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Complement activation in obesity, insulin resistance, and type 2 diabetes mellitus

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Abstract

Amplified inflammatory reaction has been observed to be involved in cardiometabolic diseases such as obesity, insulin resistance, diabetes, dyslipidemia, and atherosclerosis. The complement system was originally viewed as a supportive first line of defense against microbial invaders, and research over the past decade has come to appreciate that the functions of the complement system extend beyond the defense and elimination of microbes, involving in such diverse processes as clearance of the immune complexes, complementing T and B cell immune functions, tissue regeneration, and metabolism. The focus of this review is to summarize the role of the activation of complement system and the initiation and progression of metabolic disorders including obesity, insulin resistance and diabetes mellitus. In addition, we briefly describe the interaction of the activation of the complement system with diabetic complications such as diabetic retinopathy, nephropathy and neuropathy, highlighting that targeting complement system therapeutics could be one of possible routes to slow down those aforementioned diabetic complications.

Key words: Inflammation; Complement activation; Metabolic disorders; Obesity; Insulin resistance; Type 2 diabetic mellitus

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Core tip: Inflammatory reaction is involved in cardiometabolic diseases such as obesity, insulin resistance, and diabetes. The complement system, a key component of innate immunity, was viewed as the first line of defense against microbial. Recent research has

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come to appreciate that the complement system is involved in such diverse processes as clearance of the immune complexes, complementing immune functions, tissue regeneration, and metabolism. The review is to update the role of the activation of complement system and the progression of metabolic disorders. We provided a paradigm that targeting complement therapeutics could be one of possible routes to slow down diabetic complications.

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INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is rapidly increasing globally and affects approximately one third of the worldwide population. The etiology of T2DM revolves around obesity and insulin resistance. Metabolic disorders like obesity^[1-4], insulin resistance and diabetes mellitus^[5-8] all possess inflammatory components. Although we are still in the early stage of fully understanding the relationship between inflammation and metabolic diseases, a wealth of data points to the fundamental role of inflammation in the initiation, development and progression of those metabolic disorders^[9]. Activation of pattern recognition receptors (PRRs) that include NOD-like receptors (NLRs) and Toll-like receptors (TLRs) can initiate the immune responses by sensing both endogenous damage-associated molecular patterns (DAMPs) and exogenous pathogen-associated molecular patterns (PAMPs). Obesity-associated PAMPs and DAMPs have been revealed to trigger the NF- κ B pro-inflammation pathway, and are associated with NLRP3 inflammasome activation in adipose tissue^[10,11]. Several studies have revealed that metabolic inflammatory signaling can transcriptionally and post-transcriptionally interfere with insulin action and modulate metabolic pathways that promote insulin resistance^[12,13]. The complement system is a central component of innate immunity and contributes substantially to homeostasis by eliminating infectious microbes, cellular debris, complementing immunological and inflammatory processes, and sending “danger” signals. The complement system was originally regarded as a supportive first line of defense against microbial invaders; however, research over the past decade has come to realize that the functions of the complement system extend far beyond the defense and elimination of microbes, partaking in such diverse processes including the clearance of immune complexes, mobilization of hematopoietic stem-progenitor cells, tissue regeneration, synapse maturation, angiogenesis, and lipid metabolism^[14].

In this review paper we will look into the roles of several key components of the complement system in metabolic disorders and provide an updated overview of the complement system in the pathophysiology and development of obesity, insulin resistance, diabetic mellitus, and diabetes-related complications. In this way, we aim to elucidate the function of the complement system in the pathogenesis of metabolic disorders as well as highlight the complement system as a target for future potential therapeutics.

COMPLEMENT SYSTEM

The complement system, a crucial part of the human innate immune system, comprises of more than 50 soluble protein receptors and regulators in the plasma and cell membrane that act in a highly coordinated way to kill microbes, send danger signals, and expedite the elimination of apoptotic cells without damaging the healthy host cells. The complement system can be activated through PRRs that have evolved to recognize PAMPs and DAMPs, which include specific antibodies, mannan-binding lectin (MBL), ficolins, C-reactive proteins (CRP), C1q, and natural IgM. These PRRs activate three major complement pathways: The classical pathway (CP), the mannose-binding lectin pathway (LP), and the alternative pathway (AP). CP activation is initiated by the association of C1q with immune complexes (IgG or IgM) to form a complex with serine proteases C1r and C1s. The complex cleaves C4, then associates with the cleavage product C4b forming a new complex, which cleaves C2 (into C2a

