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An overview of lipodystrophy and the role of the complement system

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ABSTRACT

The complement system is a major component of innate immunity playing essential roles in the destruction of pathogens, the clearance of apoptotic cells and immune complexes, the enhancement of phagocytosis, inflammation, and the modulation of adaptive immune responses. During the last decades, numerous studies have shown that the complement system has key functions in the biology of certain tissues. For example, complement contributes to normal brain and embryonic development and to the homeostasis of lipid metabolism. However, the complement system is subjected to the effective balance between activation-inactivation to maintain complement homeostasis and to prevent self-injury to cells or tissues. When this control is disrupted, serious pathologies eventually develop, such as C3 glomerulopathy, autoimmune conditions and infections. Another heterogeneous group of ultra-rare diseases in which complement abnormalities have been described are the lipodystrophy syndromes. These diseases are characterized by the loss of adipose tissue throughout the entire body or partially. Complement over-activation has been reported in most of the patients with acquired partial lipodystrophy (also called Barraquer-Simons Syndrome) and in some cases of the generalized variety of the disease (Lawrence Syndrome). Even so, the mechanism through which the complement system induces adipose tissue abnormalities remains unclear. This review focuses on describing the link between the complement system and certain forms of lipodystrophy. In addition, we present an overview regarding the clinical presentation, differential diagnosis, classification, and management of patients with lipodystrophy associated with complement abnormalities.

1. Introduction

An essential mechanism in the innate immune response against pathogens is the activation of the complement system, which enhances phagocytosis and inflammation, and allows for the destruction of pathogens through osmotic lysis; it is also involved in removing damaged cells and circulating immune complexes, and in potentiating adaptive immunity (López-Lera et al., 2018). Complement is a complex network of plasma and membrane proteins that perform opposing functions, acting as “activators” or as “regulators” of the whole system. There is constitutive, low-level and harmless complement activation through the so-called Alternative Pathway (AP), which can be fully activated by certain pathogens or cellular surfaces. The initial step consists in the spontaneous hydrolysis of thioester bond present in the C3 molecule, yielding a C3b-like molecule called C3(H_2O) (Merle et al., 2015a). The structural changes that take place in C3 expose an internal domain to interact with factor B (FB), assembling a fluid-phase pre-convertase complex. In the next step, FB is cleaved by a serine protease, factor D (FD), to form the active C3 convertase complex, C3(H_2O)Bb (Hajishengallis et al., 2017; Merle et al., 2015a). Under strict controlled physiological conditions this enzymatic complex is able to cleave small amounts of C3 molecules to C3a and C3b. However, in the presence of a trigger stimulus, such as a pathogen’s surface, this process is amplified and higher amounts of C3b molecules are produced (López-Lera et al., 2018). The nascent C3b molecules interact with FB to generate the AP C3 convertases (C3bBb), which can be further stabilized by the positive

Abbreviations: AP, alternative pathway; CP, classical pathway; LP, lectin pathway; FB, factor B; FD, factor D or adipsin; FH, factor H; C3NeF, C3 nephritic factor; PL, partial lipodystrophy; GL, generalized lipodystrophy; FPLD, familial partial lipodystrophy; CGL, congenital generalized lipodystrophy; APL, acquired partial lipodystrophy; AGL, acquired generalized lipodystrophy; MPGN, membranoproliferative glomerulonephritis; C3G, C3 glomerulopathy; DDD, dense deposit disease; MAC, membrane attack complex; TG, triglycerides; ASP, acylation stimulating protein; PLIN, perilipin; FFA, free fatty acid

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regulator, properdin (Harrison, 2018).

Complement can also be activated through the Classical (CP) or Lectin (LP) pathways, triggering a multistep cascade whose central event is the proteolytic activation of the plasma protein C3, through specific C3 convertases (C4b2a) (Merle et al., 2015a).

The terminal pathway (TP) proceeds until the generation of the C5 convertases (C3bBbC3b in the AP; C4b2aC3b in the CP/LP), which switch substrate specificity from C3 to C5 (Berends et al., 2015). Finally, these convertases cleave C5 into C5b to form the lytic Membrane Attack Complex (MAC or C5b-9) (Berends et al., 2015; Merle et al., 2015a).

The complement system is subjected to the effective balance between activation-inactivation to maintain complement homeostasis and to prevent self-injury to cells or tissues (Wong and Kavanagh, 2018). Although the main role of complement is the defense against pathogens (Merle et al., 2015b), there have been increasing numbers of reports on the potential implications of complement to the biology of human tissues and systems. For example, complement contributes to normal brain development during its early stages, and in particular, the CP plays a key role in the development and refinement of synapses during postnatal development of the central nervous system (Tenner et al., 2018). Interestingly, deficiencies of components of the LP are associated with 3MC syndrome, a group of developmental disorders, which suggest that LP plays a crucial role in development (Matsushita et al., 2013). Other studies have attributed a critical function to the AP in lipid metabolism and adipogenesis (Barbu et al., 2015; Matsunaga et al., 2018; Pattrick et al., 2009; Yasruel et al., 1991).

Defective complement activation can lead to infection and autoimmunity. Alterations in the delicate activation-regulation balance may result in, among others, hematological, renal, neurological, ocular and metabolic diseases (López-Lera et al., 2018). In this review we summarize the role of the complement system in the homeostasis of adipose tissue metabolism and on the severe pathological conditions characterized by loss of adipose tissue, called lipodystrophy.

