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The complement system in human cardiometabolic disease☆

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ABSTRACT

The complement system has been implicated in obesity, fatty liver, diabetes and cardiovascular disease (CVD). Complement factors are produced in adipose tissue and appear to be involved in adipose tissue metabolism and local inflammation. Thereby complement links adipose tissue inflammation to systemic metabolic derangements, such as low-grade inflammation, insulin resistance and dyslipidaemia. Furthermore, complement has been implicated in pathophysiological mechanisms of diet- and alcohol induced liver damage, hyperglycaemia, endothelial dysfunction, atherosclerosis and fibrinolysis.

In this review, we summarize current evidence on the role of the complement system in several processes of human cardiometabolic disease. C3 is the central component in complement activation, and has most widely been studied in humans. C3 concentrations are associated with insulin resistance, liver dysfunction, risk of the metabolic syndrome, type 2 diabetes and CVD. C3 can be activated by the classical, the lectin and the alternative pathway of complement activation; and downstream activation of C3 activates the terminal pathway. Complement may also be activated via extrinsic proteases of the coagulation, fibrinolysis and the kinin systems. Studies on the different complement activation pathways in human cardiometabolic disease are limited, but available evidence suggests that they may have distinct roles in processes underlying cardiometabolic disease. The lectin pathway appeared beneficial in some studies on type 2 diabetes and CVD, while factors of the classical and the alternative pathway were related to unfavourable cardiometabolic traits. The terminal complement pathway was also implicated in insulin resistance and liver disease, and appears to have a prominent role in acute and advanced CVD.

The available human data suggest a complex and potentially causal role for the complement system in human cardiometabolic disease. Further, preferably longitudinal studies are needed to disentangle which aspects of the complement system and complement activation affect the different processes in human cardiometabolic disease.

1. Cardiometabolic disease

Cardiometabolic disease describes a spectrum of interconnected pathobiological alterations in metabolic organs and the cardiovascular system that alone and in concert increase cardiovascular disease burden (Castro et al., 2003; Gill et al., 2005). Our modern lifestyle, with excess energy intake and sedentary behaviour, forms the basis for the current epidemic of overweight and obesity. Central obesity, i.e. the accumulation of fat in and around the abdominal area, is associated with cardiometabolic traits such as dyslipidaemia, insulin resistance, type 2 diabetes (DM2), and ultimately cardiovascular disease (Kaur, 2014).

When adipose tissue depot(s) are enlarged to a size that exceeds a certain critical mass, adipocytes are presumed to be exposed to hypoxia due to adipocyte hypertrophy and decreased capillary density in the expanding adipose tissue (Trayhurn, 2013). Hypoxia itself poses a direct cellular stress signal that can induce inflammatory reactions. Additionally, nutrient excess may overcharge adipocyte metabolism and thereby induce endoplasmic reticulum stress, oxidative stress and mitochondrial dysfunction. These adverse conditions in obesity favour the release of proinflammatory adipokines and induce adipocyte apoptosis and necrosis. Macrophages that are directed towards the dying adipocytes also release proinflammatory mediators (Dali-Youcef et al., 2013). This local adipose tissue inflammation is thought to initiate adipose tissue insulin resistance and to spill over into systemic low-grade inflammation (van Greevenbroek et al., 2013). In addition,

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visceral adipose tissue, which is located around the internal organs, sensitively reacts to stress hormones such as catecholamines and glucocorticoids, leading to lipolysis (Capurso and Capurso, 2012). Central obesity will thus lead to the combined release of free fatty acids (FFAs) and adipocytokines into the hepatic and systemic circulation. This forms the unfavourable concert that can enhance the further metabolic consequences of central obesity.

The liver is directly exposed to diet-derived nutrient excess and to visceral adipose tissue products (Item and Konrad, 2012). Adipokines, FFAs and nutrient overload can impair normal substrate metabolism in the liver and thereby promote hepatic inflammation and hepatic fat accumulation (Fabbrini et al., 2010). Hepatic fat accumulation itself induces hepatocyte dysfunction. Moreover, it can contribute to hepatic insulin resistance via disruption of glucose and lipid metabolism, leading to dyslipidaemia (Yki-Jarvinen, 2010). The liver is a crucial source of many protein species; therefore, production of coagulation, immune and growth factors is also altered in hepatocyte dysfunction. In muscle, lipid overflow from insulin-resistant adipose tissue in combination with a proinflammatory environment and a sedentary lifestyle is thought to cause muscle ectopic fat deposition, which in turn promotes muscle insulin resistance (Turner et al., 2014). These multiple metabolic derangements in the main insulin-sensitive organs constitute a state of systemic insulin-resistance and once established, entail further metabolic and cardiovascular impairments.

Insulin resistance is the impaired capacity of insulin-sensitive organs such as muscle, liver, adipose tissue and the vasculature to respond to a given concentration of insulin (van Greevenbroek et al., 2013). In insulin resistance, predominantly the metabolic insulin signalling pathway is affected (Kaur, 2014). In its early stages, insulin resistance can be counteracted by compensatory hyperinsulinaemia, which aggravates metabolic stress and may facilitate the expansion of fat mass. Progressively, insulin resistance results in increased glucose levels both after food intake and in the fasting state, and further enhances dyslipidaemia in the liver. Glucotoxicity, lipotoxicity and inflammation are thought to promote beta-cell failure, which may lead to the development of DM2 (Kahn et al., 2014).