and C2b) to form the C3 convertase C4bC2b. The LP activation starts by the association of MBL/ficolins/collectin 11 to the mannose residues on microbial surfaces. MBL-associated serine proteases (MASP)-1, MASP-2, and MASP-3 are activated by the binding of MBL to microbial surfaces, which function like C1r and C1s, and cleave C4 and C2 to form the same C3 convertase as that of CP. The AP is distinctive as it is activated without PRRs. Instead, a “tick over” mechanism starts with the spontaneous hydrolysis of C3 into C3_(H₂O), which acts similar to C3b and binds factor B. The AP C3 convertase (C3bBb) is generated through a chain of reactions involving factor D and properdin^[15]. C3 convertase cleaves C3 into C3a and C3b. C3b then binds to the C3 convertase to form C5 convertases (C4bC2bC3b or C3bBbC3b), which cleaves C5 into C5a and C5b. C5b binds C6, C7, C8, and C9 molecules to form the membrane attack complex (MAC), the lytic machinery of the complement system (Figure 1). The complement system is finely tuned by positive and negative regulators, which can avoid a potentially misdirected or excessive activation of the system. However, due to dysfunction of the complement system, this defense system can be inappropriately triggered to attack host cells, which contributes to a broad range of immune, inflammatory, and age-related diseases. For example, when the dysfunction of the complement system occurs in the regulatory proteins, Factor H, the powerful cell-killing property of the complement system can be turned against the host self, causing diseases like atypical Hemolytic uremic syndrome, and paroxysmal nocturnal hemoglobinuria^[14,16-18]. Unrestrained or undue complement activation is now recognized as one of key pathogenic drivers in a wide variety of immune-mediated and inflammatory diseases, including hematological and ageing-related ocular pathologies, cancer, autoimmunity, oral dysbiotic diseases, neuroinflammatory, neurodegenerative, and metabolic disorders^[17].

Complement system and inflammation

Acute and chronic inflammation is a recognized hallmark of many diseases. It has been understood now that the complement system acts as a sensor of pathogens and a contributor in various inflammatory diseases as well, especially those disorders with complement imbalances^[17,18]. Insufficient control or excessive activation of the complement system can cause a malicious cycle between the complement system, inflammatory cells and tissue injury^[16,17]. New findings have revealed an interesting cross-talk between the complement system and the inflammatory network^[14,16,19-21]. During certain diseases and injuries, the complement and coagulation act in a coordinated fashion. Some enzymes of the coagulation system directly cleave and activate complement component C3 and C5; the products by such activation can affect coagulation. It was demonstrated that C5a, C5 activation fragment could stimulate tissue factor^[22-24]. It has been recently recognized that the complement system and TLR, both described as “first line of defense” systems, are cooperated. The cross-talk between complement components CR3, C5aR, CD46, CD55, and gC1qR and TLR, CD14, and MyD88 of TLR system has been revealed to be important for antimicrobial defense but also contributes to inflammatory diseases^[25-27]. It has been well described that the complement system essentially contributes to autoimmune and other diseases by the maturation and stimulation of B cells *via* CD21^[28]. By directly acting on T cells or antigen presenting cells (APC), the complement system can modulate different phases of T cell immunity. Locally generated C3a and C5a stimulate a shift toward Th1 immunity by enhancing T cell proliferation and cytokine release on APC. In addition, complement regulator protein, CD46 was recognized as a key regulatory player in the IL-2-dependent conversion of Th1 cells^[29,30]. C5aR and CD46 signaling were revealed to be associated with the function of $\gamma\delta$ T cells^[31,32]. Conversely, the interaction of T cells and APC induces the enhanced secretion of C3, C5, Factor B, and Factor D with the down-regulation of CD55, which causes complement activation on immune cells. In addition, stimulation of C5aR promotes the expression of activated Fc γ R, by binding to autoantibodies to induce the local secretion of C5, hence activating the C5a/C5aR signaling pathway, revealing a positive feedback loop in cooperation of complement with Fc γ R to remove immune complexes^[33]. Recent study discovered that high-galactose immune complexes associated with inhibitory Fc γ RIIB and lectin receptor dectin-1 could induce a signaling pathway that counteracts C5aR signaling pathway^[34]. Studies have also shown that C1q is involved in age-related inflammation and tissue injury *via* upregulating the Wnt pathway that enhances age-related fibrotic muscle changes in mice skeletal muscle^[35]. Lastly, the complement system has been demonstrated to regulate the functions of NKT and NK cells^[36], myeloid-derived suppressor cells^[37] and mast cells^[38]. All these discoveries highlight the crucial functions of the complement system in the inflammatory network and indicate that dysregulation of the complement system may result in substantial clinical consequences by shifting the functions of T, B, and APC immune cells.

