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Review

Acquired partial lipodystrophy and C3 glomerulopathy: Dysregulation of the complement system as a common mechanism☆

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ABSTRACT

The activation of the alternative pathway of the complement is involved in the development of several renal diseases, such as atypical haemolytic uraemic syndrome and C3 glomerulopathy. In C3 glomerulopathy, a high percentage of patients have circulating levels of the autoantibody called C3NeF, which causes systemic dysregulation of the complement system. In some cases, the presence of this antibody has been related with abnormalities of adipose tissue, causing acquired partial lipodystrophy (Barraquer–Simons syndrome). Acquired partial lipodystrophy is an extremely rare disorder affecting the distribution of subcutaneous adipose tissue and that mainly onsets during childhood. These patients, in addition to possibly presenting with all the metabolic disorders associated with the adipose tissue defect, present with C3 hypocomplementemia and C3NeF and 25% have developed C3 glomerulopathy. Although it has been known for some time how the dysregulation of the complement system affects the kidneys, it remains unknown how it exactly affects adipose tissue; nevertheless, the relationship is quite clear. In this paper, we describe the connection between the complement system with the biology of the adipose tissue and its pathogenesis reflected from acquired partial lipodystrophy.

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Lipodistrofia parcial adquirida y glomerulopatía C3: la desregulación del sistema del complemento como mecanismo común

Palabras clave:
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RESUMEN

La activación de la vía alternativa del complemento interviene en el desarrollo de varias enfermedades renales, como el síndrome hemolítico urémico atípico o la glomerulopatía C3. En esta última enfermedad un elevado porcentaje de los pacientes presentan niveles circulantes de un autoanticuerpo denominado C3NeF, causante de la desregulación del complemento a nivel sistémico. En ciertos casos, la presencia de este anticuerpo se asocia con alteraciones en el tejido adiposo, causando lipodistrofia parcial adquirida (síndrome de Barraquer-Simons), una enfermedad ultra-rara que afecta a la distribución del tejido adiposo subcutáneo y que comienza principalmente durante la infancia. Estos pacientes, además de poder presentar los problemas metabólicos asociados al defecto en el tejido adiposo, presentan hipocomplementemia C3 junto con la presencia de C3NeF y, en un 25% de los casos desarrollan una glomerulopatía C3. Aunque se sabe desde hace tiempo cómo la desregulación del sistema del complemento afecta al riñón, se desconoce de forma precisa cómo lo hace en el tejido adiposo; no obstante, su relación está bastante clara. En este artículo se va a describir la relación del sistema del complemento con la biología del tejido adiposo y su patogenia reflejada a partir de la lipodistrofia parcial adquirida.

Introduction

The complement system is a fundamental component of innate immunity playing a crucial role in the defence against infections, elimination of apoptotic cells, processing of immune complexes and modulation of adaptive immunity. The complement is a complex molecular system capable of triggering warning signals in the presence of foreign agents, differentiating between the body's own components and foreign components. Through a molecular tagging system, it is capable of identifying these foreign components to be eliminated by opsonophagocytosis or to destroy them via direct cell lysis. Complement activation takes place through three different activation pathways: the classical pathway, the alternative pathway and the lectin pathway (Fig. 1). These three pathways, closely related phylogenetically, differ in their mechanisms of activation and in the initial activation steps, but all of them converge in the formation of multi-molecular enzymatic complexes responsible for the activation of the C3 component, the C3 convertase.[1]

The classical pathway is activated mainly by the binding of C1q to antigen–antibody complexes, and the activation of the lectin pathway mainly occurs through to the recognition of mannose groups, which are characteristic of bacterial surfaces. Activation of these two pathways results in the generation of a protein complex with enzymatic activity: the C3 convertase of the classical/lectin pathways (C4b2b) capable of activating the C3 molecule, cleaving it into C3a and C3b.

The alternative pathway is constitutively active, due to the spontaneous activation of C3 in plasma through the 'tick-over' mechanism. The activation of C3 generates C3a and C3b fragments; the C3b can be associated with factor B (FB) to form C3 convertase of the alternative pathway (C3bB) in an inactive state. Each C3bB complex is activated through the proteolytic cleavage of FB by factor D (FD), resulting in fragments Ba and Bb. The resulting complex, C3bBb, is capable of amplifying the system by means of positive feedback to generate thousands of C3b molecules in a very short time.[1] The C3bBb convertase is unstable and needs to be stabilised by means of the positive regulator, properdin, which increases the half-life of this multi-molecular complex and serves as a focal point for the local amplification of the complement system.[2] The incorporation of C3b molecule to a C3 convertase results in the formation of C5 convertase. This is capable of cleaving C5, generating C5a, a potent anaphylatoxin, and C5b, which initiate in the cell surface, along with C6, C7, C8 and C9, the generation of the membrane attack complex (C5b9).

The rapid and effective dissociation of the C3bBb complex and the inactivation of C3b is a critical step for the homeostasis of the complement system, and to prevent tissue damage when it is activated. These functions are carried out by a series of soluble regulatory proteins (factor H and factor I) and of membrane regulatory proteins (MCP, DAF, CR1 and CD59) (Fig. 1). The importance of the integrity of this system reveals why the deficiencies of some of its components may lead to situations that can be fatal. Problems also arise due to an inefficient regulation, which may cause indiscriminate activation and generation of circulating fragments or tissue injury.[3]

One of the tissues which is most affected by dysregulation of the complement system is the kidney. The surfaces of the glomerulus are very sensitive to the inflammatory effects caused by complement activation both at a systemic and local level. The two conditions which have most commonly been linked to alterations of the complement system are C3 glomerulopathy (C3G) and atypical haemolytic uraemic syndrome (aHUS). In both cases, mutations have been found in genes of components or regulators of the alternative pathway,