2. The role of the complement system in adipose tissue biology

Adipose tissue is a connective tissue of mesodermal origin, which is divided into white adipose tissue and brown adipose tissue. White adipose tissue is highly specialized in the storage of energy in the form of fat. Under normal conditions white adipose tissue represents 15–20% of the body weight in men, and between 20–25% of the weight in women. For a long time, adipose tissue has been considered as a metabolically inactive tissue. However, it is now known that adipose tissue controls lipid metabolism through endocrine, paracrine and autocrine signals, which allow it to regulate metabolism in both adipocytes and other cell types of the central nervous system, liver, muscle and pancreas (Choe et al., 2016). In contrast, the main function of brown adipose tissue is the thermogenesis, that is, the production of heat and thermal homeostasis (Choe et al., 2016).

Adipocytes from white adipose tissue are responsible for storing energy in the form of triglycerides (TG) in specialized intracellular organelles, the lipid droplets. When energy is needed, TGs are rapidly hydrolyzed and free fatty acids (FFA) are released from the adipocytes and transported to other tissues (Choe et al., 2016). The brown adipose tissue is formed by adipocytes that contain abundant fat vesicles (multilocular) surrounded by a large number of mitochondria. At the molecular level, these cells are characterized by the high expression of the uncoupling protein UCP-1 (Uncoupling Protein-1), a protein that allows the generation of heat by decoupling the respiratory chain from the production of ATP (Choe et al., 2016).

On the other hand, after the discovery of leptin in 1990 (Zhang et al., 1994), adipose tissue began to be considered as a true endocrine organ. Therefore, nowadays it is known that this tissue is capable of secreting not just leptin, but also a great variety of hormones and cytokines with biological activity, known as adipokines (Bienertova-Vasku et al., 2018; Fasshauer and Blüher, 2015). These molecules act by regulating energy metabolism in other tissues such as liver and muscle, and also play specific functions in processes such as immunity, inflammation and reproduction (Choe et al., 2016; Guilherme et al., 2008; Trayhurn, 2013) (Fig. 1).

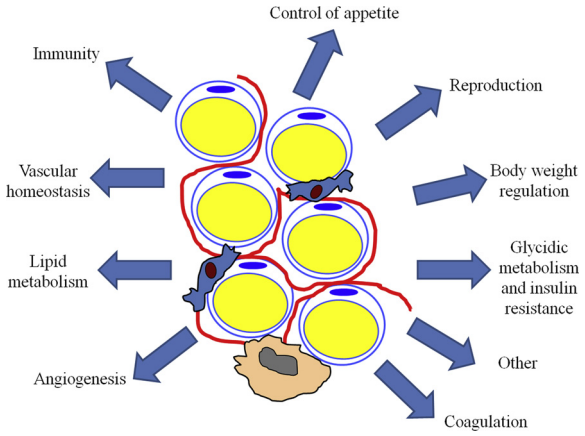

Fig. 1. Main functions of adipose tissue. Adipose tissue contributes to the regulation of several physiological and metabolic processes through the secretion of adipokines. Adipokines act to regulate control of appetite, body weight, reproduction, lipid and glycidic metabolism, insulin sensitivity, vascular homeostasis, angiogenesis and coagulation, and immunological processes, among others.

At the end of the 80 s and the beginning of the 90 s, two separate research lines converged on the fact that the complement system was an important regulator of lipid metabolism in adipose tissue. Dr. Spiegelman's group showed that mouse adipocytes secreted a tissue specific protein that they called adipsin, which had important functions for the development of adipose tissue (Cook et al., 1987; Min and Spiegelman, 1986). Years later, this protein was found to be identical to human FD, which catalyzes the initial and rate-limiting step in AP activation (White et al., 1992). These authors showed that the adipocytes not only synthesized FD, but also synthesized other components of the AP, such as C3 and FB, and the regulators properdin and FH (Choy et al., 1992; Choy and Spiegelman, 1996), all needed for the activation/regulation of complement in the vicinity of the adipocyte (Fig. 2).

Meanwhile, Dr. Cianflone's laboratory was studying a plasma protein called Acylation Stimulating Protein (ASP), which had a potent ability to stimulate TG synthesis and glucose uptake in adipose tissue (Cianflone et al., 1989). After its molecular characterization, ASP was found to be identical to an activation product of the C3 component of complement, C3adesArg, generated when C3a is "inactivated" by the action of carboxypeptidase N (Baldo et al., 1993; Cianflone et al., 1994). Subsequent studies by this group revealed that receptor 2 of the C5a component of complement (C5AR2, or also known as C5L2) was the only one capable of binding ASP and that it was also highly expressed in both pre-adipocytes and mature adipocytes (Kalant et al., 2005, 2003) (Fig. 2). Through this binding, ASP positively modulates the synthesis of TGs by drastically modifying the enzymatic kinetics of diacylglycerol acyltransferase, increasing two-fold its maximum speed (Kalant et al., 2003; Maslowska et al., 2006; Yasruel et al., 1991). Another study showed that ASP has a stimulatory effect in gene/protein expression of perilipin 1 (PLIN1) and perilipin 2 (PLIN2) during adipogenesis, which allows for the synthesis and storage of TGs into lipid droplets (Wu et al., 2011). In addition, experimental data indicate that ASP, as well as insulin, stimulates the transport of glucose into adipocytes. This is achieved due to the translocation of specific glucose transporters (GLUT1 and GLUT4) towards the plasma membrane (Germinario et al., 1993). Together, these findings provide a potential link between complement activation and adipose tissue metabolism (Fig. 2).