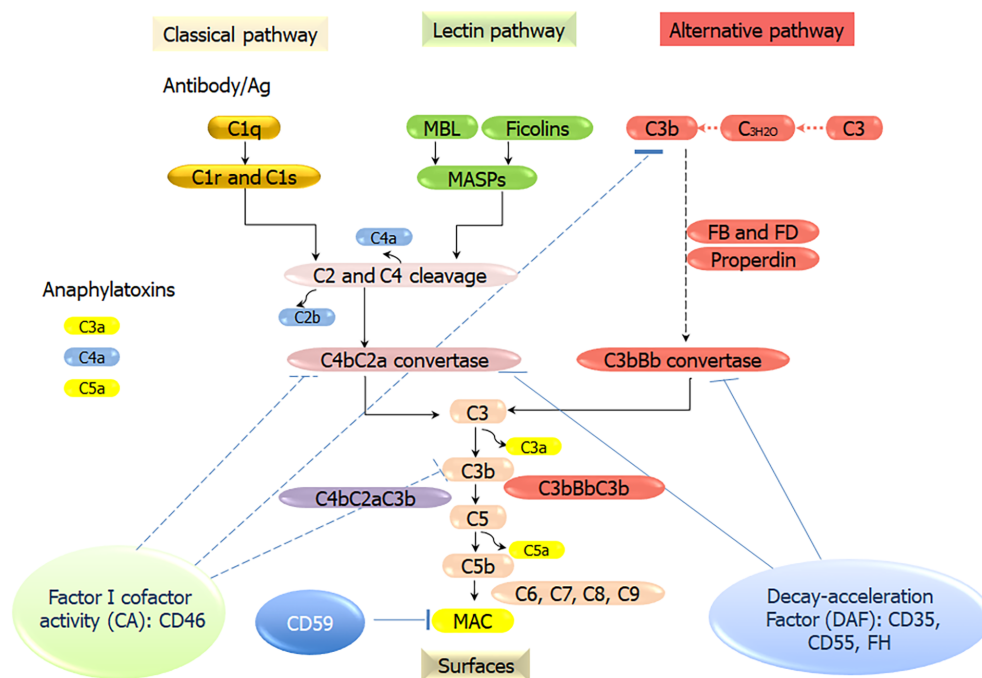


Figure 1 Overview of the activation and regulation of the complement pathways. Three different recognition and activation pathways, including classical pathway (CP), lectin pathway (LP), and alternative pathway (AP). The CP is triggered by the formation of antigen-antibody immune complexes that bind to the C1 complex (C1q, C1r2, C1s2). The LP is activated by the binding of mannan-binding lectin (MBL), ficolins, or collectin 11 to carbohydrates/mannan/other pathogen-associated molecular patterns. MBL-associated serine proteases (MASP)-1, MASP-2, and MASP-3 are activated. Serine protease C1s/C1r (CP) or MASPs (LP) sequentially cleave C4 and C2 to form C3 convertase C4bC2a. The AP C3 convertase (C3bBb) is generated through a chain of reactions involving factor B, factor D and properdin. C3b then binds with the C3 convertase to form C5 convertases (C4bC2aC3b or C3bBbC3b), which cleaves C5 into C5a and C5b. C5b binds C6, C7, C8, and C9 molecules to form the membrane attack complex (MAC), the lytic machinery of the complement system. MBL: Mannan-binding lectin-associated serine proteases; FB: Factor B; FD: Factor D; MAC: Membrane attack complex.

