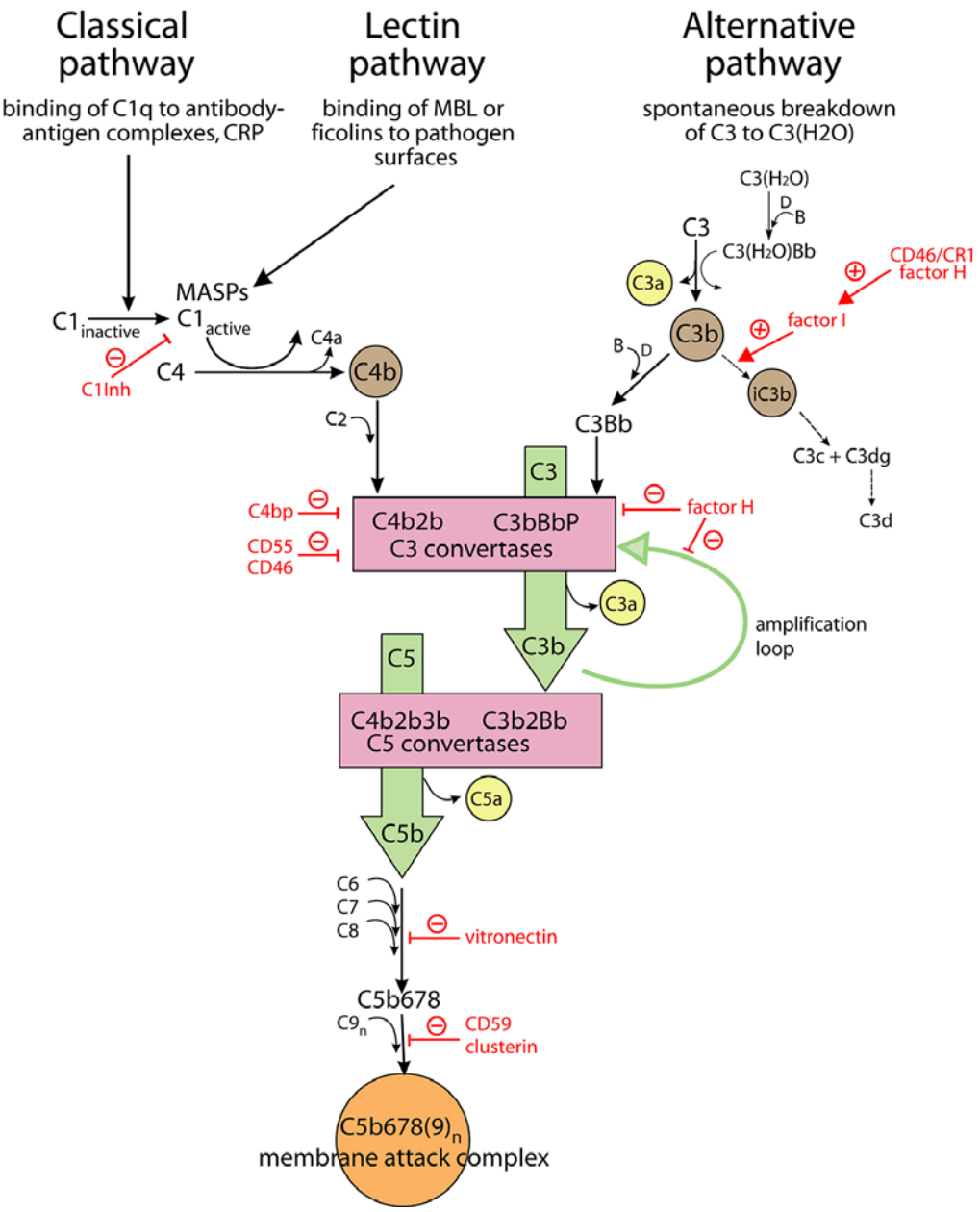

Figure 1. Schematic representation of the complement system and its regulators. Opsonins generated during complement activation are shown as brown and anaphylatoxins yellow. Complement regulators are shown as red. Adapted from Oksjoki *et al.* (16). P: properdin; MBL: mannan-binding lectin.

2.1. Activation of the complement system

The complement system consists of complement proteins and fluid phase and membrane-bound regulators. A number of complement proteins circulate as zymogens and, upon appropriate conditions, become activated by proteolytic cleavage. Thus, a component of the system often serves as a substrate for a previous component and, once activated, proteolytically activates the subsequent component. This pattern of sequential activation produces an expanding cascade of activity, in which the activation of a single molecule can lead to generation of thousands of active molecules in the following steps. Thus, many regulatory mechanisms are needed to prevent uncontrolled complement activation and tissue damage.