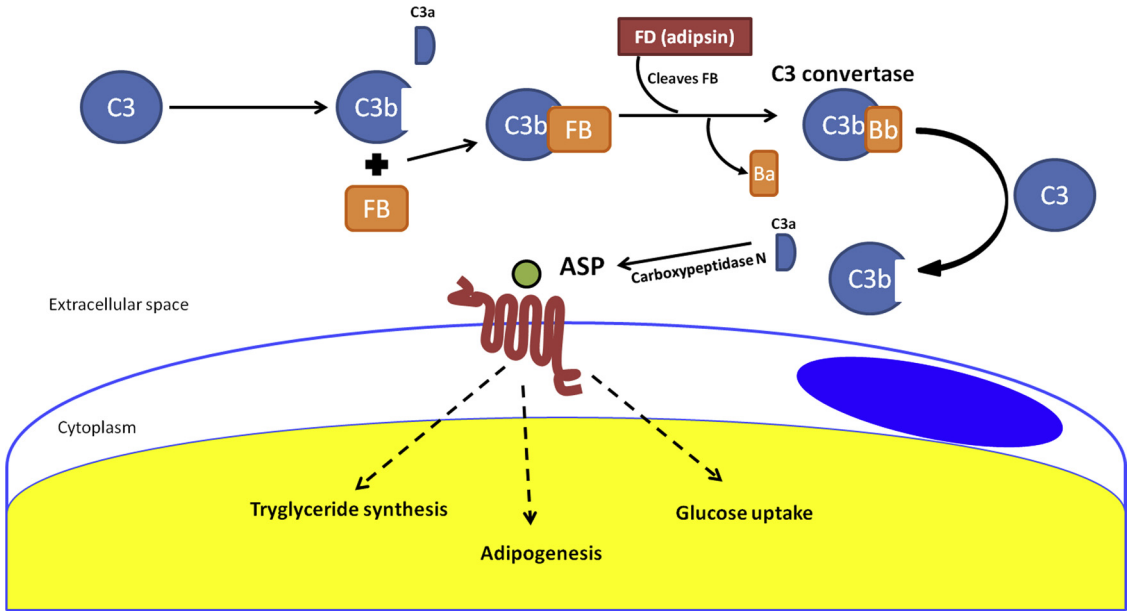

Fig. 2. Role of the complement system in the biology of adipocytes. Adipocytes secrete complement components such as C3, factor B (FB) and factor D (FD, adipsin), which are capable of activating the alternative pathway in its vicinity. The nascent C3a is inactivated by the action of carboxypeptidase N, giving rise to C3adesArg (ASP, Acylation Stimulating Protein). When ASP binds to its receptor, C5AR2, it is capable of stimulating the synthesis of triglycerides during adipose tissue maturation, adipogenesis and glucose uptake.

A large number of reports have demonstrated the correlation between ASP and various metabolic disorders (diabetes, metabolic syndrome, cardiovascular disease, nephrotic syndrome, and polycystic ovary syndrome) in the presence or absence of obesity (Cianflone et al., 2003; Maslowska et al., 1999; Yang et al., 2006; Yu et al., 2006). By contrast, weight loss (in obese people) is accompanied by a substantial decrease in ASP levels (Celik et al., 2013; Cianflone et al., 2005; Fisette et al., 2013; Mishra et al., 2018, 2017; Saleh et al., 2013; Xia and Cianflone, 2003). In animal studies, mice deficient in $C3^{-/-}$, $FB^{-/-}$ or $FD^{-/-}$, compulsorily deficient in ASP, significantly reduce adipose tissue mass, as reflected by weight loss and hypoleptinemia (Cianflone et al., 2003; Coan et al., 2017; Munkonda et al., 2012; Murray et al., 2000; Paglialunga et al., 2010, 2008). In addition, these mice are resistant to diet-induced obesity and develop insulin resistance, compared to wild type mice (Murray et al., 2000). These previously described consequences have also been observed in experiments in which the action of ASP has been blocked by the administration of blocking antibodies against ASP or against its receptor, C5AR2 (Cui et al., 2007; Paglialunga et al., 2010). As a result of adipose tissue dysfunction, the hyperlipidemia that occurs in these conditions is compensated through the ectopic deposit of fat in liver and muscle (Cui et al., 2007; Paglialunga et al., 2010, 2008).

A recent work compared FD levels in novel mouse strains with complete lipodystrophy, the fld mouse with partial lipodystrophy, an FD-deficient mouse (Wu et al., 2018). FD was undetectable in mice with complete lipodystrophy demonstrating that adipose tissue is capable to synthesize almost all of the circulating FD in mice (Wu et al., 2018). Surprisingly, in contrast to these results, Spiegelman and colleagues demonstrated that FD/adipsin mRNA was decreased in genetic and chemical models of obesity (Cook et al., 1987; Flier et al., 1987; Platt et al., 1989). Both observations demonstrate that the synthesis of FD is dependent of the adipose tissue status.