COMPLEMENT ACTIVATION IN METABOLIC DISORDERS

Complement activation in obesity

Many complement components can influence the biology of adipose tissue. T2MD arises from the setting of inflammation and is especially targeted in obesity-related adipose tissue, particularly in white adipose tissue (WAT), which is also the site of numerous substances involved in pro-inflammatory pathways^[39]. WAT secretes active cytokines such as TNF α , CRP, interleukins, plasminogen activator/inhibitor, fibrinogen, monocyte chemoattractant protein-1 and the anti-inflammatory factor adiponectin. Obesity induces adipocytes to go through hypertrophy and hyperplasia and gets invaded by macrophages and other immune cells^[40]. This leads to a shift leaning towards the production of more pro-inflammatory than anti-inflammatory adipokines that results in chronic, low-grade inflammation^[41]. Adipocytes are a primary source of human factor D, which plays an important role in the activation of alternative complement pathway. Adipsin, the mouse homolog of factor D, is essential for the differentiation of pre-adipocytes, revealing that the function of the complement system is far beyond the defense against microbial intruders. Further studies demonstrated that components from alternative complement pathways, C3, Factor B, properdin, Factor H, and Factor I are expressed in adipose tissue, emphasizing the hypothesis that local complement activation can substantially affect adipose tissue biology. In an aged population, complement C3 has been described as a strong marker of insulin resistance^[42]. New studies have shown that adipose tissue can activate the alternative complement pathway in T2DM, which exhibits characteristic of the low-grade inflammation^[43,44]. Increased C3 levels are associated with inflammation *via* cross-talk with TLR4 action of enhancing the production of pro-inflammatory cytokines *via* C3aR and C5aR signaling pathways^[45,46]. Additionally, significantly increased levels of other complement components C3 and Factor D were found significantly in obese individuals as well^[43,47,48]. The expression of complement in adipocyte can be used as a proxy measure of adipose tissue insulin resistance^[49]. C3adesArg, identical to serum-derived acylation stimulating factor (ASF) has an important role in adipose tissue biology^[50]. C3adesArg enhances adipocyte triglyceride synthesis, and increases plasma triglyceride levels, which are expected to be part of the causes in increasing insulin resistance and leading to the development

of metabolic syndromes^[51]. Reduced glucose tolerance and delayed postprandial triglyceride and non-esterified fatty acids clearance were reported in both C3- and Factor B-deficient mice as compared with wild-type mice on low-fat and high-fat diets^[52]. Moreover, increased plasma levels of C3adesArg are also observed in obese individuals and patients suffering from type II diabetes^[14,53]. Furthermore, receptors for C3a (C3aR) and C5a (C5aR1 and C5aR2) have been documented to be expressed in adipocytes^[49]. Thus, adipose, in addition to producing complement components, is a potential target of complement action as well. Upon high-fat diet feeding, C3aR expression is increased in WAT. Both macrophage and adipose tissue within WAT express significant amount of C3aR. C3aR^{-/-} mice on high fat diet transiently resist diet-induced obesity during 8-wk period compared with wild type mice. Improvement in glucose tolerance and insulin resistance are revealed in C3aR^{-/-} mice. Furthermore, macrophage from C3^{-/-} mice were polarized to the M1 phenotype, which demonstrated a considerable decrease in pro-inflammatory functions. Obesity-associated PAMPs and DAMPs have also been shown to activate nucleotide-binding domain and leucine-rich repeat-containing (NLR) protein NLRP3 inflammasome in adipose tissue^[54]. In summary, the effects of complement components ASP, Factor B, C3a, C5a, and of their receptors in adipose tissue play essential roles in adipose tissue biology as well as the development of metabolic disorder.

Complement activation in insulin resistance

Insulin resistance is linked with elevated circulating complement factor C3 level, which involves the terminal and alternative complement pathways. Accumulating evidence revealed that anaphylatoxin C3a interaction with its receptor C3aR plays a role in metabolic disorders such as diabetes, obesity, and atherosclerosis. Animal studies revealed that improper complement stimulation exacerbates high-fat-diet-induced insulin resistance. C3 is particularly studied in insulin resistance due to its cleavage product, C3adesArg, also known as ASP, which has insulin-like properties by stimulating the uptake of glucose and the synthesis of triglycerides in adipose tissue^[55]. The development of insulin resistance can be further explained by understanding ASP resistance in adipose tissue. Obesity-induced adipose tissue activates the alternative complement pathway, thereby creating C3adesArg, among other factors. This leads to a pro-inflammatory state due to an influx of pro-inflammatory biomarkers leading to ASP resistance, which contributes to the development of insulin resistance^[55]. Another explanation could be that activated macrophages from adipose tissue, which can produce pro-inflammatory cytokines, like IL-6 and TNF- α , which can inhibit the insulin receptor functions and thereby induce insulin resistance^[56]. The increased levels of C3 production from adipocytes also leads to increased macrophage infiltration into adipose tissue, thereby exacerbating insulin resistance^[57]. Additionally, it was found that C1q in the CP could cause adipocyte apoptosis, which in turn leads to the infiltration of macrophages into adipose tissue and causes insulin resistance^[58,59]. Clearly the components from complement system, especially complement C3, play crucial roles in causing insulin resistance. Thus, inhibition of the C1 and/or C3 complement activation and/or its regulators could be potential therapeutics for insulin resistance.

