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Review

Dense deposit disease

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ABSTRACT

Dense deposit disease (DDD) is an orphan disease that primarily affects children and young adults without sexual predilection. Studies of its pathophysiology have shown conclusively that it is caused by fluid-phase dysregulation of the alternative pathway of complement, however the role played by genetics and autoantibodies like C3 nephritic factors must be more thoroughly defined if we are to make an impact in the clinical management of this disease. There are currently no mechanism-directed therapies to offer affected patients, half of whom progress to end stage renal failure disease within 10 years of diagnosis. Transplant recipients face the dim prospect of disease recurrence in their allografts, half of which ultimately fail. More detailed genetic and complement studies of DDD patients may make it possible to identify protective factors prognostic for naïve kidney and transplant survival, or conversely risk factors associated with progression to renal failure and allograft loss. The pathophysiology of DDD suggests that a number of different treatments warrant consideration. As advances are made in these areas, there will be a need to increase healthcare provider awareness of DDD by making resources available to clinicians to optimize care for DDD patients.

1. Introduction

Dense deposit disease is a glomerular pathology characterized by intramembranous electron-dense change within the glomerular basement membrane (GBM). Dense deposit disease (DDD) is associated with deposition of complement C3 within the glomeruli with little or no staining for immunoglobulin. The presence of C3 without significant immunoglobulin suggested to early investigators that DDD was due to abnormal activation of the complement alternative pathway (AP). There is now strong evidence that DDD is caused by uncontrolled AP activation (reviewed in Appel et al., 2005; Smith et al., 2007). DDD was renamed membranoproliferative glomerulonephritis type II (MPGN2), a term that is inappropriate because: (1) it implies a relationship with MPGN1 and MPGN3, which unlike DDD are immune complex diseases; and (2) it implies that the membrano-proliferative pattern of injury is characteristic when in fact it is present in only 25% of DDD patients (Smith et al., 2007; Walker et al., 2007). Mild mesangial cell hypercellularity is most common (45%), but crescentic (18%) and acute proliferative–exudative (12%) patterns of injury also occur (Habib et al., 1975; Walker et al., 2007).

The densities in DDD, which are implicit in its name, appear in the GBM by light microscopy as elongated but brightly eosinophilic, variably refractile deposits. By electron microscopy, they are 'sausage-shaped' homogeneous densities within the lamina densa (Walker et al., 2007). Mass spectrometry on laser micro-dissected glomeruli isolated from paraffin-embedded tissue of DDD cases has confirmed that the diseased glomeruli contain components of the AP and terminal complement complex (TCC), consist with fluid-phase AP dysregulation (Sethi et al., 2009).

We will first summarize the clinical manifestations of DDD. We will then discuss the role of genetic factors and autoantibodies in DDD with particular emphasis on recent advances. Finally we will speculate on treatment strategies that are under development or warrant consideration. Understanding complement biology is a prerequisite for understanding DDD pathophysiology. Therefore we will briefly overview complement biology.

1.1. Complement activation and regulation

The complement system is the cornerstone of innate immunity. As one of the first lines of host defense, it plays a major role in microbial killing, immune complex handling, apoptotic cell clearance, tissue homeostasis and modulation of adaptive immunity (Volonakis and Frank, 1998; Walport, 2001a, 2001b). Critical to these functions is the sequential triggering of a series of cascades

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that result in the formation of metastable protease complexes which can culminate in formation of membrane attack complex (MAC). In the broadest terms, complement activation occurs in five sequential steps the first of which is its initiation by one of three independent pathways – the classical (CP), the lectin (LP) or the alternative (AP). Once activated, the second step is the formation of C3 convertase, which exponentially amplifies the initial triggering pathway (step 3) and provides the protein complex from which C5 convertase is generated (step 4). C5 convertase triggers the TCC with generation of MAC and the potent anaphylatoxin, C5a (step 5).

During complement activation, damage to self surfaces may occur. This is limited *in vivo* by a complex group of proteins that regulate complement activation at many steps in the cascade. These proteins modulate the generation and breakdown of the C3 and C5 convertases both in the circulation ('fluid-phase') and on cell surfaces and extra-cellular membranes ('surface-phase'). Many complement regulatory proteins are also involved in other activities (e.g. cell adhesion and extracellular matrix interactions) (Zipfel and Skerka, 2009). Examples of fluid-phase regulators include: complement factor H (CFH) and complement factor I (CFI), which down regulate the AP; C1 inhibitor (C1INH), which down regulates the CP and LP; and C4 binding protein (C4BP), which down regulates the CP. Fluid-phase regulators of the TCC include clusterin and vitronectin (Preissner and Seiffert, 1998; Schwarz et al., 2008). Relatively recently, complement factor H-related protein 1 has been demonstrated to down regulate C5 activation (Fritsche et al., 2010; Heinen et al., 2009).