3. Diagnosis and classification of lipodystrophy syndromes

Lipodystrophy refers to a group of rare diseases characterized by a generalized or partial lack of adipose tissue (Akinci et al., 2018a). Adipose tissue dysfunction in lipodystrophy is associated with severe insulin resistance and with severe multisystem metabolic abnormalities such as diabetes, hypertriglyceridemia, and lipid accumulation in the liver (Oral, 2003). Adipose tissue has important metabolic functions in the body. Briefly, the adipose tissue stores energy in the form of triglycerides, and secretes adipokines such as leptin and adiponectin. These adipokines have endocrine and paracrine functions that regulate glucose and lipid metabolism (Akinci et al., 2000; Chan and Oral, 2010). Although lipodystrophy syndromes are rare, pathogenic and phenotype similarities suggest that possible findings from the lipodystrophy model may be applied to common diseases such as metabolic syndrome and type 2 diabetes. Advances in medical research have enhanced our knowledge about the factors involved in the pathogenesis of lipodystrophy which opens the door to a much deeper understanding of common metabolic problems.

The current classification of lipodystrophy is based on clinical and morphometric characterization (Table 1). Traditionally, lipodystrophy has been clinically classified as generalized or partial lipodystrophy, both of which can be genetic or acquired (Araújo-Vilar and Santini, 2019; Brown et al., 2016). There is a rough correlation between the degree of fat loss, and metabolic abnormalities. Lipodystrophy is highly heterogeneous, making diagnosis, classification and accurate assessment of the treatment response challenging. Patients may present with distinctive clinical features even in the presence of pathogenic variants of the same gene (Akinci et al., 2017; Garg et al., 2001). The Lamin A/C (*LMNA*) gene represents one of the best examples of this phenomenon (Montenegro et al., 2018). Thus, genetic testing is important for making the diagnosis as it may lead to the discovery of disease-causing variants in novel genes as well as new pathogenic variants of previously known genes.

Generalized lipodystrophy (GL) is a very rare disease. The genetic defect can be determined in most patients with CGL, which classically includes, but is not limited to, 1-Acylglycerol-3-Phosphate O-Acyltransferase 2 (*AGPAT2*), Berardinelli-Seip congenital lipodystrophy 2 (*BSCL2*), Caveolin 1 (*CAV1*), and Polymerase I and Transcript Release Factor (*PTRF*) (Hussain and Garg, 2016). The age at onset of GL can help distinguish acquired generalized lipodystrophy (AGL). Generalized fat loss is not present at birth but develops later. The presence of an autoimmune condition such as panniculitis, autoimmune hepatitis, type

Table 1
Clinical classification of lipodystrophy.

Generalized Lipodystrophy
Congenital Generalized Lipodystrophy (CGL)
- CGL1 (*AGPAT2*)
- CGL2 (*BSCL2*)
- CGL3 (*CAV1*)
- CGL4 (*PTRF*)
- *LMNA* p.T10I, *LMNA* (Lamin C-specific), *LMNA* (other variants), *PPARG* (Biallelic)
Acquired Generalized Lipodystrophy (AGL)
Partial Lipodystrophy
Familial Partial Lipodystrophy (FPLD)
- FPLD1 (Kobberling)
- FPLD2 (Dunnigan; *LMNA*)
- FPLD3 (*PPARG*)
- FPLD4 (*PLIN1*)
- FPLD5 (*CIDEC*)
- FPLD syndromes associated with lipomatosis
- FPLD6 (*LIPE*), *MFN2*
- Other FPLD Syndromes
- *AKT2*, *ADRA2A*, *CAV1*, *PCYT1A* (Biallelic)
Acquired Partial Lipodystrophy (APL)
Progeroid syndromes
LMNA, ZMPSTE24, POLD1, WRN, FBN1, BANF1, KCNJ6, SPRTN
Other Complex Lipodystrophy Syndromes
PIK3R1, PSMB8, OPA3, AREDYLD
HIV associated lipodystrophy
Local lipodystrophy

ADRA2A: Adrenoceptor α 2A, *AGPAT2*: 1-acylglycerol-3-phophate O-acyltransferase 2, *AKT2*: AKT serine/threonine kinase 2, *BANF1*: Barrier to autointegration factor 1, *BSCL2*: Berardinelli-Seip congenital lipodystrophy type 2, *CAV1*: caveolin 1, *CIDEC*: Cell death inducing DFFA like effector c, *FBN1*: Fibrillin-1, HIV: Human immunodeficiency virus, *KCNJ6*: potassium inwardly-rectifying channel subfamily *J* member 6, *LIPE*: Hormone sensitive type lipase E, *LMNA*: Lamin A/C, *MFN2*: mitofusin 2, *OPA3*: optic atrophy 3, *PCYT1A*: phosphate cytidylyltransferase 1 alpha, *PIK3R1*: Phosphatidylinositol 3-kinase, regulatory subunit 1, *PLIN1*: Perilipin 1, *POLD1*: DNA polymerase delta 1, catalytic subunit, *PPARG*: Peroxisome proliferator-activated receptor gamma, *PSMB8*: Proteasome subunit beta-type 8, *PTRF*: Polymerase I and transcript release factor, *SPRTN*: Spartan, *WRN*: Werner syndrome RecQ like helicase, *ZMPSTE24*: zinc metallopeptidase STE24.

