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Is complement a culprit in infection-induced forms of haemolytic uraemic syndrome?

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ABSTRACT

Haemolytic uraemic syndrome (HUS) accounts for the most common cause of childhood acute renal failure. Characterized by the classical triad of a microangiopathic haemolytic anaemia, thrombocytopaenia and acute renal failure, HUS occurs as a result of Shiga-toxin producing microbes in 90% of cases. The remaining 10% of cases represent a heterogeneous subgroup in which inherited and acquired forms of complement dysregulation have been described in up to 60%. Emerging evidence suggests that microbes associated with HUS exhibit interaction with the complement system. With the advent of improved genetic diagnosis, it is likely that certain cases of infection-induced HUS may be attributed to underlying defects in complement components. This review summarises the interplay between complement and infection in the pathogenesis of HUS.

Introduction

Haemolytic uraemic syndrome (HUS) is characterised by microangiopathic haemolytic anaemia, thrombocytopaenia and acute renal failure. Renal histopathology reveals thrombotic microangiopathy (TMA), characterised by occlusive thrombi in glomerular capillaries, small arterioles and arteries, detachment of endothelial cells (ECs) from the glomerular basement membrane, mesangiolysis and widening of the subendothelial space by electron-lucent material (Fig. 1). EC injury is the key initiating event in the pathogenesis of TMA, leading to EC dysfunction, apoptosis and necrosis with exposure of the subendothelial matrix (Bauwens et al. 2011). Activation of platelets, leukocytes and the coagulation cascade contribute to intravascular microthrombosis (Ruggenenti et al. 2001). A number of triggers for EC injury have been identified in HUS. Most cases follow infection with Shiga toxin producing enteric pathogens (Lynn et al. 2005). Others present following pneumococcal infection (Waters et al. 2007). The majority of remaining patients have an inherited defect of complement regulation. In this review we will summarise the role of complement in the pathogenesis of HUS, before considering the molecular mechanisms employed by microbial pathogens in the pathogenesis of HUS and whether these may involve the complement system. Finally, we will examine the role of infection in triggering HUS in genetically susceptible individuals.

Overview of alternative complement pathway

Complement proteins provide an important host defense mechanism by recognizing and eliminating microbial pathogens during infection (Zipfel et al. 2007). Activation of C3, a key complement effector, occurs by three major pathways: the alternative pathway (AP), the classical pathway (CP) and the lectin pathways (Fig. 2). The AP is initiated by the spontaneous hydrolysis of plasma C3 to generate C3b, triggering formation of a C3-convertase, C3bBb. Subsequent formation of the lytic membrane attack complex (MAC) occurs with binding of C3b to C3bBb which generates a C5-convertase that cleaves C5 (Zipfel and Skerka 2009).

Abbreviations: HUS, haemolytic uraemic syndrome; TMA, thrombotic microangiopathy; ECs, endothelial cells; AP, alternative pathway; CP, classical pathway; MAC, membrane attack complex; CFH, complement factor H; SCRs, short consensus repeats; CFI, complement factor I; DAF, decay accelerating factor; MCP, membrane-bound cofactor protein; aHUS, atypical HUS; THBD, thrombomodulin; EHEC, enterohaemorrhagic *Escherichia coli*; GABS, Group A *beta-hemolytic streptococcus*; HIV, Human Immunodeficiency Virus; Stx, Shiga toxin; Stx-HUS, Shiga toxin-induced haemolytic uraemic syndrome; PMNs, polymorphonuclear leukocytes; Gb3cer, globotriaosylceramide; pHUS, pneumococcal HUS; T, Thomsen-Friedenreich antigen; GEC, glomerular endothelial cells; HAART, highly active antiretroviral therapies; PEX, plasma exchange therapy; VZV, varicella zoster virus; C4BP, C4b-binding protein; TAFIa, thrombin activatable fibrinolysis inhibitor; HMEC, human microvascular endothelial cells; HUVEC, human umbilical vein endothelial cells; VEGF, vascular endothelial growth factor.

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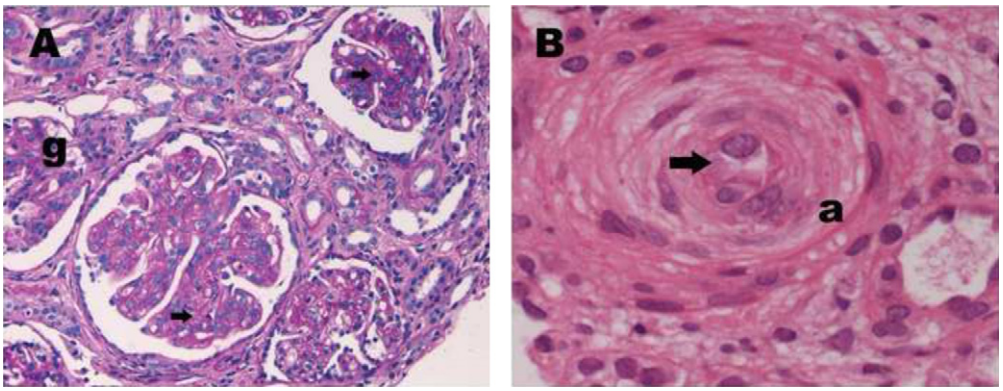

Fig. 1. Renal histopathological features of thrombotic microangiopathy. A renal biopsy demonstrating features of acute thrombotic microangiopathy (TMA) with segmental vasculitic changes and fibrin thrombi within the glomerular capillary loops. Concentric intimal thickening was noted in adjacent afferent arterioles. The tubulointerstitial compartment was normal.

