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The role of the complement system in metabolic organs and metabolic diseases

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Abstract

Emerging evidence points to a close crosstalk between metabolic organs and innate immunity in the course of metabolic disorders. In particular, cellular and humoral factors of innate immunity are thought to contribute to metabolic dysregulation of the adipose tissue or the liver, as well as to dysfunction of the pancreas; all these conditions are linked to the development of insulin resistance and diabetes mellitus. A central component of innate immunity is the complement system. Interestingly, the classical view of complement as a major system of host defense that copes with infections is changing to that of a multi-functional player in tissue homeostasis, degeneration, and regeneration. In the present review, we will discuss the link between complement and metabolic organs, focusing on the pancreas, adipose tissue, and liver and the diverse effects of complement system on metabolic disorders.

Keywords

Complement; Insulin resistance; Pancreas; Diabetes; Adipose tissue; Liver; Steatosis

1) Introduction: The crosstalk between the immune system and metabolism

Emerging evidence the recent years, points to an important crosstalk between the innate and adaptive immune systems and metabolic disease. Immune cells and inflammation are not only an epiphenomenon of the dysfunction of metabolic and endocrine organs. Immune cells (e.g., macrophages and T cells), cytokines (e.g., TNF and IL-6) and further factors such as the inflammasome system all contribute directly and significantly to the metabolic

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dysfunction seen in insulin target organs, such as adipose tissue (AT), or in the liver in the course of obesity. In fact, the obesity-associated chronic low-grade inflammation seen in the AT and the liver is unequivocally linked to the development of non-alcoholic fatty liver disease, insulin resistance and type 2 diabetes mellitus (T2DM), and their associated cardiovascular complications. On the other hand, the inflammation in the pancreatic islets, including (but not limited to) the presence of macrophages and IL-1 β -dependent reactions, contributes directly to the islet dysfunction in the course of T2DM pathogenesis. Specifically, pancreatic islet inflammation is thought to be directly associated with apoptosis in the islets. All the aforementioned pathogenetic links between inflammation and metabolic diseases are supported by promising clinical studies that show a benefit for immunomodulatory agents, such as antagonists of IL-1 or salicylates in T2DM [1–9].

Several components of the immune response have been implicated in the crosstalk between the immune system and metabolism. A prominent example is the interaction between toll-like receptor (TLR)-4 and lipid metabolism, based on the interaction of TLR-4 with free fatty acids, either directly or via the free fatty acid carrier, fetuin-A, which triggers NF κ B activation and pro-inflammatory pathways in immune cells [10, 11]. The TLR-4 / free fatty acid interaction promotes AT inflammation and insulin resistance in diet-induced obesity [10,11].

A major component of human innate immunity is the complement system. The best-studied function of this humoral system, which consists of a cascade of proteases and soluble factors, is in innate immunity and microbial killing. However, for more than a decade now, the complement system has been implicated in a multitude of processes in the course of development, degeneration, and regeneration [12–15]. The complement cascade can be activated through three different pathways: the classical, alternative and lectin pathways. The classical pathway is initiated by the activation of the C1 complex by antigen-antibody complexes recognized by the complement component C1q. The lectin pathway shares similarities to the classical pathway; however, its starting point is the recognition of mannose residues on pathogen surfaces by mannose binding lectin (MBL) and ficolin. Both the classical and lectin pathways then continue with activation of C4 and C2, into C4a and C4b and C2a and C2b, respectively. C4b and C2b form the C3 convertase, resulting in the cleavage of C3 into C3a and C3b. Together with C4bC2b, C3b then forms the C5 convertase. The C3 and C5 conversions are the central reactions in complement activation. C3b is involved in opsonization and phagocytosis, in part via an interaction with the multi-ligand receptor complement receptor-3 (or Mac-1- integrin); C3a and C5a are anaphylatoxins with very potent chemoattractant activity that amplify leukocyte recruitment to the inflamed tissue; the fast conversion of C5a *in vivo* leads to C5aDesArg, which may also drive local inflammation [16]. C5b, together with C6–C9, forms the terminal “membrane attack complex” (MAC), which is capable of lysing pathogens. When the alternative pathway occurs on microbial surfaces, spontaneous hydrolysis of C3 into C3(H₂O) enables the association of factor B (fB), which is then cleaved by factor D (fD) to Ba and Bb. The alternative pathway C3 convertase is stabilized by properdin and can function to activate C3 associated with the surface of pathogens or cells [17–20]. The protection of host from complement activation is conferred by expression of complement regulatory proteins, such as C1 esterase inhibitor, decay accelerating factor (DAF), factor H (fH), CR1, CD46, CD59, factor I (fI), and vitronectin, whereas carboxypeptidases serve to degrade anaphylatoxins into their less active, desarginated (desArg) forms [12, 14, 21]. Intriguingly, at the site of inflammation or wound healing, host proteases such as neutrophil elastase or the hemostatic factors kallikrein or thrombin, can directly cleave C3 and C5, thereby triggering complement activation and anaphylatoxin release without activation of the whole cascade [13, 22–24]; thus, they make the complement system a central player in