1 diabetes, and low complement C4 levels may help to establish the diagnosis (Misra and Garg, 2003). Partial lipodystrophy (PL) can be inherited (familial partial lipodystrophy, FPLD) or acquired (acquired partial lipodystrophy, APL). FPLD is characterized by partial loss of adipose tissue that primarily affects the lower limbs. An accumulation of subcutaneous adipose tissue can be noted in some parts of the body such as the face and neck and the mons pubis (Ajluni et al., 2017). Several genes such as *LMNA* and Peroxisome Proliferator Activated Receptor Gamma (*PPARG*) have been linked to FPLD (Agarwal and Garg, 2002; Speckman et al., 2000). On the other hand, adipose tissue loss develops later in life in acquired lipodystrophy. Adipose tissue loss follows a cephalocaudal pattern in APL, which first manifests in the face and gradually progresses downwards (from the face, neck, shoulders, arms, and forearms, extending to the thoracic region and upper abdomen), sparing the lower body (Misra et al., 2004). The etiology of acquired lipodystrophy is not well understood but there is a link to autoimmune conditions such as low circulating complement C3 levels, Drusen maculopathy, renal involvement associated with abnormalities of the AP, and systemic autoimmune disorders such as dermatomyositis and systemic lupus erythematosus (SLE) (Akinci et al., 2000).

Previous studies seldom reported metabolic abnormalities in patients with APL (Misra et al., 2004). Our group, however, recently showed that metabolic abnormalities can be detected in most APL patients in long term follow-up (Akinci et al., 2015). More than two third of APL patients registered in the Turkish national registry had at least one metabolic abnormality. APL patients who developed diabetes also had relatively low levels of leptin. A very recent case study by our group also presented several APL patients with severe metabolic abnormalities despite receiving the standard medical treatment (Ozgen Saydam et al., 2019). It is not clear if these patients represent a subcategory of APL with a tendency to develop metabolic abnormalities. These patients had a more advanced fat loss and lower adiponectin levels compared to APL patients with less severe or no metabolic abnormalities. On the other hand, this observation may be a part of the natural history of APL.

The first data sets evaluating the natural history and mortality in different lipodystrophy syndromes are now emerging. Data from rural Brazil suggest that patients with CGL1 and CGL2 have an extremely high mortality rate at an early age, predominantly due to sepsis (especially with CGL2) (Lima et al., 2018). Data from Turkey suggest that patients (predominantly CGL1) also have decreased survival rates, but die more from cardiovascular complications. Diabetes, diabetic complications, acute pancreatitis, liver and kidney-related complications constitute important causes of mortality in both CGL1 and CGL2 (Akinci et al., 2016). Evidence indicates that cardiovascular events are the key complications in FPLD. Unfortunately, no data is available on acquired lipodystrophy, but in our personal experience suggests that autoimmune conditions are one of the principal causes of mortality in this group of patients.

4. The role of the complement system in lipodystrophy

4.1. Acquired partial lipodystrophy (Barraquer-Simons syndrome)

APL was the first lipodystrophy described 135 years ago (Mitchell, 1885). However, the etiology of this syndrome remains obscure. This lipodystrophy is the best documented in terms of the involvement of the complement system. In 1972 Williams et al. reported a single case of a patient with PL in the face and trunk associated with complement consumption and membranoproliferative glomerulonephritis (Williams et al., 1972). One year later, Alper and collaborators demonstrated that the hypocomplementemia observed in patients with APL was due to a factor present in the serum, which enhanced the proteolytic activity of C3 (Alper et al., 1973). Further studies proved that this factor was an IgG and/or IgM, called C3 nephritic factor (C3NeF), an auto-antibody with the capacity to stabilize the assembled AP C3 convertase, previously described in patients with membranoproliferative glomerulonephritis (MPGN) (Daha and van Es, 1979; Davis et al., 1978; Ljunghall et al., 1974; Spitzer et al., 1969; Thompson and White, 1973). A comprehensive study analyzed complement abnormalities in various types of lipodystrophy, proving that most of the patients with PL have hypocomplementemia (Sissons et al., 1976). From 21 patients with PL, 17 had low serum C3, with normal C4 and C2, concentrations, accompanied in 14 by C3NeF (Sissons et al., 1976). Only 7 patients presented with renal disease, of which 6 had biopsy-proven MPGN (Sissons et al., 1976). Therefore, this work established the association between C3 hypocomplementemia, PL and renal disease.

The relation between AP dysregulation, C3NeF and MPGN has been well documented (Noris et al., 2018). Most of the patients with APL developed a type of MPGN called dense deposit disease (DDD, also named MPGN type II) (Corvillo and López-Trascasa, 2018; Misra et al., 2004), although there is one case with IgA nephropathy (de Lucas-Collantes et al., 2016). C3NeF is present in 80% of patients with DDD (Noris et al., 2018). This disease is characterized by an acute deterioration of renal function caused by massive deposition of C3 breakdown products along the glomerular basement membrane (Fakhouri et al., 2010).

