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Review

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 multifunctional 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.

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 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-1beta-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 NFkappaB 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

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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(H_2O) 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 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 insulitis 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 shows 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 insulitis and T1DM [53]. Remarkably, C3-deficient mice and mice with hematopoietic cell-specific C3 deficiency are protected from development of insulitis and diabetes [53].

An inhibitory role for complement in the development of insulitis 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.