most thrombo-inflammatory responses and in many homeostatic or pathological processes in the tissue.

The role of complement in metabolism and metabolic disorders has come into the foreground recently and has received increasing scientific attention. The present review will discuss the role of the complement system in the course of metabolic disease, with a special focus on the pancreas/islets and the insulin target organs, AT and liver.

2) The role of complement in physiology and pathology of the pancreas

The pancreas is an organ with a major regulatory role in metabolism, since it is the source of insulin and other hormones regulating glucose homeostasis. The β -cells of the pancreatic islets produce and secrete insulin upon glucose stimulation. Interestingly, the complement degradation product, acylation stimulating protein (ASP), can stimulate glucose-dependent insulin secretion from islets [25]. In contrast, complement fH, which is produced remotely by the liver and also locally in the pancreas, is thought to suppress insulin secretion of β -cells in a rather indirect manner [26].

In T2DM, the dysfunction (i.e., impaired insulin secretion), apoptosis, and loss of β -cells with long-term hyperglycemia [27, 28] involves pro-inflammatory signaling, including local cytokine release and an accumulation of activated macrophages [29, 30]. A further hallmark of the islets in type 2 diabetic patients is the ectopic accumulation of extracellular amyloid fibrils, which is partially mediated by excess free fatty acids (FFA) and exerts cytotoxic effects on β -cells [31, 32]. Intriguingly, amyloid fibrils can trigger local complement activation via C1q [33, 34], thereby facilitating local inflammation and macrophage activation, ultimately promoting β -cell death. Nevertheless, immunohistology studies have shown that there is limited MAC deposition on the islets that colocalizes with amyloid polypeptide fibrils [34]. This limited MAC deposition could be attributed to the fact that amyloid fibrils interact with C4BP and fH, which inhibit complement activation [34]. Thus, amyloid fibrils may also limit complement activity in the islets. These data highlight the ambivalent role of complement factors in the pancreatic islets and their failure in the course of T2DM.

In type 1 diabetes mellitus (T1DM), β -cell destruction is the result of an autoimmune reaction against insulin or islet antigens [35–39]. Interestingly, non-obese diabetic (NOD) mice, which are a model for T1DM, lack C5 because of a 2-base pair deletion in the coding region [40]. *In vitro*, treatment of a rat pancreatic β -cell line with serum from newly diagnosed T1DM patients inhibited their capacity for insulin secretion [41, 42], a phenomenon that was dependent on C1q and C3, since depletion of these complement components reversed the inhibitory effect of the serum of T1DM patients [41]. Furthermore, complement activation, as assessed by the presence of MAC in the serum, was higher in newly diagnosed patients with T1DM than in control individuals, whereas conditioned medium of isolated rat islet cells treated with sera from T1DM patients displayed increased terminal complement activation when compared to medium from cells treated with control serum [41, 43]. These observations have led to a hypothesis that islet apoptosis in T1DM may be partially mediated by complement activation [41, 43, 44].