Complement activation in diabetic mellitus

The role of complement activation in diabetes mellitus has not been fully investigated. Some components of the complement system are thought to be involved in both Type I and II diabetes mellitus. Nevertheless, accumulating experimental and clinical evidence demonstrates a connection between the activation of the complement system and the pathogenesis of diabetic mellitus^[60-63]. Pro-inflammatory cytokines IL-6 and IL-1 enhance complement C3 production from the liver^[64,65]. The C3 gene is also observed highly expressed in adipose tissue^[66]. Pro-inflammatory cytokines generated in adipose tissue, an organ with endocrine functions, have been associated with insulin resistance and impaired glucose uptake^[67-69]. Systemic low-grade inflammation with the actions cytokines might explain the connection between C3 and the incidence of diabetes. Another possible link between C3 and diabetes could be due to C3adesArg or ASP, the proteolytic fragment of C3, which is a paracrine metabolic factor that can stimulate glucose uptake and lipid storage in adipose tissue^[70,71]. ASP insufficiency was linked to the reduction of body weight in mice^[72], and the correlation of high ASP levels and insulin resistance was observed in nondiabetic subjects^[43,73]. However, C3-knockout mice have shown only modest alterations in insulin function and glucose metabolism, suggesting the activation of the C3-ASP system might function differentially in human and mice^[74]. Complement C3 also provides a key link between inflammation and thrombosis in diabetes. It was reported that complement C3 interacts with fibrin leading to prolonged fibrinolysis in patients with T1DM and T2DM^[75,76]. Another study has found that levels of C4 and C3 are both increased in

patients with diabetes^[77]. Complement C4 has been less studied in metabolic disorders. Nevertheless, accumulated data suggested that C4 plays a role in T1DM^[78-80]. TLR4 can interact with free fatty acids or free acid carrier (fetuoin-A) to trigger the NF- κ B pro-inflammation pathway in cells, which promotes adipose tissue inflammation and insulin resistance in diet-induced obesity^[81,82]. Recent study demonstrated that C3a can increase insulin secretion^[83]. To confirm this result, the study used complement factor D knockout mice which responded poorly to glucose tolerance due to a defect in insulin production^[84]. In the same population, the authors of the study restored serum factor D levels, which increased plasma insulin levels, then additionally reversed this *via* treatment with a C3aR antagonist. Such findings allow for the conclusion that factor D is involved in the alternative complement pathway activation and C3a signaling, ultimately allowing for insulin secretion^[84]. CD59 is a known complement inhibitor, but recent studies have shown a specialized function involving the secretion of insulin in β cells^[84,85]. Specifically, CD59 seems to play a role in maintaining lipid raft stability in β cells to maintain basal insulin release rates. In addition, CD59 facilitates recycling of exocytotic core proteins to allow for the secretion of insulin granules^[85]. Collectively, the components in the complement system, such as, C3, C4, factor D, and CD59 were shown to be involved in the pathogenesis of diabetic mellitus. Regulation of the activation of complement system might slow the pathological process of diabetes mellitus.