Depending on the nature of the activator, three different activation pathways have been described: the classical, lectin, and alternative pathway (Figure 1). Each pathway utilizes different proteins to recognize the activators and to initiate the complement cascade. The *classical pathway* is primarily activated when C1q recognizes antigen-bound immunoglobulins (IgG and IgM) or C-reactive protein (CRP). This is followed by the cleavage of C4 and C2 to form the classical pathway C3

Table 1. Complement regulatory proteins and their main functions

Regulatory protein	Main function
Soluble regulators	
C1-inhibitor	Binds and inactivates C1r and C1s
C4b-binding protein	Accelerates decay and inhibits CP C3 convertase, cofactor for factor I
Factor H	Accelerates decay and inhibits AP, C3 convertase, cofactor for factor I
Factor I	Cleaves and inactivates C3b and C4b in the presence of cofactor
Properdin	Stabilizes AP C3 convertase
S protein	Prevents assembly of C5b-9
Clusterin	Prevents assembly of C5b-9
Membrane-bound regulators	
DAF (CD55)	Accelerates decay of AP and CP C3 and C5 convertases
MCP (CD46)	Cofactor for factor I
Protectin (CD59)	Prevents assembly of C5b-9
CR1 (CD35)	Accelerates decay of AP and CP C3 and C5 convertases, cofactor for factor I
CRIg	Binds to C3b and inhibits AP C3 and C5 convertases

CP, classical pathway; AP, alternative pathway; DAF, decay-accelerating factor; MCP, membrane cofactor protein

convertase C4b2b. Activation of the *lectin pathway* involves binding of plasma mannan-binding lectin (MBL) or ficolins to carbohydrate groups on the surface of microorganisms. Analogously to the classical pathway, mannan-binding lectin-associated serine proteases (MASPs) can activate C4 and C2 to generate the classical pathway C3-convertase, C4b2b. In contrast to the activation of the classical and the lectin pathways, activation of the alternative pathway involves constant low-grade spontaneous activation of C3 in plasma. If the formed C3b is bound to a complement-activating surface, it may bind factor B, which is then cleaved by factor D, allowing the formation of the alternative pathway C3-convertase, C3bBb. Binding of properdin to C3b stabilizes the complex and allows significant C3 convertase activity. The terminal pathway is activated when C3b forms a complex with C3-convertases and generates two C5-convertases, C4b2b3b and C3bC3bBb, which belong to the classical and alternative pathways, respectively. These convertases can cleave C5, thereby yielding one C5b and one anaphylatoxin C5a molecule. Association of C5b with C6, C7, C8, and multiple C9 molecules ultimately leads to the generation of C5b-9, also known as the membrane attack complex (MAC) (1).

2.2. Regulation of the complement system

The powerful cytolytic potential of the complement system needs to be effectively regulated in order to avoid harmful tissue damage and complement attack against normal host cells. Indeed, complement is regulated by various regulatory proteins both in the fluid phase and on the host cell surface. The fluid phase regulators include C1-inhibitor (C1INH), C4b-binding protein (C4bp), factor H, factor I, properdin, S protein, and clusterin. Surface-bound inhibitors include decay-accelerating factor (DAF), membrane cofactor protein (MCP), protectin (CD59), complement receptor 1 (CR1), and the newly described CRIg (2). The main functions of these regulators are summarized in Table 1, and their sites of action are depicted in Figure 1. Due to the efficient regulation of the complement, even in the presence of potent activators, 30-100 molecules of C3 have to be cleaved to generate one C5, and 1-10 molecules of C5 have to be cleaved to generate one C5b-9 (3).

2.3. Effector mechanisms

The complement system exerts its effects by generating a variety of functional molecules. The complement proteins C1q, C3b, iC3b, and C4b act as opsonins, i.e., they bind to target particles and promote their non-inflammatory uptake via complement receptors present on phagocytes. Moreover, complement-opsonized immune complexes can bind to complement receptor 1 (CR1) on the surface of erythrocytes, which then allows their destruction in the spleen and liver and also prevents the deposition of immune complexes in peripheral tissues. Complement activation leads to the generation of two anaphylatoxins, C3a and C5a, which play an important role in inflammation by inducing the expression and release of various cytokines and adhesion molecules, by acting as chemoattractants to leukocytes, and by increasing vascular permeability. The generation of C5b-9 leads to the formation of pore-like structures in the cell membrane and lysis of non-nucleated target cells such as erythrocytes and bacteria. Interestingly, nucleated cells have a number of ways to avoid lysis by C5b-9, and sublytic amounts of C5b-9 may activate the target cells to release a wide array of cytokines and growth factors and, instead of killing them, induce their proliferation. Finally, C3d, the "inactivated" form of C3b, can significantly enhance antibody production by binding to CR2 receptors on B-lymphocytes (4). The complement system also has important links to the coagulation system (5). Thus, plasmin can cleave and activate C3. Moreover, C4bp and protein S form complexes in which protein S loses its anticoagulant activity (6). Furthermore, C1Inh is the major plasma inhibitor of activated factor XII and kallikrein (7). Finally, the inactivator of the C3a and C5a anaphylatoxins is identical to carboxypeptidase N, the major bradykinin-inactivating enzyme present in plasma.