A recent study demonstrated plasma C3 levels to be higher in patients with T1DM than in healthy individuals [45]. Interestingly, the higher C3 levels in T1DM patients were correlated with prolonged clot lysis, which may be the result of an interaction between C3 and fibrin [45]. Also, the levels of MBL, a major player in the lectin pathway, are elevated in patients with T1DM [46, 47]. These observations were recently confirmed in mice with streptozotocin-induced T1DM [48]. However, the exact role of MBL in the development of

autoimmune insulinitis is not entirely clear, although MBL does contribute to diabetic vascular [49, 50] and renal [48, 51] complications.

Whole-genome transcript analysis of pancreata from patients with T1DM show gene-upregulation for both effector and regulatory/inhibitory components of the complement system [52]. Upregulation of C3 and fB has been confirmed in the pancreata of mice with multiple low-dose streptozotocin-induced diabetes, a model for insulinitis and T1DM [53]. Remarkably, C3-deficient mice and mice with hematopoietic cell-specific C3 deficiency are protected from development of insulinitis and diabetes [53].

An inhibitory role for complement in the development of insulinitis may be exerted by the complement receptor of the immunoglobulin superfamily (CRIg) [54]. CRIg is expressed on tissue-resident macrophages and has been implicated in the phagocytosis of complement-deposited pathogens/cells, suppression of complement activation, and as a regulator of T-cell activation (reviewed in [55]). Interestingly, CRIg expression is negatively correlated with diabetes development in NOD mice [54], whereas injection of a CRIg-Fc chimeric protein in NOD mice reduces the development of diabetes [54]. Whether the protective effect of CRIg+ macrophages on diabetes is a result of their capacity for limiting T-cell proliferation or their activity in promoting phagocytosis needs to be elucidated in further studies.

3) The role of complement in adipose tissue biology

AT biology can be influenced by a variety of complement components. Adipocytes are a major source of adipsin, which is identical to the murine factor D [56, 57] that participates in alternative complement activation, as described above in section one. Interestingly, adipsin contributes to the maturation of preadipocytes into adipocytes [56, 58], suggesting that this complement component has functions over and above its role in innate immunity. Subsequent studies have demonstrated the presence of further components of the alternative pathway, including C3, fB, properdin, fH, and fI, in the AT [57, 59, 60], providing a basis for the hypothesis that local complement activation can influence AT biology.

An interesting role as a regulator of AT biology has been attributed to the C3- degradation product C3a^{desArg} [61], which is identical to the serum-derived ASP [61, 62]. ASP and C3 levels are higher in young obese children [63]. C3 and ASP production can be increased by chylomicrons and insulin [64–66], suggesting that ASP production can be stimulated postprandially. Moreover, murine plasma ASP levels show a positive correlation with plasma levels of FFA and cholesterol [67]. In contrast, no differences have been observed in fasting or postprandial ASP levels in patients with familial combined hyperlipidemia when compared to normal controls [68].

ASP stimulates lipogenesis in adipocytes in a synergistic fashion with insulin through diverse mechanisms, including increased glucose uptake and utilization via enhanced surface translocation of glucose transporters (Glut1, 3 and 4); as well as stimulation of triglyceride (TG) synthesis via elevated diacylglycerol acyltransferase activity [69, 70]. ASP also acts in an anti-lipolytic fashion, inhibiting the release of FFA derived from lipolysis and stimulating the re-esterification of FFA [71]. Thus, ASP promotes enhanced lipid storage in adipocytes. C3-deficient mice and fB-deficient mice (both lacking ASP) display glucose intolerance, delayed TG and FFA clearance, and a rather anti-adipogenic phenotype with decreased TG storage [67, 72]. However, ASP is not the only factor altered in C3- and fB-deficient mice; thus the degree to which the metabolic changes seen in these mice are attributable solely to the absence of ASP is not entirely clear. Furthermore, in C3 deficiency, an increased lipid uptake in the liver and muscle, with increased fatty acid oxidation in these organs, is accompanied by decreased lipid uptake in white and brown AT [73] and reduced