Complement in diabetic complications

The pathophysiology of T2DM occurs in the setting of baseline and/or excessive chronic inflammation, contributing to the progression of diabetes. Emerging evidence has shown that complement-mediated chronic inflammation is linked to diabetic microvascular complications. In T2DM patients, the end product of complement activation, sC5b-9 and the MASP-2 were elevated. Such an environment contributes to endothelial dysfunction and reactive oxidative species production that plays a major role in the pathophysiology of diabetic complications. High concentration of complement C3 is reported to be connected to the increased risk of diabetic retinopathy, nephropathy, and neuropathy^[86]. A study by Fujita *et al.*^[87] revealed the possible connection between complement activation, inflammation, and the development of atherosclerosis in diabetic conditions. Obesity-induced adipocytes overproduce C3desArg (ASP) from C3 and factor B. In this case, C3 is converted to C3a and C3b in the process C3 “tick over” AP. Then C3a is converted into C3desArg (ASP), which plays a role in insulin resistance as well as chronic inflammation. C3b goes through the terminal pathway and generates the MAC, which contributes to the formation of atheroma. The continuous activation of the complement AP in T2DM with obesity and dyslipidemia significantly contributes to microvascular complications^[87]. This study suggests that significantly increased plasma ASP/C3a levels in severe microangiopathy may cause to the acceleration of such complications. Another recent study showed that a high concentration of complement C3 was associated with an increased risk of diabetic complications, such as retinopathy, nephropathy and neuropathy^[86,88]. The complement system and inflammation are closely interconnected. Studies have shown that key complement proteins (such as C3, C4, MBL and Factor D) are correlated with a known marker of inflammation, like CRP^[60,61,89]. Adipocytokines released from obesity-activated adipocytes induce the production of pro-inflammatory cytokines, causing the dysfunction of vascular endothelial cells and organ damage. After analyzing the relationship between complement-mediated inflammation and diabetic microangiopathy in obese T2DM patients *vs* normal individuals, plasma levels of C3, C4, iC3b, C3desArg (ASP), Factor B, and Bb were found to be significantly increased in T2DM patients. Furthermore, the level of complement components and their activation intermediates in plasma was tested with respect to the level of complication of the disease. The results of study revealed that the early phase of the alternative complement pathway was excessively activated, suggesting complement-mediated inflammation may contribute to the acceleration of diabetic microangiopathy. A statistical study revealed a close correlation between C3desArg (ASP), highly sensitive CRP, and body mass index. In the macroalbuminuric and proliferative retinopathy patient groups, plasma C3desArg (ASP) was significantly elevated. Diabetic retinopathy complement activation occurs in choriocapillaries of those with diabetic retinopathy. It was found in the eyes of patients with diabetic retinopathy with intense positive staining for MAC deposits, C3d and C5b-9^[90,91]. Additionally, there was a reduction of CD55 and CD59 which are inhibitors of the complement pathway in the vessels of those with diabetic retinopathy^[92]. Such findings may point to the activation of the AP in diabetic retinopathy^[91]. The enhanced expression of C3 mRNA and protein in the glomeruli was positively correlated with the disease status of diabetic kidneys^[93]. The increased levels of the complement components (such as C1q, MBL, MASP-2, factor B, C3 and

C5b-9) were found in diabetic nephropathy in rat, suggesting that the complement system is involved in aggravating the pathophysiology of this disease^[94]. Specifically, most of these factors were found in the renal tubules, suggesting that complement also plays a role in tubular injury, not just in glomerular damage in diabetic nephropathy^[94]. MAC was increased in diabetic patients' blood vessels as well as their kidneys. MAC insertion into cell membranes and into the glomerular mesangium will activate several intracellular signaling pathways leading to the production of reactive oxygen species^[62,95-97]. Several other downstream effects of the insertion of MAC include cell proliferation and thrombosis formation. MAC can upregulate fibroblast growth factor and platelet-derived growth factor in glomerular mesangium causing the proliferation of mesangial cell, upregulation of TGF- β , MCP-1 and activation of collagen IV. Moreover, pro-inflammatory molecules such as P-selectin, vascular cell molecule 1, and E-selectin leak out through the MAC complex^[98]. These effects of MAC could further explain the pathogenesis of diabetic nephropathy. Normally, MAC is inhibited by membrane proteins including Decay-acceleration factor (DAF) and CD59. Thus the decreased level of DAF or CD59 could result in increased level of MAC in diabetics. In the hyperglycemic state, the glycation of CD59 would increase the activation of MAC and then increase the release of the downstream effects of MAC, which contributes to the development of atherosclerosis and diabetic nephropathy^[62,96]. Complement activation has been reported to cause nerve damage in peripheral neuropathies^[99]. A recent study demonstrated that a single missense mutation of the CD59 gene, which results in the deficiency of the complement regulatory protein CD59 on the cell surface, causes chronic peripheral neuropathy in children^[100]. It is also reported that there were activated complement proteins and MAC neoantigen are found in sural nerve biopsies from individuals with diabetes^[101]. Moreover, the co-localization of MAC and CD59 was observed in the same nerve biopsies analyzed in that study^[95]. In summary, the activation of the complement system is clearly involved in the diabetic complications, including nephropathy, retinopathy and neuropathy.