3. COMPLEMENT SYSTEM IN CARDIOVASCULAR DISEASES

Complement has been suggested to play a role in the pathogenesis of various cardiovascular diseases. Thus, signs of complement activation have been detected in atherosclerotic arterial walls, in infarcted myocardium as well as in arterial aneurysms, and a lack of complement-

mediated clean-up within the arterial wall has been shown to predispose to vasculitis. Animal studies have provided supportive evidence that complement activation may play a significant role in these pathological processes.

3.1. Atherosclerosis

Atherosclerosis is characterized by a chronic inflammatory reaction involving components of both innate and adaptive immunity. Various complement activation products (8), complement regulatory proteins, and complement receptors (9) have been detected in atherosclerotic lesions, and the deposition of C5b-9 has been shown to correlate with the disease state (10, 11). It has even been suggested that complement activation could be an initiating event in the inflammatory reaction characteristic of atherosclerosis. This suggestion was based on the observation that the deposition of C5b-9 in cholesterol-fed rabbits correlates temporally with the deposition of lipids in the intima and precedes the accumulation of inflammatory cells (12).

During recent decades, various studies have tried to elucidate the agents/structures activating the complement system in atherosclerotic lesions. The fact that normal arterial intima lacks signs of complement activation suggests that complement-activating structures are either generated or deposited in the arterial wall during atherogenesis. Indeed, modified lipoproteins and apoptotic/necrotic cells have been shown to activate the alternative complement pathway and the classical complement pathway by binding immunoglobulins and CRP *in vitro* (13-15), and signs of complement activation via these pathways have been detected in atherosclerotic lesions *in vivo* (16).

Our efforts to elucidate the regulation of complement activation in atherogenesis showed that, while the superficial proteoglycan-rich layer of the intima contains markers of both classical and alternative pathway activation, this area is devoid of C5b-9, which is present only deeper in the musculoelastic layer of the intima. We also demonstrated that the superficial proteoglycan-rich layer of the intima contains inhibitors of the alternative and classical pathways, factor H and C4bp, respectively, and that they stain in a strictly reciprocal pattern with the terminal complement product C5b-9 (17, 18). Thus, it appears that the layers of atherosclerotic lesions, i.e. the superficial proteoglycan-rich layer and the deep musculoelastic layer, differ in their capacity to regulate complement activation. In the deep musculoelastic layer, colocalization of C5b-9 with properdin indicates that C5b-9 has been generated as a result of alternative pathway activation. This is well in line with the previous studies showing that the deep layer of the intima contains enzymatically-modified low-density lipoprotein (LDL) particles known for their ability to activate the alternative pathway of complement (19). The presence of clusterin (20) and vitronectin (21) in the arterial intima suggests that the terminal complement pathway in the arterial intima is regulated by these molecules, both of which inhibit membrane insertion of C5b-7 and C9 polymerization. Activation of the complement cascade and its regulation in atherosclerotic intima are summarized in Figure 2.

In addition to the extracellular complement regulatory proteins acting in the fluid-phase or while bound to the proteoglycan matrix, complement activation in the arterial wall is controlled also by various cell surface regulatory proteins. Membrane cofactor protein (MCP, CD46), which limits complement activation by acting as a cofactor for factor I-mediated cleavage of C3b (and C4b), is ubiquitously expressed by all nucleated cells (22) and thus may be involved in complement regulation in the arterial intima. The endothelial cells of the normal arterial wall constitutively express the cell surface complement inhibitors decay-accelerating factor (DAF, CD55) (9), which inhibits both classical and alternative pathway C3 and C5 convertases, and CD59 (23, 24), which prevents the assembly of C5b-9 on cell membranes (25). Such constitutive expression of the two inhibitors on endothelial cells appears reasonable, since endothelial cells are constantly exposed to C3b generated in the circulation. In contrast, the expression of these inhibitors in other cells present in atherosclerotic lesions is highly variable. Thus, DAF has been detected in 20-60% of lesional cells, the majority of them being macrophages and smooth muscle cells (26). In addition, DAF has been also detected extracellularly in atherosclerotic lesions, a finding consistent with the fact that DAF can be released from its glycolipid membrane anchor by phospholipase C (27). Similarly, CD59 is expressed by macrophages and T cells in atherosclerotic lesions, whereas only a fraction of smooth muscle cells express this inhibitor (24). In addition, CR1, a regulator of both classical and alternative pathway C3 convertases, is mainly expressed by macrophages in lesions (28), and macrophages also in the arterial intima are likely to express the newly described CRIg (2). The limited expression of cell surface regulators on smooth muscle cells suggests that these cells are the initial targets of complement attack in the lesions. This suggestion is supported by the observation that C5b-9 colocalizes with smooth muscle cells in early lesions (29). Interestingly, cell culture studies have shown that the deposition of C5b-9 on smooth muscle cells leads to cellular proliferation (30) as well as to the expression of monocyte chemotactic protein-1 (31) and interleukin-6 (32) by smooth muscle cells, all of which are believed to be important in the development of atherosclerotic lesions. In more advanced lesions, C5b-9 is co-localized also with macrophages (33), likely due to apoptosis and necrosis of the lipid-laden macrophages.