leptin levels [72]. However, in another study, no differences were found in the fasting levels of TG, cholesterol, or free fatty acid in C3-deficient mice, as compared to wildtype mice [74]. In addition, the clearance of TG and FFA in response to oral fat loading was not affected by C3 deficiency [74]. These discrepancies in the metabolic phenotype of C3 deficiency can possibly be attributed to the different genetic backgrounds of the mice used in the various studies. Furthermore, ASP administration in C3 deficient mice on a high fat diet increased AT inflammation and insulin resistance [75]. Thus, the metabolic functions and the inflammatory actions of C3 and ASP may both contribute to the role these factors play in obese AT dysfunction and insulin resistance development. Thus, the exact role of ASP and C3 in lipid metabolism and insulin resistance is not entirely clear and requires further studies.

The functional receptor through which ASP signals has not been clearly elucidated [76–79]. C5L2 has been postulated to act as a receptor for ASP [78, 79]. C5L2 is a receptor for anaphylatoxin C5a and its desarginated form C5a^{desArg}; however, whether and to what extent it transmits pro-inflammatory signaling is not settled [76, 77, 80, 81]. The binding of ASP to C5L2 is controversial, given that other reports have not demonstrated a direct interaction between them [76, 77]. Interestingly, C5L2-deficient mice fed a diabetogenic diet display delayed postprandial TG clearance and reduced adipocyte size, as well as higher glucose uptake and lipid deposition in the liver, which are associated with worsened insulin resistance and a rather pro-inflammatory profile [82, 83]. If C5L2 indeed exerts a decoy action for C5a [76, 77], the C5L2 deficiency phenotype could be linked to a higher activity of the C5a-C5aR axis. Indeed the C5a-C5aR axis may promote AT inflammation and insulin resistance [84] (and Phieler et al., unpublished observation). Recent experimental evidence suggests that antagonists of C3aR and C5aR administered to diet-induced obese rats prevent metabolic dysfunction and cause a decrease in body weight [84], which could be ascribed to the effects of C3a and C5a on adipocytes with regard to incorporation of glucose and FFA and inhibition of lipolysis, as well as on macrophages with regard to pro-inflammatory cytokine secretion [84]. These findings are consistent with C5a's effect in shifting macrophages into a pro-inflammatory phenotype [85]. They are also consistent with the improved insulin sensitivity and reduced diet-induced macrophage accumulation in the AT that are seen in mice deficient in the receptor for anaphylatoxin C3a (C3aR) [86, 87]. Finally, another action of anaphylatoxins that requires further attention is the direct influence they are thought to exert on food intake regulation by mediating prostaglandin levels in the central nervous system [88]. In conclusion, the effects of complement components ASP, C3a, C5a, and of their receptors in the AT are highly varied and clearly far from being completely understood.

4) The role of complement in liver homeostasis and fatty liver disease

The liver and hepatocytes represent the main source of plasma complement proteins, including factors of all three activation pathways (classical, lectin, and alternative) as well as fluid-phase regulators. [89–91]. In addition, parenchymal (hepatocytes) and non-parenchymal cells (Kupffer cells, stellate and sinusoidal endothelial cells) express complement receptors C3aR, C5aR, and C5L2, which can also be upregulated by pro-inflammatory factors and under conditions of stress [79, 92, 93]. Many different roles have been suggested for hepatic complement, including induction of acute-phase responses, glucose release, synthesis of pro-inflammatory factors, and clearance of immune complexes (reviewed in [91]); here we will primarily focus on the roles of complement in alcoholic and non-alcoholic fatty liver disease.