Several of these proteins including CFH, CFHL1, C4BP, CFHR1, clusterin and vitronectin also attach to cell surfaces and biomembranes (like the GBM and Bruch's membrane) (Ferreira and Pangburn, 2007; Manuelian et al., 2003; Sanchez-Corral et al., 2004). This attachment adds a protective layer known as the 'surface zone' to limit formation of active complement products (Zipfel and Skerka, 2009). Examples of membrane-bound complement regulators include CR1 (complement receptor 1, CD35), CD55 (decay-accelerating factor, DAF), CD46 (membrane cofactor protein, MCP), CD59 and the complement receptor of the immunoglobulin superfamily (CRIg, also known as VSIG4 (V-set and Ig domain-containing 4)) (He et al., 2008; Isaak et al., 2006; Khera and Das, 2009; Kimberley et al., 2007; Roozendaal and Carroll, 2007; Seya and Atkinson, 1989; Spendlove et al., 2006; Wiesmann et al., 2006). Their expression and distribution vary from cell type to cell type, which has important implications for complement-related diseases. An important distinction between fluid-phase and membrane-bound regulators is that while membrane-bound convertase regulators control the three initiating pathways by inactivating both C3 and C4 (CR1 and CD46, for example), fluid-phase regulators are pathway specific and control the AP, CP or LP by acting exclusively on either C3 or C4 (Zipfel and Skerka, 2009).

To understand the progress that has been made with respect to the pathophysiology of DDD it is important to understand the activation and regulation of the complement AP. Essential to the activation of the AP is cleavage of C3 to C3b, a change that is accompanied by a dramatic rearrangement of the domains of C3b (Gros et al., 2008; Janssen et al., 2005, 2006). For example, migration and rotation of the thioester-containing domain (TED) of C3b exposes the thioester to particles, basement membranes and cell surface, facilitating the attachment of C3b to these sites (Morgan et al., 2011). Complement factor B (CFB) then complexes with C3b to form C3bB, which is cleaved by complement factor D into two factors, Ba and Bb, the latter remaining bound to C3b. C3bBb is the AP C3 convertase and generates additional C3bBb by cleaving C3. This self-propagation results in exponential amplification of the AP, necessitating tight control in the fluid phase and on self-surfaces.

CFH is the key regulator of C3 activation through the AP (Fig. 1A). Several elegant studies have clarified the mechanism of its interaction with C3b and C3 convertase, offering insight into normal complement region and its perturbation in association with disease-related mutations (Janssen et al., 2006; Morgan et al., 2011; Pechtl et al., 2011; Schmidt et al., 2008; Wu et al., 2009). Only the first four domains (also called short consensus repeats (SCRs) or complement control protein domains (CCPs)) of CFH are necessary for fluid-phase AP regulation (Schmidt et al., 2008). These SCRs bind to C3b in an extended configuration that spans multiple domains of C3b including the α′NT, MG1, MG2, MG6, MG7, CUB and TED (Wu et al., 2009). This extensive interface is necessary because binding affinity of CFH for C3b is low. It also provides an explanation for how CFH blocks the interaction of CFB and promotes decay-acceleration activity (DAA) and cofactor activity.

DAA is mediated by SCRs 1 and 2 of CFH. These domains bind α′NT, MG2, MG6 and MG7 of C3b, and probably dissociate Bb from C3b by a combination of electrostatic repulsion and steric hindrance (Wu et al., 2009). Cofactor activity with CFI, another important function of CFH, is facilitated by the shape of CFH, which provides a contact interface for CFI to associate with the CFH–C3b complex by binding to SCRs 1–3 of CFH. CFH also stabilizes C3b so that CFI can sequentially cleave the scissile bonds C3b to produce iC3b and the C3f fragment (Wu et al., 2009).

The complex nature of these interactions make CFH, C3b and C3 convertase prone to functional interference with even small modifications in amino acid sequence, as has been illustrated by variations in AP activity associated with common polymorphisms of CFH and C3 (Abrera-Abeleda et al., in press; Heurich et al., 2011; Tortajada et al., 2009). These studies also provide a basis for understanding how DDD-associated variations and mutations can lead to dysregulation of the C3 convertase and uncontrolled AP activity. In addition, the importance of CFH and CFI in AP regulation is evident from the complement C3 levels seen in these respective deficiency states (reviewed in Botto et al., 2009). In each case, unregulated AP activation results in severe secondary C3 depletion.

2. Clinical manifestations

DDD primarily affects children and young adults without sexual predilection (Lu et al., 2007; Smith et al., 2007). A recent review by Lu et al. of 98 DDD patients reported a median age-at-diagnosis of 14 years. At presentation, 90% of these patients had proteinuria, 84% had hematuria and over 50% were hypertensive (Lu et al., submitted for publication).

DDD patients also develop drusen – electron-dense deposits in the retina between the collagenous layer of Bruch's membrane and the retinal pigmented epithelial cells – which carries a ∼10% risk for long-term visual problems (Chadha and Wright, 2009; Ritter et al., 2010). In some patients (less than 5% of cases in our series), DDD is seen with acquired partial lipodystrophy (APL), a disease characterized by the loss of fat from the face, extending to involve the neck, shoulders, arms, forearms and thorax. Renal disease can either precede or follow the loss of fat (Appel et al., 2005; Smith et al., 2007).

Although few families report multiple affected persons, which is consistent with DDD being a complex disease, it is striking that in 16% of DDD families there is at least one family member with type 1 diabetes (T1D) (Lu et al., submitted for publication). This occurrence is far greater than expected based on the 1.4:1000 familial prevalence of T1D in the general US population as reported by the Centers for Disease Control (2008) (Lu et al., submitted for publication).

Once diagnosed, DDD interminably progresses to end-stage renal failure (ESRF) with a mean renal survival time of 10.24 years (Lu et al., submitted for publication). ESRF is the more likely outcome if DDD is diagnosed in childhood, and of children, females have a more aggressive disease course. Transplantation is asso-