What have animal experiments taught us about the role of complement activation in atherogenesis? Geertinger and Sørensen, and later the Mainz group led by Sucharit Bhakdi, found that a cholesterol-rich diet induced less atherosclerosis in rabbits deficient in C6 than in controls with a fully functional complement system (34, 35). Similarly, an anticomplement agent K-76COONa was found to suppress the development of diet-induced atherosclerosis in rabbits (36). Finally, inhibition of the complement system by injections of vaccinia virus complement control protein significantly reduced lesion size in C57Bl/6 mice fed a high-fat diet (37). However, in mouse models with genetically induced (extreme) hyperlipidemia, contrasting effects on atherogenesis have been obtained. Thus, in apolipoprotein E-null ($apoE^{-/-}$) mice

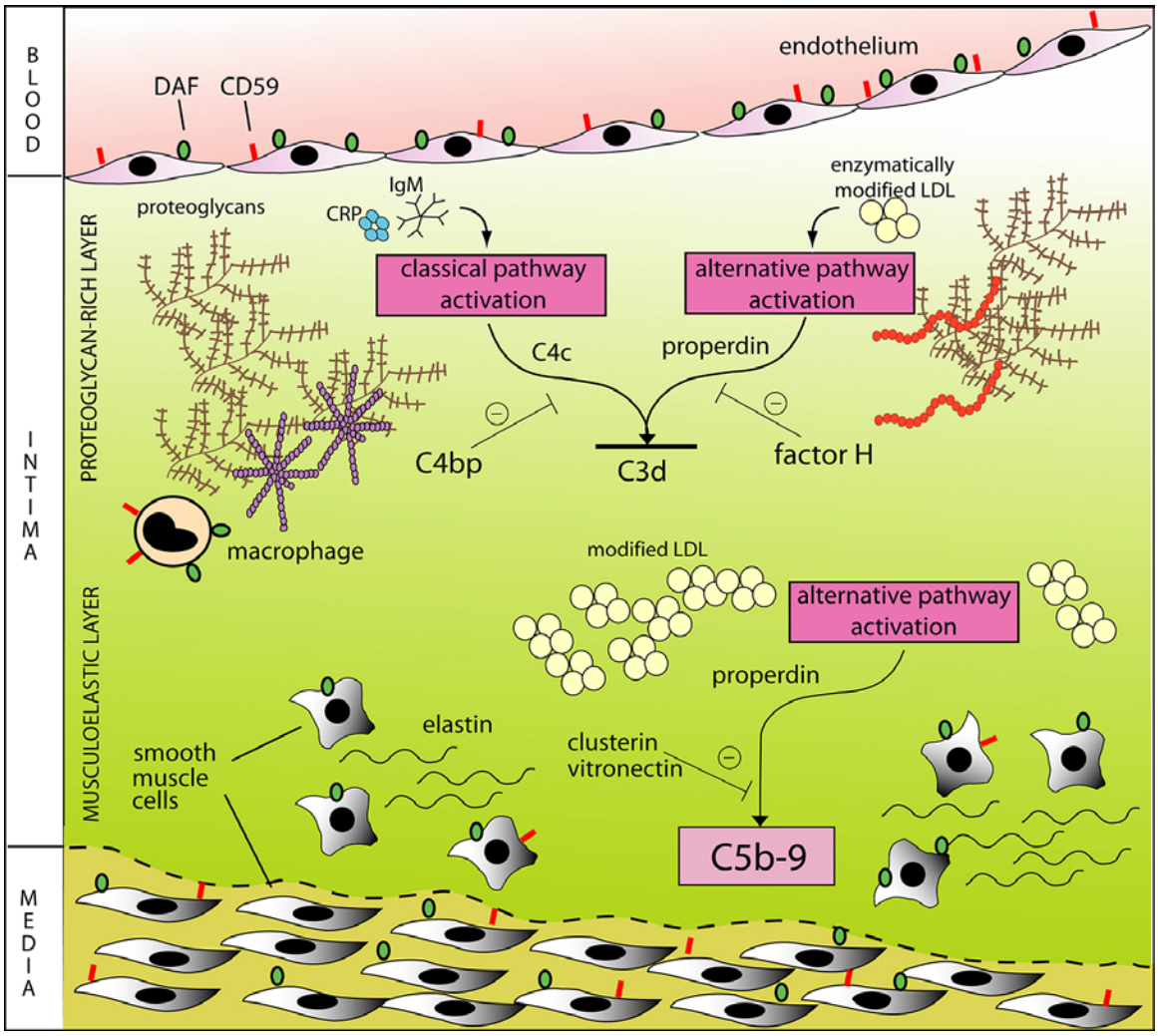

Figure 2. Regulation of the complement system in atherosclerotic lesions: a 2-layered system. In the superficial proteoglycan-rich layer, which contains factor H and C4bp, complement activation is limited to the C3 level. Thus, although this area contains activators of the complement system (IgM, CRP) and markers of actual complement activation via the classical (C4c) and alternative pathways (properdin), no terminal C5b-9 is generated. In the deeper musculoelastic layer, possibly due to the absence of the 2 inhibitory molecules, complement activation proceeds to the assembly of C5b-9. The presence of properdin, but not C4c, in this area suggests that C5b-9 has been generated as a result of activation of the alternative pathway of the complement. Interestingly, this deep intimal layer also contains modified lipoprotein particles, which have been shown to be capable of activating the complement via the alternative pathway.