Fatty liver disease is the most common liver dysfunction worldwide and is usually divided into alcoholic-, and non-alcoholic-fatty liver disease (NAFLD) [94, 95]. Both conditions are

associated with steatosis and the accumulation of lipids in hepatocytes, which together trigger an inflammatory response that results in progression to steatohepatitis. Steatohepatitis is associated with serious sequelae, including fibrosis, cirrhosis, and even hepatocellular carcinoma [96, 97]. Complement is thought to be a component of the inflammatory response that is linked to both pathologies.

In alcoholic fatty liver disease, excessive ethanol consumption induces an imbalance in lipid metabolism of the liver involving several mechanisms, including increased lipogenesis, reduced lipolysis, reduced AMP-activated protein kinase (AMPK) activity, production of reactive oxygen species (ROS) and pro-inflammatory cytokines, and activation of natural killer (NK) cells [95, 98]. In this context, increased ethanol ingestion in rodents can result in acute and chronic deposition and activation of complement in the liver, including hepatic accumulation of complement factors C1, C3b, C8, and C9 and elevated plasma levels of C3a, accompanied by a reduction in complement inhibitors such as complement receptor 1-related gene/protein-y and CD59 [99–105].

The role of complement in the pathogenesis of alcoholic liver disease has been underscored by studies of mice deficient in complement components. C3-deficient mice have been found to be protected from alcohol-induced steatosis and from microvesicular and macrovesicular hepatic triglyceride accumulation [102, 103]. In addition, C3-deficient mice on an ethanol diet have a decreased expression of lipogenic enzymes, elevated serum and liver adiponectin levels, and a reduced ethanol-mediated induction of serum alanine aminotransferase (ALT) activity [101–103]. Whereas mice deficient in the complement regulatory molecule decay accelerating factor CD55/DAF show enhanced ethanol-induced hepatic steatosis, injury and inflammation, mice deficient in C5 are not protected from steatosis but instead display decreased serum ALT and hepatic inflammation [103]. Thus, C3 and C5 may contribute through different mechanisms to the pathogenesis of alcohol-induced liver disease.

A role for the classical complement pathway in alcoholic liver disease has also been demonstrated, since C1q, C3b, iC3b, and C3c are found to be deposited in the vicinity of apoptotic Kupffer cells in ethanol-fed C1q-proficient but not C1q-deficient mice [104]. Consistently, C1q-deficient mice displayed decreased steatosis and inflammatory markers (TNF and IL-6) after both acute and chronic ethanol treatment [104]. On the other hand, abrogation of the terminal complement cascade in C6-deficient rats leads to a reduced ethanol-induced deposition of other complement factors (C1, C3, C8, and C9) but an increased pro-inflammatory profile, implying a potentially protective role for C6 in alcoholic liver disease progression [100]. It is clear that additional studies about the specific mechanism of each of the complement components are required to fully elucidate the role of complement in the progression of alcohol-induced liver disease.

The role of complement in NAFLD and non-alcoholic steatohepatitis (NASH) is even less well characterized. Patients with NAFLD showed increased C3 deposition and plasma C3 and ASP levels that are correlating with insulin resistance [106–108]. The accumulation of C3 in biopsies of NAFLD patient is associated with higher hepatic mannose-binding lectin and C1q, an enhanced presence of C9 and MAC, as well as higher hepatocyte apoptosis, neutrophil infiltration, and IL-8 and IL-6 expression. All these factors are positively correlated with the degree of steatosis [106]. In addition, patients with a progressive NASH have an elevated expression of the C3 gene in the liver [109]. However, because liver function is decreased in cirrhosis, the serum concentrations of C3 and C4 are reduced in severe cirrhosis [110].

