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Complement inhibition in C3 glomerulopathy

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ABSTRACT

C3 glomerulopathy (C3G) describes a spectrum of glomerular diseases defined by shared renal biopsy pathology: a predominance of C3 deposition on immunofluorescence with electron microscopy permitting disease sub-classification. Complement dysregulation underlies the observed pathology, a causal relationship that is supported by well described studies of genetic and acquired drivers of disease. In this article, we provide an overview of the features of C3G, including a discussion of disease definition and a review of the causal role of complement. We discuss molecular markers of disease and how biomarkers are informing our evolving understanding of underlying pathology. Research advances are laying the foundation for complement inhibition as a targeted approach to treatment of C3G.

Contents

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1. Introduction

The term C3 glomerulopathy (C3G) was designated by an expert consensus panel in 2012 to describe a spectrum of diseases with a distinctive renal histology: *predominant* (not isolated) glomerular C3 fragment deposition on immunofluorescence [1]. While this pattern has been reported for several decades, innovation came in the realization that this renal biopsy characteristic represents a set of diseases that shared in common an underlying pathology: abnormal complement activation, deposition, or degradation. This unique pathology distinguishes C3G as one of the five pathogenic subtypes of glomerular disease [2].

Animal models with discrete complement gene abnormalities provide support for complement involvement in C3G. The discovery of both genetic and acquired drivers of complement dysregulation in well-described patients has validated the role of complement in this setting. We provide here an overview of the features of C3G, including a brief discussion of disease definition (both pathology and clinical characteristics) and review the evidence for our understanding of the role of complement. We also discuss the molecular markers of disease, as they relate to our understanding of underlying pathology. Currently, C3G remains a disease without an approved, effective treatment. Our evolving understanding of complement in disease lays the foundation for considering complement inhibition as a targeted approach to treatment.

2. Complement biology

Understanding normal complement biology is essential to understanding the underlying pathology of C3G and the potential role of complement inhibition in this setting. While the complement system is comprised of three interrelated pathways, the *classical pathway*, *lectin pathway* and the *alternative pathway* [3] (Fig. 1), dysregulation of the latter is characteristic of C3G.

The alternative pathway (AP) of complement is unique for several reasons. First, unlike the other pathways, it requires no specific triggering protein and remains continuously active through a process known as *tickover*. The initial AP protein, C3, is activated spontaneously through hydrolysis to form C3(H_20). Tickover is responsible for constant, low-level activation of the AP. It is this feature that underscores the importance of proteins that control and protect self-tissues from perpetual complement activity.

Activated C3 recruits complement factor B (FB) and then factor D (FD). FD cleaves C3(H20) bound FB into Bb, releasing Ba and forming the AP C3 convertase [C3(H_20)Bb], a potent serine protease. This protease facilitates a process known as *amplification,* another unique feature of the AP. As a result of amplification, the convertase exponentially cleaves additional C3 into C3b and C3a, creating more C3 convertase enzymes (C3bBb). The AP functions as the *effector arm* of both the classical and the lectin pathway. Activity initiated from either of these pathways is amplified through the AP.

While the exact structure of the terminal pathway enzyme has recently been called into question [4], the association of additional C3b molecules with the C3 convertase complex creates the terminal pathway enzyme, the C5 convertase (~C3bBbC3b). C5 convertase cleaves C5 into C5b, the first component of the terminal complement complex, and C5a. C5b associates with C6 and C7, with subsequent interaction with C8 inducing the binding of several C9 units to form the lytic complex C5b-C9, also referred to as membrane attack complex. This lytic complex forms the basis of complement-mediated killing of target bacteria. Finally, in addition to the production of the terminal complement complex, the generation of the C3a and C5a anaphylotoxins during complement activation augments the immune role of the AP. Both anaphylotoxins play a central role in complement-mediated inflammation [5,6].

Table 1
AP Complement Control Proteins.

Factor H (FH)	Binds to C3b; inhibits conversion of C3bB to C3bBb; promotes decay of C3bBb; acts as a cofactor for FI
MCP (membrane cofactor protein)	Acts as a cofactor activity for FI-mediated inactivation of C3b
CR1 (complement receptor 1)	Accelerates decay of surface–bound C3 convertase; acts as a cofactor activity for FI-mediated inactivation of C3b
DAF (decay accelerating factor)	Accelerates decay of surface–bound C3 convertases; destabilizes C3/C5 convertases of the AP
Vitronectin	Binds C5b-7 and inhibits C9 polymerization
Clusterin	Binds C5b-7 and inhibits generation of C5b-9
Protectin (CD59)	Binds C8 and C9 in the assembling membrane attack complex and inhibits C5b-9
Thrombomodulin	Enhances FH cofactor activity, activates TAFI-mediated C3a and C5a inactivation
Factor I (FI)	Degrades C3b

A number of complement control proteins have been identified. Those that act to control the activity of the AP (and indirectly the terminal complement pathway) include complement factor H (FH), membrane cofactor protein (MCP), decay accelerating factor (DAF), complement receptor 1 (CR1) and complement factor I (FI). (Table 1.) Complement control is necessary to limit adverse, host cell damage from a continuously active complement system, or from an AP that has been triggered by an innate immune trigger.

The individual proteins and protein breakdown products generated during AP activation may be measured in the laboratory. When complement control is lost, either through a genetic abnormality (i.e. of a complement control or central protein gene) or through the development of an acquired driver of disease, C3 G may result. Evidence suggests that these AP biomarkers inform underlying pathology as well as have the potential to augment the definition of both disease and disease activity [7].

3. Defining C3 glomerulopathy

3.1. A disease definition based on renal pathology

The diagnosis of C3G is based *solely* on renal biopsy findings. While there is burgeoning evidence that both molecular studies and/or complement biomarkers offer greater disease definition, no other specific finding is required for diagnosis. The necessary criterion for diagnosis is a "predominance" of C3 deposition on immune fluorescence staining of the renal biopsy [1]. Prior to assigning this diagnosis, an attempt must be made to rule out a post-infectious glomerulonephritis (PIGN), an acute, self-limited glomerulonephritis that is *often* also marked by a predominance of C3 deposition on renal biopsy. The data supporting a role for chronic complement activation in the setting of PIGN is less convincing – a concept that has significant treatment implications.

The C3 Glomerulopathy Meeting Consensus Statement defined "predominance" as 2 orders of magnitude above other stains [1]. Importantly, what is not required for diagnosis is the *complete absence* of immune globulin deposits. Small amounts of immune globulin, particularly IgM, may be present and do not deter from diagnosis. Interestingly, Hou et al. reported that some degree of fluidity in biopsy findings may be expected when repeat biopsies are performed [8]. They documented in their cohort that it is possible