PERSPECTIVES AND THERAPEUTICS

Recent studies have revealed the functional link between immune and metabolic systems, which are two central pillars of survival pathways evolved from common ancestors. Human complement system is a global mediator of our innate immune system. It is recently understood that the complement system not only contributes substantially to homeostasis by eliminating infectious microbes, and cellular debris, complementing immunological and inflammatory processes and immune surveillance, but also contributes to various immune, inflammatory-related diseases. Undoubtedly, complement system may not be the chief driving force in these conditions, but it may still be a vital factor that can tip the scales between the initiation and resolution of inflammatory processes. It has been receiving increasing attention that the complement system plays a major regulatory role in metabolism and metabolic disorders. Accumulating evidence suggests that metabolic disorders like diabetes, obesity, insulin resistance, and atherosclerosis possess important inflammatory components. In [Table 1](#), we highlight those functions of some key complement components in obesity, insulin resistance, and diabetes mellitus ([Table 1](#)). In the past few years there is increasing attention in the development of therapeutic modulators of the complement system^[17]. Such therapy should modify the complement system to sufficiently and precisely control the aberrant levels while allowing for the beneficial players to continue contributing to immune surveillance^[91]. Some drugs are in clinical use for diseases other than metabolic diseases or diabetic complications. Given the strong etiologic components of the complement system activation, those medications might be worth to be evaluated for their ability to slow or halt the progression of metabolic disorders or related complications. Future studies are warranted to test the efficacy of long-term inhibition of activation of the complement system in the context of progression of T2DM and its related complications.

Table 1 The roles of complement proteins in obesity, insulin resistance, diabetes

Complement protein	Obesity	Insulin resistance	Diabetes
C3	Increases adipose tissue inflammation ^[45,46] ; Highly expressed in adipose tissue ^[70,71]	Marker of insulin resistance ^[42]	Proinflammatory cytokine causing systemic low-grade inflammation, insulin resistance and impaired glucose uptake ^[67-69] ; Link between inflammation and thrombosis ^[75,76] ; Higher concentrations associated with increased risk of diabetic complications ^[86]
C3a and C3aR	Increased levels of C3 in obese individuals ^[43,47,48] ; Increased C3aR in white adipose tissue ^[49]	Improved glucose tolerance and insulin resistance in C3aR ^{-/-} mice ^[54,55,84]	Proinflammatory cytokine enhanced by cross-talk with TLR4 and C3 ^[45,46] ; C3a augments insulin secretion from mouse pancreatic beta cells ^[83]
C3adesArg (ASP)	Increased levels found in obese individuals ^[14,53] ; Obesity induced adipose tissue creates this product leading to a pro-inflammatory state and ASP resistance ^[53]	Insulin-like properties by stimulating uptake of glucose and synthesis of triglycerides in adipose tissue ^[55]	Stimulating glucose uptake and lipid storage in adipose tissue ^[70,71] ; Plays a role in chronic inflammation and contribute to microvascular complications ^[87]
C5a and C5aR	Expressed in adipocytes ^[49] ; Play role in adipose tissue biology and development of metabolic disorders		Affect coagulation and contribute to inflammation ^[22-27]
Factor I and H	Increased in adipose tissue, activated by complement activation and affecting adipose tissue biology ^[41,42]		
sC5b-9 and MASP-2			Elevated in T2DM; Contributing to endothelial dysfunction and ROS production in diabetes pathophysiology ^[62,95-97] ; MASP-2 contributes to complications of diabetes ^[94]
CD 59 and MAC			Decreased levels of CD 59 in diabetics ^[62] ; Increased levels of MAC found in diabetic patients and contributes to pathophysiology of complications ^[62,95-97]

MAC: Membrane attack complex; ROS: Reactive oxygen species; MASP: Mannan-binding lectin-associated serine proteases; ASP: Acylation stimulating factor; T2DM: Type 2 diabetes mellitus; TLR: Toll-like receptors.

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