In rodents, Gregoire and colleagues have reported that mice given a high-fat diet showed enhanced hepatic expression of factor D (adipsin), a key component of the alternative

pathway, suggesting a possible role for this complement component in the development of NAFLD [111]. This effect was more pronounced in mice deficient for intercellular adhesion molecule-1 (ICAM-1) [111].

Interestingly, liver expresses C5L2 abundantly [79], and this receptor has been associated *in vitro* [79] and *in vivo* [82, 83] with triglyceride synthesis. C3^{-/-} mice and C5L2-deficient mice on a high-fat diet are prone to develop enhanced hepatic steatosis as a result of increased hepatic triglyceride content, increased lipogenesis-related gene expression, hepatic glucose uptake, and reduced fatty acid oxidation, as determined by hydroxyacyl-Coenzyme A dehydrogenase activity [83, 101, 102]. Together, these findings, suggest a protective role for C3 and C5L2 in the development of hepatic steatosis. In contrast, no significant increase in high-fat diet-induced hepatic triglyceride accumulation has been observed in C3-deficient mice in other studies [103, 112].

The role of complement factor C3 in regulating hepatic steatosis has been reinforced in a different model, partial hepatectomy-induced liver regeneration. Hepatectomy is a procedure associated with transient triglyceride accumulation in the liver as a result of the induction of lipogenic enzymes [113]. However, C3-deficient mice, unlike C3-proficient mice, develop enhanced steatosis after hepatectomy. The effect of C3 deficiency is likely a result of the absence of ASP, as shown by ASP reconstitution experiments [114]. Intriguingly, in addition to regulating steatosis after partial hepatectomy, complement is also linked to the regulation of the subsequent proliferative response. Mice deficient in either C3 or C5 show an increased lethality and decreased regenerative potential after partial hepatectomy [115–117]. Double deficiency in C3 and C5 results in an aggravated phenotype which can be reversed by concomitant administration of C3a and C5a [115, 116]. Further studies have implicated NFκB and STAT-3 activation; IL-4, IL-6, and TNF production; NKT cell recruitment; and activation of the Akt/PI3K/mTOR and ERK pathways in the complement-dependent regulation of liver regeneration [115, 116, 118, 119]. Finally, a role for C5L2 and ASP in liver regeneration has also been suggested, since administration of ASP in C3^{-/-} mice restores adequate liver regeneration [114]. Given the detrimental actions of complement, and especially C3, as proinflammatory molecules in hepatic ischemia-reperfusion injury [120], a delicate balance must exist between complement-mediated injury and regeneration [114]. In particular, C3 deficiency or C3 inhibition protects mice from hepatic ischemia-reperfusion injury, even in obesity, which normally exacerbates ischemia/reperfusion injury [112]. However, when ischemia-reperfusion injury is combined with hepatectomy, C3 deficiency results in more severe hepatic injury [114].

Taking all these data together, despite the role of C3 in promoting alcohol-induced steatosis, the role of complement in diet-induced steatosis is unclear. On the other hand complement seems to counteract the development of hepatic steatosis associated with partial hepatectomy, and to be required for liver regeneration. Future investigations are required to explain these different actions of complement in the liver.

Both alcoholic- and non-alcoholic liver diseases are associated with a higher risk of liver fibrosis. In a study using inbred mouse strains either susceptible or resistant for liver fibrosis [121], a deletion in the locus encoding C5 in chromosome 2 was found to be responsible for conferring resistance to hepatotoxin-induced fibrosis. Susceptibility to fibrosis could be reconstituted in a fibrosis-resistant strain by introducing a wildtype C5 gene. On the other hand, fibrosis in a susceptible mouse strain was blocked by C5aR antagonists. These results have been confirmed in humans by showing that C5 haplotypes are correlated with the degree of liver fibrosis in chronic hepatitis C-infected patients [121]. However, in another study, no correlation was found between variants and polymorphisms of C5 and chronic hepatitis C-induced hepatic fibrosis or other chronic liver disorders [122].