Mathieson et al. published the only evidence of complement-mediated lysis of adipocytes (Mathieson et al., 1993). In this work the authors described in vitro experiments that show lysis of adipocytes using the serum of patients with C3NeF (Mathieson et al., 1993). When adipocytes were exposed to the C3NeF-containing serum or purified IgG, a significant increase in lactate dehydrogenase and sC5b-9 occurred (Mathieson et al., 1993). Moreover, adipocyte lysis was reduced when either EDTA, or a monoclonal antibody that blocks the function of FD,

were added (Mathieson et al., 1993). Although this result provides strong support for the mechanism through which complement leads to adipose tissue loss, several questions remain unanswered. C3NeF is not exclusive to patients with APL, and it is involved, and in a greater proportion, in other pathological conditions not associated with lipodystrophy (Levy Erez et al., 2017). Why C3NeF is capable to lysing adipocytes in patients with APL and not in other individuals, could perhaps be explained by some unknown genetic susceptibility. Viral infections are considered to be the main trigger in the onset of APL. The infection could induce the release of IL-1 and TNF-α and these cytokines increase the expression and secretion of C3, FD and FB by adipocytes. The activation of the AP in the vicinity of the adipocytes may be enhanced in the presence of C3NeF, causing the lysis of adipocytes. Also it remains unclear why adipocyte loss in APL is localized to the upper body. Some authors attribute this characteristic pattern to regional differences in the expression of FD by adipocytes (Hussain and Garg, 2016; Lenane and Murphy, 2000; Misra et al., 2004; Oliveira et al., 2016; Small et al., 2016; Vantyghem et al., 2012). However, this assumption has not been proven. In an interesting work, Wu et al. measured FD levels in samples from patients with GL (CGL and AGL) and FPL. This study showed that FD was not detectable in the mouse with complete lipodystrophy, in contrast to the patients with GL, in whom FD levels were reduced but still detected (Wu et al., 2018). This is most likely because the patients with lypodystrophy still have a small amount of adipose tissue as compared with the lipodystrophic mice that were genetically engineered to be completely devoid of adipose tissue. Also, the quantity of FD produced by adipose tissue in patients with GL is sufficient to maintain a correct activity of the AP, which explain that they not have an increased incidence of *Neisseria* infections in contrast with patients with FD deficiency (Wu et al., 2018). However, the authors did not study the existence of regional differences in their expression and, therefore, the role of FD in the developing of the APL remains unanswered.

Finally, complement fragment deposits have not been analyzed in biopsies of patients with APL. A recent work showed that the adipose tissue of a patient with APL was formed by shrunken adipocytes with numerous small lipid droplets detaching from the surface of the adipocytes, suggesting a defect in TG storage (Velter et al., 2018). Although this finding is interesting, the authors did not evaluate the presence of complement activation products in the tissue. Therefore, the association between complement activation and APL remains unexplained and further studies are needed.

4.2. Acquired generalized lipodystrophy (Lawrence syndrome)

The pathogenesis of AGL can be variable, and the exact mechanisms of fat loss remain unknown. In patients with panniculitis and autoimmune varieties, it is suspected that the loss of adipose tissue is immunological in origin (Garg, 2004). The first evidence of autoantibodies against adipocytes was reported in a 33-year-old male patient with AGL, insulin-resistant diabetes mellitus and acanthosis nigricans. The authors demonstrated the presence of IgG deposits around adipocytes using direct immunofluorescence in a subcutaneous biopsy of the patient (Hübler et al., 1998). Patni et al. presented three male patients diagnosed with GL, with subsequent development of pilocytic astrocytoma (Patni et al., 2015). All gained body fat or weight after surgical removal of the tumor and / or chemotherapy. The authors hypothesized that the tumor could give rise to anti-adipocyte antibodies, which could have induced the lysis of adipocytes. With respect to this evidence, it is interesting to note that lymphomas, particularly peripheral T-cell lymphomas, occur in approximately 7% of patients with AGL (Brown et al., 2016). Recently, we have published the description of novel autoantibodies against PLIN1 in a cohort of patients with AGL (Corvillo et al., 2018). These autoantibodies were present in patients with the autoimmune variety of the disease and caused abnormal, significantly elevated basal lipolysis in adipocytes. Our results provide strong support for the conclusion that PLIN1 autoantibodies are a cause of GL in these patients (Corvillo et al., 2018). All these data, as well as the clinical or serological association with various autoimmune diseases, lead to the conclusion that AGL is an autoimmune disease.

Other studies have related complement activation and adipocyte destruction in patients with AGL (Eren et al., 2010; Savage et al., 2009). Savage et al. described three unrelated patients with AGL with evidence of activation of the CP and autoimmune hepatitis (Savage et al., 2009). The three patients showed very low levels of C4, along with, in some cases, elevated circulating immune-complexes and higher MAC production. In addition, during an aggressive immunosuppressive therapy two patients showed C4 levels fluctuation, which normalized in one in response to the treatment (Savage et al., 2009). These results suggest that CP activation, but not genetic deficiency, was a factor in these patients. The authors emphasized the decrease of adiponectin levels, (Savage et al., 2009), an adipokine that has the ability to bind C1q, inducing the CP activation (Wang and Scherer, 2016). The extreme hypoadiponectinemia present in these patients could be consequence of the CP activation in adipose tissue, which could lead to adipocyte destruction in the course of a complement-mediated mechanism (Savage et al., 2009). However, congenital low C4 levels are associated with a higher risk of developing autoimmune diseases (Li et al., 2017). Several reports have associated that null allotypes at either the C4A or C4B locus are more frequent in patients with autoimmune hepatitis and SLE, which explains the low C4 levels in these patients (Boeckler et al., 2005; Constans et al., 1998; Doherty et al., 1994; Lin et al., 1989; Moulds et al., 1993; Munoz et al., 1982; Naves et al., 1998; Scully et al., 1993; Segurado et al., 1992; Senaldi et al., 1989; Sturfelt et al., 1990; Vergani et al., 1985; Vergani and Mieli-Vergani, 1996; Wilson, 1994; Yang et al., 2004b, 2004a). In addition, there are no publications about C4 consumption in patients exclusively affected by AGL (without autoimmune hepatitis), and therefore it is not clear whether this observation is characteristic of lipodystrophy, or rather a consequence of the autoimmune process itself.