fed a high-fat diet, the development of atherosclerosis was similar in C5-deficient and C5-sufficient mice (38). Finally, C3 deficiency on LDL receptor-null ($LDLR^{-/-}$) or $LDLR^{-/-}$/$apoE^{-/-}$ double mutant backgrounds led to the development of even larger atherosclerotic lesions (39, 40). Importantly, analysis of these lesions showed that they were rich in lipid and contained small quantities of collagen and smooth muscle cells (39), which indicates that lesion maturation was impaired in the absence of C3 and suggests an important role for C5b-9 in inducing smooth muscle cell proliferation in atherosclerotic lesions.

Despite the appreciable inconsistency of the net effect of complement activation on experimentally induced atherosclerosis, evidence suggests a protective role for the classical pathway. This is probably due to its suggested role in the clearance of apoptotic cells and immune complexes. Accordingly, the absence of components of the classical complement pathway may aggravate vascular inflammation and lead to vasculitis, like systemic lupus erythematosis. Consistently, the absence of C1q increased atherosclerosis in $LDLR^{-/-}$ mice, and the lesions contained more apoptotic cells than those of their complement-sufficient littermates (41). Similarly, in humans, the lack of early classical pathway components C1q, C2, and C4 has been found to be associated with increased incidence of cardiovascular disease (42, 43).

Dysfunctions in the complement regulatory proteins have also been suggested to play a role in

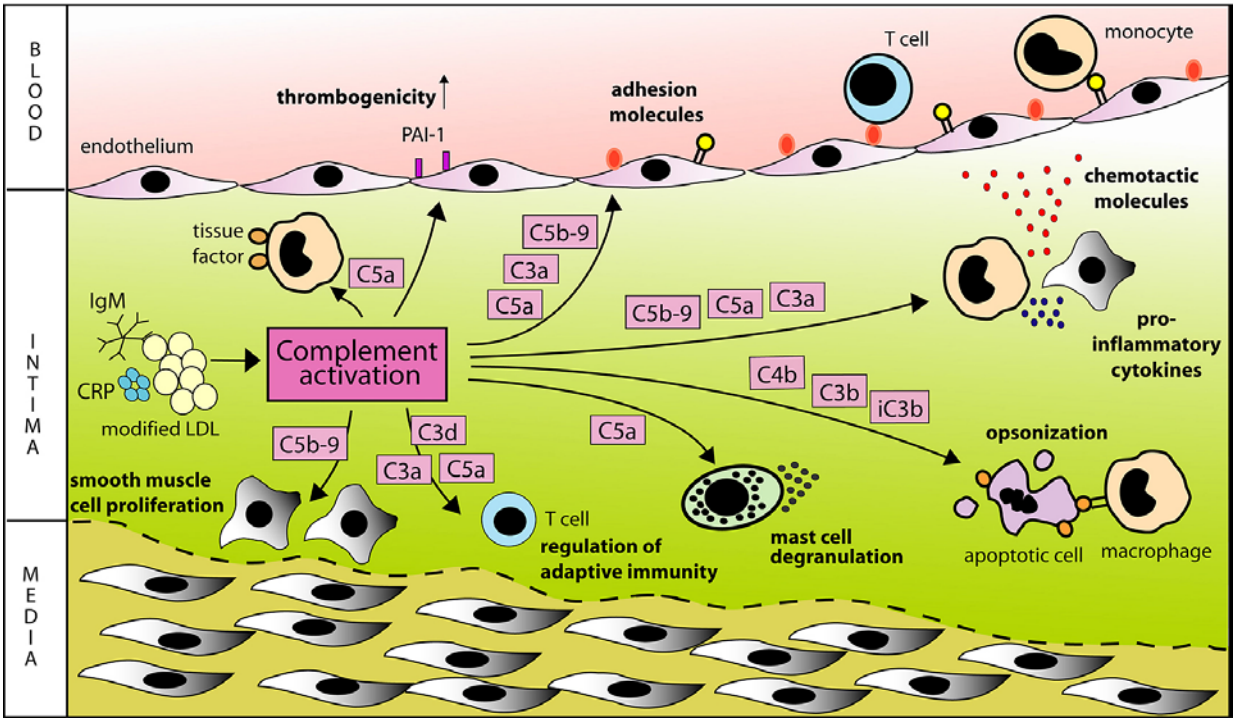

Figure 3. Summary of the biological effects of complement activation in atherosclerotic arterial intima. Complement activation generates effector molecules (pink rectangles) including anaphylatoxins (C3a and C5a), opsonins (C4b, C3b, iC3b), C3d, and the membrane attack complex C5b-9, all of which have distinct cell-type specific effects in the arterial intima.