5) Conclusion

Increasing evidence points to multiple functions of the complement system beyond pathogen killing. Interestingly, the effects of complement seem to be context- and organ-dependent. Here we have focused on the role of complement in metabolic organs such as pancreas, AT, and the liver in metabolic diseases (Fig. 1). Complement components C3 and C5 and their derivatives C3a, C3a^{desArg} (ASP), and C5a are central players influencing the physiology and pathology of these metabolic organs. Basal levels of complement activation have rather beneficial metabolic effects, ranging from stimulation of insulin secretion in pancreatic β -cells (ASP, fH) [25, 26] to insulin-like actions with regard to adipocyte maturation and energy regulation (adipsin, ASP, C3a, C5a) [56, 69, 70, 84]. In contrast, increased complement action can contribute to metabolic pathology. In the pancreas, complement activation can contribute to β -cell apoptosis in T1DM [41, 43, 44, 53] and T2DM [33, 34]. In obesity, anaphylatoxins promote leukocyte recruitment to the AT, thereby facilitating inflammation and the associated insulin resistance [83, 84, 86].

Interestingly, the complement system contributes to both liver homeostasis and disease. Depending on the context, complement factors act in either a beneficial or detrimental manner. Exacerbated complement activation can aggravate the course of liver ischemia/reperfusion injury [114]. The effects of complement activation during alcoholic liver disease and NAFLD are highly diverse. For instance, while C3 inhibition results in reduced steatosis in alcoholic liver disease [102, 103], it did not change or rather enhanced the steatosis associated with high-fat diet [101, 102, 112] and liver regeneration [114]. Similarly, C5 inhibition, on the one hand, compromises liver regeneration [115, 116], whereas it prevents alcoholic ingestion-mediated inflammation [103] as well as hepatotoxin-induced fibrosis [121].

Complement's ubiquitous presence throughout the body's tissues and its diverse activation mechanisms render this system a versatile player not only in host defense but also in complex metabolic and regenerative functions. Deepening our understanding of the divergent actions of the complement system may result in novel, promising treatment alternatives for a multitude of diseases, including metabolic disorders.

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Highlights

- Complement plays a major role in metabolic organs and in metabolic diseases
- Complement components affect insulin secretion and adipocyte maturation
- Complement contributes to the pathogenesis of T1DM and T2DM
- Complement regulates liver inflammation and steatosis

Fig. 1. The role of complement in obesity-related metabolic disorders

A) During obesity, increased plasma and tissue concentrations of free fatty acids (FFA), glucose (Glc), insulin, and chylomicrons are found. These factors can promote complement activation, resulting in the production of elevated levels of anaphylotoxins C3a and C5a as well as C3adesArg (ASP), both locally and systemically. B) By the binding of C3a and C5a to their respective receptors C3aR and C5aR, complement components could promote triglyceride (TG) formation through the inhibition of lipolysis, enhanced Glc and FFA uptake, and indirect reduction in FFA release. In addition, C5L2 has been shown to promote lipid incorporation into TG via diglyceride acyltransferase (DGAT) activation. Adipocytes in the obese AT are able to produce several complement factors, including factor D (adipsin), fP (properdin), factor B, factor H, and C3. C) Anaphylotoxin C3a, and potentially C5a, can promote adipose tissue macrophage (ATM) recruitment, macrophage polarization to a pro-inflammatory phenotype, and secretion of pro-inflammatory factors, contributing to obesity-induced insulin resistance. D) C3a can potentially regulate TG accumulation in hepatocytes and hepatic steatosis. C3 has also been linked to C1q and membrane attack complex (MAC) deposition as well as hepatocyte apoptosis, although the exact mechanisms remain unclear. In addition, hepatocytes can promote neutrophil recruitment via pro-inflammatory factors such as IL-6 and IL-8, as well as complement activation. Furthermore, C5a has been implicated in liver fibrosis development. E) Complement has also been shown to impair food intake and energy expenditure by acting on the central nervous system.