4.3. Localized lipodystrophy due to reactions to insulin

Approximately 30% of patients with diabetes are affected by this pathology, characterized by local changes in subcutaneous adipose tissue, either lipohypertrophy or lipoatrophy (Radermecker et al., 2007). Most authors agree that this lipodystrophy is due to some type of allergic reaction to allergens presents in insulin injections (Gentile et al., 2016; Levandoski et al., 1982; Radermecker et al., 2007; Reeves et al., 1980). With the emergence of recombinant human insulin as treatment, hypersensitivity reactions have dramatically decreased and now account for 1–3% of cases (Radermecker et al., 2007).

Complement system deposition has been described in skin biopsies at the sites of insulin injection (Reeves et al., 1980). Although the exact pathogenic mechanism that leads to lipoatrophy remains unknown, there is an immunological theory. The proposed hypothesis is that the anti-insulin antibodies react against insulin-crystals formed on the dermis, which cause complement activation, local inflammation and the necrosis/apoptosis of adipocytes (Radermecker et al., 2007; Reeves et al., 1980).

5. Management of patients with lipodystrophy

In lipodystrophy patients, adipose tissue dysfunction results in metabolic derangements which are fueled by insulin resistance. The body stores fat at ectopic sites such as the liver because of the inability to store energy in the subcutaneous adipose tissue, which leads to the modification of glucose output and an increase in de novo lipogenesis. Altered levels of FFA, dietary and endogenously-synthesized lipids and lipid intermediates in the circulation cause a process called lipotoxicity (Garg and Misra, 2004). Patients with lipodystrophy have reduced levels of the adipokines such as leptin and other adipokines such as

adiponectin. Leptin is an important circulating signal for the regulation of body weight and fuel metabolism. Low levels of leptin contribute to an increased appetite. Patients with lipodystrophy may suffer from complications of diabetes secondary to poor metabolic control, episodes of acute pancreatitis due to severe hypertriglyceridemia, hepatic cirrhosis as a result of steatohepatitis, chronic kidney disease, reproductive problems, and premature cardiovascular disorders (Akinci et al., 2018a).

The development of animal models of lipodystrophy was an important step in lipodystrophy research that led the investigators to explore the fundamental relationship between lipodystrophy and insulin resistance (Savage, 2009). These models have confirmed the importance of adipose tissue in the pathogenesis of the metabolic abnormalities of lipodystrophy (Moitra et al., 1998). A-ZIP mice developed generalized loss of adipose tissue and exhibited many metabolic abnormalities associated with insulin resistance, similar to those observed in humans with severe GL (Reitman and Gavrilova, 2000). Later studies confirmed that, regardless of the strategy used for fat ablation, fatless animals developed severe insulin resistance, hypertriglyceridemia and ectopic lipid accumulation (Savage, 2009).

Several groups successfully treated the metabolic consequences of lipodystrophy in these transgenic mice. Transplanting fat tissue from wild type animals reversed these metabolic derangements, proving in an unequivocal manner, that it was the absence of fat that was responsible for the metabolic problems (Gavrilova et al., 2000). The critical role of leptin as a mediator of the metabolic effects of adipose tissue was demonstrated by Shimomura and colleagues (Shimomura et al., 1999). Replacement of leptin in aP2–SREBP-1c transgenic mice produced dramatic benefits in metabolic parameters, insulin action, and hepatic steatosis. These beneficial effects of leptin were not only a result of leptin's effect on food intake but also of its direct effects on carbohydrate and lipid metabolism (Yamauchi et al., 2001). Supporting these findings, transplantation of fat from the leptin-deficient ob/ob mice was far less effective for metabolic rescue, reinforcing the idea that adipocyte leptin deficiency played a central role in the development of metabolic abnormalities in lipodystrophy (Colombo et al., 2002). Another study showed that insulin resistance in lipoatrophic mice could be completely reversed by the combination of physiological doses of adiponectin and leptin (Yamauchi et al., 2001). However, the fact that full-length adiponectin is a complex molecule that undergoes significant posttranslational modifications, circulates at very high concentrations and has a short plasma half-life limits its potential therapeutic use in humans (Scherer, 2019).