Continuous activation of circulatory C3 is regulated by several proteins which act both in the fluid phase and at the cell membrane (Fig. 2). Of these, complement factor H (CFH), a plasma glycoprotein consisting of 20 short consensus repeats (SCRs), plays a major role in the inactivation of C3bBb. CFH binds to complement factor I (CFI), which cleaves C3b to iC3b (co-factor activity) (Pangburn et al. 1977). CFH also inhibits the formation of C3bBb and promotes the dissociation of C3bBb (decay-accelerating activity). Binding of CFH by its C-terminus to cell surface polyanions increases its affinity for surface-bound C3b. Other regulatory proteins include five structurally related proteins to CFH (CFHR1–5) which share different degrees of identity with CFH (Zipfel and Skerka 2009). Membrane-bound complement regulators including complement receptors 1 and 2, decay accelerating factor (DAF), membrane-bound cofactor protein (MCP; CD46), protectin (CD59) and complement receptor of the immunoglobulin superfamily (CRIg) regulate complement by a variety of mechanisms (Fig. 2).

Inherited defects of complement regulation

Complement dysregulation in aHUS was first observed almost fifteen years ago (Warwicker et al. 1998). Mutations have since been identified in genes encoding both complement regulators (*CFH, CFI, CFHR 1/3* and *CFHR 1/4A* and *MCP*) (Bienaime et al. 2010; Caprioli et al. 2001, 2003, 2006; Chan et al. 2009; Couzi et al. 2008; Cruzado et al. 2009; Dragon-Durey et al. 2004, 2009; Esparza-Gordillo et al. 2006; Fremeaux-Bacchi et al. 2004, 2006; Heinen et al. 2009; Kavanagh et al. 2005, 2008; Manuelian et al. 2003; Moore

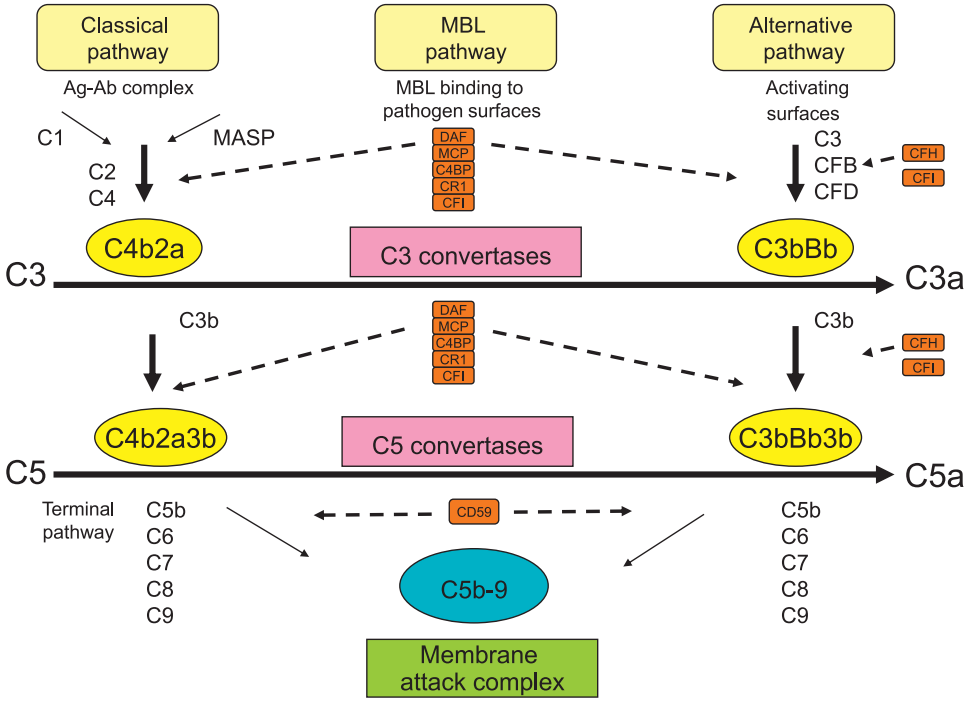

Fig. 2. Activation and regulation of Complement. Activation of C3 occurs by the alternative pathway, classical pathway or lectin (MBL) pathways following a variety of triggers. This results in formation of a C3 convertase enzyme (producing C3a and C3b) and subsequent generation of C5a and the membrane attack complex (MAC). Regulation of complement activation occurs by three major mechanisms. (i) co-factor activity (for the CFI-mediated cleavage of C3b) exhibited by CFH, MCP and CR1 (ii) decay-accelerating activity (dissociation of the C3 convertase) by CFH, MCP and DAF, and (iii) inhibition of MAC by CD59. Ag, antigen; Ab, antibody; MASP, Manose associated serine protease; MBL, Mannose binding lectin; DAF, Decay accelerating factor; MCP, Membrane cofactor protein; CR1 complement receptor-1; CFB, complement factor B; CFD, complement factor D; CFH, complement factor H; CFI, complement factor I.