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Review

The alternative pathway of complement and the thrombotic microangiopathies

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ABSTRACT

Thrombotic microangiopathies (TMA) are disorders defined by microangiopathic hemolytic anemia, non-immune thrombocytopenia and have multi-organ involvement including the kidneys, brain, gastrointestinal, respiratory tract and skin. Emerging evidence points to the central role of complement dysregulation in leading to microvascular endothelial injury which is crucial for the development of TMAs. This key insight has led to the development of complement-targeted therapy. Eculizumab is an anti-C5 monoclonal antibody, which has revolutionized the treatment of atypical hemolytic uremic syndrome. Several other anti-complement therapeutic agents are currently in development, offering a potential armamentarium of therapies available to treat complement-mediated TMAs. The development of sensitive, reliable and easy to perform assays to monitor complement activity and therapeutic efficacy will be key to devising an individualized treatment regime with the potential of safely weaning or discontinuing treatment in the appropriate clinical setting.

Contents

1. Thrombotic microangiopathy – a spectrum of complement-mediated disorders

Thrombotic microangiopathies (TMAs) are defined by their common clinical feature: microangiopathic hemolytic anemia, non-immune thrombocytopenia, and organ injury [1–3]. They are systemic conditions with the potential of multi-organ involvement, including the kidneys, brain, gastrointestinal tract,

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respiratory tract and skin; and they affect both children and adults. Crucial to the development of TMA is injury to the microvascular endothelium: endothelial cell injury and activation leads to platelet and neutrophil recruitment, which eventually leads to thrombus formation, inflammation and subsequent organ failure [1,4,5].

Classically, TMA was categorized into two clinically distinct, but pathologically indistinguishable entities, depending on whether lesions in the brain or kidneys prevail: thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). TTP was first described in a 16-year old girl with an acute febrile illness with anemia, petechiae, paralysis and coma by Moschowitz in 1923. Autopsy revealed hyaline thrombi in terminal arterioles and capillaries throughout most organs including the kidneys [6]. It is now known to be due to the deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), a protease that cleaves von Willebrand factor (vWF) multimers upon shear stress-induced conformational change and endothelial cell release [7,8]. On the other hand, HUS was initially described in 5 children with the clinical triad of hemolytic anemia, thrombocytopenia, and acute renal failure by Gasser et al. in 1955 [9]. The form of HUS associated with Shiga toxin-producing (enterohemorrhagic) *Escherichia coli* represents the main cause of TMA in childhood (90% of all HUS cases) [10,11]. Later, the term atypical HUS (aHUS) was used to refer to all non-EHEC-associated HUS patients who usually had recurrent disease associated with a more severe clinical course and poorer outcomes. Subsequently, complement genetic mutations leading to complement dysregulation were found in patients with aHUS. Secondary TMAs that occur after trigger events such as pregnancy and transplantation were not initially thought to involve complement dysregulation. However, underlying complement genetic mutations are now increasingly recognized to occur in patients with secondary TMAs.

The historical nomenclature of TMAs (i.e. TTP, HUS and aHUS) is problematic as it emphasizes distinct differences in the individual pathogenesis of disease, which today is conflicting with the notion of shared pathogenetic mechanisms. These insights are critical as they identify new therapeutic targets within the various disease entities. Recent evidence demonstrates the central role of complement dysregulation in the pathogenesis of TMAs (Fig. 1): conditions leading to TMA can serve as triggers on the background of a complement regulatory defect or serve to activate complement on their own (Fig. 1) [10].

The objective of this review is to provide an overview of the role of complement in the evolving classification of a new spectrum of complement-mediated TMAs.

2. Complement activation and regulation

The complement system is part of the innate immune system, which has several physiological functions: 1) initiates and mediates the inflammatory reaction, 2) targeting and removing invading microbes by phagocytosis (opsonization), and 3) microbial killing with formation of the membrane attack complex [12]. It consists of 3 main pathways of activation: the mannose-binding lectin (MBL), the classical (CP) and the alternative pathways (AP) (Fig. 2). Upon

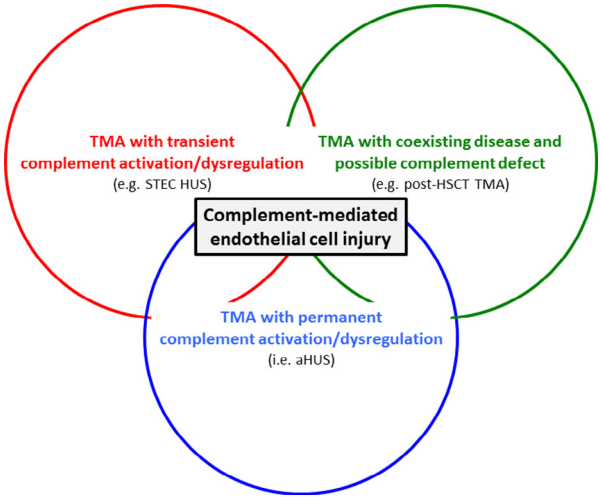

Fig. 1. The spectrum of thrombotic microangiopathies (TMAs). Recent evidence suggests a central role of complement dysregulation in the pathogenesis of TMAs: 1) complement driven TMA (i.e. atypical HUS) where there is an underlying complement defect; 2) complement enhanced TMA where e.g. Shiga toxin transiently activates complement in STEC HUS; and 3) TMA with coexisting diseases (e.g. SLE, pregnancy).

activation, these 3 pathways converge to cleave C3 (by C3 convertases, C4b2a and C3bBb). While activation of the MBL and CP occurs after binding to bacterial surfaces and immune complexes respectively, the AP is constitutively active, generating C3b, which binds to pathogens and host cells, therefore requiring tight regulation [13]. Because C3b (the activation product of C3) can generate new C3 convertases (C3bBb) that continually generate more C3b molecules, the AP acts as an amplifier of its own activation. The same enzymes that cleave C3 (C4b2a and C3bBb) can bind the C3b to form the C5 convertases (C4b2a3b and C3bBb3b) that activate C5 further downstream in the cascade to generate the potent anaphylatoxin, C5a, and C5b that can initiate the formation of the membrane attack complex, C5b-9 (Fig. 2).

The AP efficiently coats unprotected cell surfaces with significant amounts of covalently bound C3b within a few minutes. This process is inhibited by complement factor H (CFH) both in the fluid phase and on cell surfaces. CFH acts as a cofactor to complement factor I (CFI) to cleave C3b, promotes disintegration of C3bBb and competitively prevents C3b deposition on cell surfaces [14–17]. Cell surfaces are also protected against complement attack by specific membrane-bound regulators: 1) complement receptor 1 (CR1/CD35), which promotes the inactivation of C3b to iC3b, 2) membrane cofactor protein (MCP/CD46), which acts as a cofactor to CFI for inactivation of C3b, 3) decay accelerating factor (DAF/CD55), which accelerates the disintegration of the C3 and C5 convertases, and 4) protectin (CD59), which blocks the formation of the membrane attack complex (Fig. 3) [18–20].

3. Complement dysregulation is central to TMA pathology

The regulation of complement activation is critical in maintaining endothelial cell integrity. Loss of regulation