Metreleptin is an analog of human leptin made through recombinant DNA technology. The primary function of leptin is the regulation of appetite through an interaction with specific leptin receptors located in the hypothalamus. Sadaf Farooqi and colleagues (Stephen O'Rahilly's group) reported the treatment with recombinant leptin of a nine-year-old patient with congenital leptin deficiency that had resulted in sustained weight loss, predominantly as a result of fat loss (Farooqi et al., 1999). The principal effect of leptin on energy balance was mediated by its suppressive effects on food intake. Ultimately, an open-label, prospective, phase II study on a small cohort of nine patients who were severely affected with lipodystrophy was started at the NIH (Oral et al., 2002b). The study was designed as a two center, open label, proof of concept study. Eight patients had GL and one patient had FPLD, and all patients had baseline serum leptin level of less than 4 ng/ml. The metabolic effects of metreleptin were observed for several weeks after the treatment. As a result of treatment, a significant decrease in HbA1c was observed (1.9%) in eight of the nine patients who had diabetes. The insulin-tolerance test showed a significant improvement in whole-body sensitivity to insulin. Triglyceride levels decreased by 60%. Liver volume decreased by an average of 28% and levels of the hepatic enzymes ALT and AST declined. Daily caloric intake decreased in parallel with a decrease in the resting metabolic rate. All but one patient lost weight with an important fraction of the weight loss mostly attributed to the decrease in liver volume. When treatment was discontinued, levels of fasting triglyceride and insulin began to increase within 48 h, which was corrected by the resumption of metreleptin therapy. Later studies confirmed that hyperphagia improved shortly after the treatment with metreleptin (Araujo-Vilar et al., 2015). Food-seeking behavior and related neural activity diminished and satiety was restored (McDuffie et al., 2004; Schlögl et al., 2016). Fasting glucose and HbA1c declined as result of improved peripheral glucose disposal and both hepatic glucose output and hepatic steatosis also improved (Chan et al., 2011; Diker-Cohen et al., 2015; Petersen et al., 2002; Safar Zadeh et al., 2013). Although metreleptin dramatically reduced triglycerides, it did not alter HDL cholesterol levels (Akinci et al., 2018b; Ebihara et al., 2007).

Metreleptin also has other well-established benefits. Metreleptin improves proteinuria (Javor et al., 2004; Lee et al., 2019), normalizes gonadotropin secretion (Oral et al., 2002a), and improves fertility (Musso et al., 2005; Reed et al., 2013). Androgen levels decrease after metreleptin in lipodystrophic women with PCOS (Abel et al., 2016; Lungu et al., 2012). Leptin also has immunoregulatory functions which were studied in the earlier cohorts of patients, demonstrating a subtle, baseline defects in T-cell populations and cytokine secretion capability, both of which recovered following leptin replacement (Oral et al., 2006).

Although the primary function of leptin is the regulation of appetite through an interaction with specific leptin receptors located in the hypothalamus, metreleptin also improves insulin sensitivity independently of food intake. In a very recent study, Brown and colleagues studied the effects of metreleptin in patients with lipodystrophy whose food intake was kept constant with a controlled diet in an inpatient metabolic ward setting (Brown et al., 2018). The study showed that metreleptin increased peripheral and hepatic insulin sensitivity, decreased fasting glucose and triglyceride levels, and decreased liver fat content in patients with lipodystrophy independently of food intake.

Leptin deficiency appears to be an important contributor to insulin resistance in lipodystrophy. Ectopic fat accumulation contributes to severe insulin resistance and leads to alterations in hepatic glucose output. Other adipokines, cytokines and hepatokines are likely involved but further studies are needed to determine their roles. The current treatment strategy involves leptin; however, several other approaches are under investigation. Metreleptin was approved by the Food and Drug Administration (FDA) in 2014 for the treatment of GL. It is also approved in Europe and the United Kingdom for patients with GL $>$ 2 years of age and for PL patients $>$ 12 years of age who have not responded to conventional therapies. Two important data sets summarize all of the data available which was also presented to authorities. Although they were not parallel studies and none of them were placebo-controlled or blinded, they basically reflect the efficiency of metreleptin in different settings of lipodystrophy. The effect of metreleptin is robust in GL. Metreleptin therapy results in less dramatic and heterogeneous improvements in patients with PL, although a subset of patients with PL may benefit from metreleptin (Oral et al., 2019). However, these studies include a very limited number of patients with APL. Still, a trial of metreleptin is an option for patients with APL when standard treatments fail to achieve good metabolic control. However, the evidence so far is too scanty to yield a realistic description of those patients with APL who are more likely to respond to metreleptin. Thus, further research is needed to identify the efficacy and safety of long-term metreleptin therapy in patients with APL.

6. Conclusions

During the last decades, numerous studies have shown that the complement system has key functions in the biology of certain tissues. For example, complement contributes to normal brain and embryonic development and to the homeostasis of lipid metabolism. However, the complement system is involved in a wide range of diseases, from

infections and autoimmunity associated with complement deficiencies, to inflammation and tissue damage caused by excessive complement activation. An example of overactivation of the complement system is showed in the autoimmune forms of the lipodystrophy syndromes. The case of APL is the best known, although the link between AP overactivation and adipocytes destruction remain unanswered. The activation of CP (C4 consumption) in patients with AGL is even more unusual and probably its connection may be a consequence and not the cause of the disease. The last evidence of the role of the complement system is in localized lipodystrophy causing by insulin injections. In this disease, insulin crystals formed into dermis cause local inflammation and complement activation. This is the unique case in which lipodystrophy recovered after remove insulin injections.

In lipodystrophy patients, adipose tissue dysfunction results in metabolic derangements, as insulin resistance, fat storage at ectopic sites, dyslipemia and reduced levels of the adipokines such as leptin and adiponectin. Currently, the treatment is not focused in the improvement of complement abnormalities, but in the improvement of metabolic derangements using metreleptin, recombinant human leptin. Under leptin replacement, patients with lipodystrophy regulate the appetite, reduce drastically triglycerides and glucose levels, improve insulin resistance and reduce the liver volume, among others benefits. This therapy has proven to be a success in patients with GL and in a subset of patients with PL.

Conflict of interest

Dr. Akinci has attended Scientific Advisory Board Meetings organized by Aegerion Pharmaceuticals. He has received honoraria as speaker from AstraZeneca, Lilly, MSD, Novartis, Novo Nordisk, Boehringer-Ingelheim, Servier and Sanofi-Aventis.

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