atherogenesis. Recent studies have posed the question of whether the Y402H polymorphism of the factor H gene, which locates within the binding site for heparin and C-reactive protein and plays a major role in age-related macular degeneration (44-46), might also play a role in atherothrombotic events. Two case-control studies failed to reveal any association between this polymorphism and the risk of myocardial infarction (MI) or ischemic stroke (47) or angiographically verified coronary artery disease (48). In contrast, a prospective study comprising more than 5000 healthy individuals showed that the presence of the 402H variant of factor H was associated with an increased risk for MI (49). This supports the notion that the complement inhibitory factor H protects against the development of atherosclerosis and its thrombotic complications, i.e. against atherothrombosis.

It is important to note that hyperlipidemic animal models are far from optimal for studies of the very late stages of atherosclerosis, i.e. plaque rupture and ensuing thrombotic complications. Therefore, our notions about the possible role of complement in late atherothrombotic events are mainly based on observational findings in human subjects. Indeed, human studies provide some clues that complement might play a role in promoting plaque instability and cause acute cardiovascular events. In support of this notion, complement has been shown to be activated especially in vulnerable plaques prone to rupture (50). In addition, high levels of circulating anaphylatoxins (51) and C5b-9 (52) have been reported in patients with acute coronary syndromes compared to patients with stable coronary artery disease. Finally, elevated plasma levels of C5a have been shown to independently predict future major adverse cardiovascular events in patients with established atherosclerosis (53). A summary of the effects of complement activation in atherosclerotic arterial intima is depicted schematically in Figure 3.

3.2. Arterial aneurysms

An arterial aneurysm is a local widening (dilatation) of an artery. The arterial wall at the site of the aneurysm is weakened and prone to rupture. Here, we will only deal with saccular aneurysms of the intracranial cerebral arteries and aneurysms of the abdominal aorta. Saccular aneurysms are pouch-like protrusions of intracranial cerebral arteries and are typically located at arterial bifurcations. Rupture of such an aneurysm causes a subarachnoidal hemorrhage, which leads to death in 35-50% of cases and also causes severe morbidity. Interestingly, recent studies have demonstrated that the wall of rupture-prone aneurysms possesses characteristics that are different from those of non-rupture-prone ones. Thus, it was shown that the wall of a ruptured aneurysm contains increased numbers of inflammatory cells (54, 55), increased protease activity (56), reduced numbers of smooth muscle cells, and the extracellular matrix has undergone extensive modification (55). A recent paper suggested that complement activation might be involved in this adverse remodeling, which renders the arterial wall rupture-prone (57). Indeed, the amount of deposited C5b-9 was significantly increased in ruptured saccular aneurysms compared to non-ruptured ones. C5b-9 showed a band-like

pattern of staining in the outer wall of the aneurysm, and it stained reciprocally to the complement inhibitor CD59. Of note, C5b-9 was also present in non-ruptured saccular cerebral arterial aneurysms, suggesting that complement may play a role not only in the actual rupturing, but also in the pathobiology of aneurysm formation.

Similarly to saccular cerebral arterial aneurysms, abdominal aortic aneurysms are characterized by prominent inflammatory activation and loss of extracellular matrix, notably elastin. In addition, complement activation has also been suggested to play a role in the pathogenesis of aortic aneurysms. In such aneurysms, the C3 content was 125-fold compared to normal aortic wall. In addition, various C3 degradation products were detected, suggesting that complement activation had occurred within the diseased aortic wall (58).

3.3. Ischemia-reperfusion injury

Ischemic injury occurs when blood flow and, consequently, oxygen delivery to end-organ tissue is compromised due to e.g. atherothrombotic events or as a result of surgical procedures such as bypass graft surgery. Reperfusion, although necessary to prevent permanent tissue death caused by ischemia, may accelerate the process initiated during ischemia or induce new pathological changes that increase inflammation and the extent of tissue damage, and may also result in cellular death. At least three major factors are important in the pathophysiology of ischemia-reperfusion (I/R) injury: neutrophil infiltration, oxidative stress, and complement activation. The importance of complement activation as a mediator of tissue damage in I/R injury has been demonstrated by the signs of complement activation in affected tissues as well as by animal studies demonstrating that either genetic or pharmacologic inhibition of the complement system attenuates I/R injury. Although we will focus here mainly on myocardial I/R injury, complement activation is known to play a role in I/R injury of even other end organs, including the brain, the kidney, and the intestine.