The multiple metabolic derangements originating from central adiposity also affect the cardiovascular system. Insulin resistance in the microvasculature increases peripheral vascular resistance, favours the development of hypertension and contributes to systemic insulin resistance by blunting insulin-mediated perfusion and nutrient supply in peripheral tissues (Karaca et al., 2014). Inflammation, dyslipidaemia and hyperglycaemia initiate endothelial dysfunction and promote atherosclerosis (Libby, 2012). Impaired regulation of the production of coagulation and fibrinolytic factors by liver and adipose tissue establishes a hypercoagulable, prothrombotic state (Faber et al., 2009). Notably, these cardiometabolic impairments aggravate each other in vicious circles. This explains why a disbalance, once established in either adipose tissue, liver or cardiovascular system, facilitates the development of further cardiometabolic impairments. The clustered occurrence of cardiometabolic risk factors is amongst others reflected in the metabolic syndrome (MetS), which combines central adiposity, dyslipidaemia, hyperglycaemia and hypertension (Kaur, 2014).

Taken together, there is a strong interrelatedness between various obesity-associated cardiometabolic risk factors. Moreover, there is also great interindividual variability in the response to adiposity, as a great part of obese individuals preserves normal glucose tolerance (Phillips, 2013). One biological system that may participate in the unfavourable response to (central) fat accumulation and may contribute to essential pathophysiological mechanisms in cardiometabolic disease is the complement system. The complement system has long-known connections to several features of cardiometabolic disease, and recent discoveries further corroborate these relations. In this review, we will summarize current evidence on the role of the complement system in several processes of adiposity-associated cardiometabolic disease, with particular focus on the available human data.

2. The complement system

The complement system is a complex protein network of the innate immune system. It consists of soluble and membrane-bound proteins functioning in cascades of stepwise protease activation (Ricklin et al., 2010). Complement can be activated by three major pathways, the classical pathway, the lectin pathway and the alternative pathway (Noris and Remuzzi, 2013). Activation of any of the three pathways can lead to the cleavage of C3, and subsequent activation of C5, C6, C7, C8 and C9 of the terminal pathway. C1q and MBL are pattern recognition molecules of the classical and the lectin pathway, respectively; and C1s, C1r, MBL-associated serine proteases (MASP), C2 and C4 further participate in classical and lectin pathway activation of C3 (Degn and Thiel, 2013). The alternative pathway activates C3 spontaneously in combination with Factor B (FB), Factor D (FD) and properdin (Harboe and Mollnes, 2008). Furthermore, activation of C3 and C5 via extrinsic proteases of the coagulation, fibrinolysis and the kinin systems has nowadays been recognized as a fourth complement activation pathway (Oikonomopoulou et al., 2012).

During complement activation, the anaphylatoxins C3a and C5a are released, but also multiple other protein fragments are produced, such as C4d, Bb, C3c and C3d (Klos et al., 2013; Nesargikar et al., 2012). Completion of the terminal pathway results in the formation of membrane-bound and soluble C5b-9 complexes (C5b-9, also known as membrane-attack complex and sC5b-9, respectively) (Tegla et al., 2011). There are multiple complement inhibitors that can regulate the degree of complement activation (Noris and Remuzzi, 2013). C1-Inhibitor (C1-INH) and C4b-binding protein (C4BP) are regulators of the classical and the lectin pathway, while Factor H (FH), factor I (FI) and properdin are regulators of the alternative pathway. Complement can trigger responses via binding of anaphylatoxins to their receptors (C3a-receptor (C3aR), C5a-receptors (C5aR1 and C5aR2)) but also via surface bound fragments that can be recognized by other cellular receptors such as complement receptors (CR) 1-4 (Bohana-Kashtan et al., 2004; Klos et al., 2013). Protein complexes of the terminal pathway insert into cell membranes and thereby induce intracellular signals or disturb membrane integrity, eventually promoting cell lysis (Tegla et al., 2011). Complement is ubiquitously present, and human cells express a variety of complement regulators to protect themselves from complement attack. The body has to maintain a delicate balance between complement activation and inhibition, as unbalanced complement control can result in immune dysregulation and tissue damage (Ricklin and Lambris, 2013). Consequent on its role in multiple processes in various organs, the complement system may contribute to the development and progression of cardiometabolic disease.

3. The complement system in adipose tissue

Adipose tissue is considered a metabolically active immune organ (Makki et al., 2013). It is also a source and a target of many complement factors. Human adipose tissue produces and secretes many factors of the classical, lectin, alternative and terminal pathways (Table 1). In vivo, both adipose and non-adipose cells (such as endothelial cells or macrophages) are likely to contribute to adipose tissue complement production, but studies using isolated adipocytes have shown that at least C1q, C1r, C1s, C2, C3, C4, C6, C7,

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