While deposition of complement proteins in ischemic myocardium takes place slowly over a period of hours (59), complement activation occurs very rapidly (in minutes) upon reperfusion (60). Thus, the explosive manner in which reperfusion injury manifests itself is opposite to the slow and progressive cell death associated with persistent low-grade ischemia. Although complement activation undoubtedly has beneficial effects on the clearance of damaged cells from the affected tissue, excessive activation may also accelerate tissue damage. In addition to potential directly harmful effects, e.g. induction of necrosis and apoptosis of myocardium by C5b-9 (61), complement activation may also promote tissue damage by indirect mechanisms, i.e. by increasing the expression of adhesion molecules (62-65) and by locally increasing cytokine secretion (63, 66-68). In addition, the complement-derived anaphylatoxin C5a is chemotactic to neutrophils and also activates them to produce oxidative agents (69). Thus, complement activation targets the infiltration of inflammatory cells to the target site. Furthermore, in experimental animals, anaphylatoxins have been shown to induce coronary vasoconstriction by releasing vasoactive mediators (histamine, prostanoids)(70, 71) and thereby to exacerbate cardiac ischemia in the setting of acute myocardial infarction.

Both ischemia and reperfusion cause the deposition of activated complement proteins and C5b-9 in the myocardium (59, 72, 73). As demonstrated in C6-deficient rabbits, the absence of C5b-9 deposition reduces the size of experimental myocardial infarction in rabbits (74). However, inconsistency prevails regarding the pathway of activation in the myocardium during I/R, and the exact mechanisms triggering complement activation are not completely understood. It seems evident, however, that activation of the lectin and alternative pathways is of importance at least in rodents. Thus, it has been shown in the rat that ischemia followed by reoxygenation induces MBL-dependent complement activation on endothelial cells, and that MBL and C3 colocalize *in vivo* in the myocardium following I/R (75). In addition, blocking of the lectin pathway with an antibody against MBL significantly decreases myocardial I/R injury, neutrophil infiltration, and the expression of pro-inflammatory genes (76). Similarly, MBL-deficient mice are protected from cardiac reperfusion injury and sustained cardiac function (77). The lectin pathway has been suggested to become activated when lectin binds to the myocardial neo-antigens that are generated during I/R (75, 76) or, alternatively, by the recognition of natural, self-reactive IgM (78). In addition, the deficiency of factor D, a protease important in the alternative pathway, decreases intestinal I/R injury in mice, suggesting that the alternative pathway also contributes to complement-mediated tissue damage (79). In contrast, C1q-deficient mice were not protected from myocardial I/R injury, suggesting only a minor role for the classical pathway of activation in this setting (77). Although the classical pathway of activation may not play a prominent role in myocardial I/R injury in rodents, it may do so in humans. Indeed, it has been shown that CRP activates complement in infarcted human myocardium (80, 81). One explanation for the observed difference between rodents and man could relate to the fact that, in contrast to human CRP, rodent CRP does not efficiently activate complement. In rats, injection of human CRP into the circulation after coronary ligation significantly increased the size of myocardial infarction in a complement-dependent fashion (81). Of interest, a recent study showed that administration of Bis(PC)-H, a small molecule that blocks the ligand-binding face of CRP, significantly decreased infarct size after coronary occlusion and human CRP administration in rats (82). The experiments using human CRP in rodents should, however, be interpreted with caution, as CRP does not necessarily play a similar role in rodents as in man.

Complement-mediated myocardial injury may also be increased by the relative deficiency of complement regulators in the diseased myocardium. Thus, the expression of protectin (CD59), which is strong in healthy myocardium, is significantly reduced in infarcted myocardium, which in turn allows excessive activation of the complement system in the ischemic areas (59, 83). In

addition, hypoxia of human endothelial cells decreases the expression of the complement regulators MCP, DAF, and CD59 in these cells, making them more susceptible to be attacked by the complement system (84). The protective role of inhibitors is supported by the finding that renal I/R injury is exacerbated in CD59-deficient mice (85).

The above-mentioned studies have provided a basis for therapeutic interventions designed to modulate the activation of the complement system and thus to prevent complement-mediated tissue injury in I/R. In various animal models of experimental I/R injury, complement inhibitors including C1-inhibitor (C1INH), the serine protease inhibitor FUT-175, various forms of soluble complement receptor 1 (sCR1), and antibodies against C5 and C5a have been shown to be protective. In humans, when acute MI was treated with thrombolysis, adjunctive treatment with C1INH, which mainly inhibits the classical and lectin pathway, decreased the release of cardiac enzymes in a small study involving 22 patients (86) whereas pexelizumab, a recombinant humanized single-antibody chain fragment against C5 that blocks generation of C5a and C5b-9, neither affected infarct size nor adverse clinical outcomes in the larger COMPLY trial involving 943 patients (87). When acute MI was treated with primary angioplasty, pexelizumab was found to reduce mortality at 90 days without effects on infarct size or other outcomes in the COMMA trial involving 960 patients (88) whereas pexelizumab did not affect death or other adverse outcomes in the large phase III APEX AMI trial involving 5745 patients (89). Finally, when acute MI was treated with emergency coronary artery bypass graft (CABG) surgery, adjunctive treatment with C1INH limited myocardial injury as measured by cTnI in a small study involving 57 patients (90). In the setting of elective CABG surgery, FUT-175 inhibited inflammation and maximal CK-MBm release in a small study involving 20 patients (91) and TP10, a soluble form of complement receptor 1, reduced the incidence of death or MI at 30 days in male but not female patients in a study involving 564 patients (92). In addition, pexelizumab was shown to limit myocardial injury, cognitive decline and blood loss in a small study with 35 patients (93), decrease a composite endpoint of death or MI in the phase II CABG trial involving 914 patients (94) and decrease a composite endpoint of death or MI in the PRIMO-CABG trial involving 3099 patients (95). However, the effect of pexelizumab on the the primary endpoint, death or MI at 30 days, in the large phase III trial PRIMO-CABG II involving 4254 patients did not reach statistical significance (96). Taken together, complement inhibitors appear to have a beneficial effect on I/R injury but the current drugs have not yet proven effective enough for routine clinical use.

3.4. Heart failure

Complement activation has been suggested to play a role in the pathophysiology of heart failure. Patients with symptomatic heart failure have significantly higher serum C5b-9 concentrations than age-matched controls, and patients with the highest levels of C5b-9 had the highest likelihood of developing severe heart failure and clinical adverse outcomes within 6 months (97). Deposits of C5b-9 on myocardial cells have been observed in the failing but not in the normal human myocardium (98, 99), and the deposition of C5b-9 was similar regardless of whether the cause of cardiac failure was ischemic or non-ischemic (99). Interestingly, after hemodynamic unloading of the heart with a left ventricular assist device support, C5b-9 deposition was decreased to a level equivalent to that in normal myocardium (99). Zwaka and co-workers found that, in the myocardium of patients with dilated cardiomyopathy, C5b-9 staining correlated with IgG deposition as well as tumor necrosis factor-α (TNF-α) expression in myocardium (98). Moreover, in culture of cardiac myocytes, C5b-9 was shown to induce expression of TNF-α, which, again, has been suggested to play a major role in myocardial dysfunction (discussed in (98)).

On the basis of these findings, it appears that antibodies activate the classical complement pathway in failing myocardium. Several autoantibodies have been detected in patients with cardiomyopathy (100-102), and notably, autoantibodies against troponin I, which are released during myocardial injury, are capable of inducing dilated cardiomyopathy in a mouse model (103). Indeed, blocking of complement receptors or depletion of C3 prevented the development of experimental autoimmune myocarditis in the mouse (104). Interestingly, DAF is one important receptor for coxsackievirus B3, a major virus causing human myocarditis and heart failure (105).

4. PERSPECTIVES

Targeted pharmacological inhibition of the complement system is currently under investigation as a potential therapeutic option in various disease processes. These drugs have been widely studied in acute, short-term situations, such as MI or cardiopulmonary bypass. A much more challenging goal is to develop drugs for the treatment of chronic cardiovascular diseases, such as atherosclerosis and heart failure. The ideal inhibitor would prevent complement activation in target tissues without affecting systemic complement activation, which is essential for effective immune defense. One step toward this direction is the development of antagonists of anaphylatoxin receptors. Such antagonists would limit complement-induced inflammation while leaving other complement effector mechanisms intact. Another approach is targeting complement inhibitors to specific tissues with the aid of molecular engineering, like the generation of hybrid molecules of complement inhibitors and antibodies (106) or decoration of complement inhibitors with the oligosaccharide sialyl Lewis^x that targets the inhibitor to activated vascular endothelium (107). Recent discovery of the structure of C3b should aid in the development of novel drugs to control complement activation, especially via the alternative pathway (108). Only therapeutic success accomplished with drugs targeted specifically at the various components of the complement system will provide the ultimate proof needed to establish a significant role for this system in the pathobiology of cardiovascular diseases.

5. ACKNOWLEDGMENTS

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Abbreviations: apoE: apolipoprotein E; C1INH: C1-inhibitor; C4bp: C4b-binding protein; CABG: coronary artery bypass graft; CR1: complement receptor 1; CRP: C-reactive protein; DAF: decay accelerating factor; I/R: ischemia-reperfusion; MAC: membrane attack complex; MASP: mannan-binding lectin-associated serine protease; MBL: mannan-binding lectin; MCP: membrane cofactor protein; MI: myocardial infarction; LDL: low-density lipoprotein; LDLR: LDL receptor; sCR1: soluble complement receptor 1; TNF-α: tumor necrosis factor-α

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Send correspondence to: Dr Petri T. Kovanen, Wihuri Research Institute, Kalliolinnantie 4, FIN-00140 Helsinki, Finland, Tel: 358-9-681411, Fax: 358-9-637476, E-mail: petri.kovanen@wri.fi

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