The role of complement in C3 glomerulopathy.

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Projects

The role of complement in autoimmune disease
Details

Abstract

C3 glomerulopathy describes a spectrum of disorders with glomerular pathology associated with C3 cleavage product deposition and with defective complement action and regulation (Fakhouri et al., 2010; Sethi et al., 2012b). Kidney biopsies from these patients show glomerular accumulation or deposition of C3 cleavage fragments, but no or minor deposition of immunoglobulins (Appel et al., 2005; D'Agati and Bomback, 2012; Servais et al., 2007; Sethi and Fervenza, 2011). At present the current situation asks for a better definition of the underlining disease mechanisms, for precise biomarkers, and for a treatment for this disease. The complement system is a self activating and propelling enzymatic cascade type system in which inactive, soluble plasma components are activated spontaneously and lead into an amplification loop (Zipfel and Skerka, 2009). Activation of the alternative pathway is spontaneous, occurs by default, and cascade progression leads to amplification by complement activators. The system however is self-controlled by multiple regulators and inhibitors, like Factor H that control cascade progression in fluid phase and on surfaces. The activated complement system generates a series of potent effector components and activation products, which damage foreign-, as well as modified self cells, recruit innate immune cells to the site of action, coordinate inflammation and the response of the adaptive immune system in form of B cells and T lymphocytes (Kohl, 2006; Medzhitov and Janeway, 2002; Ogden and Elkon, 2006; Carroll, 2004; Kemper and Atkinson, 2007; Morgan, 1999; Muller-Eberhard, 1986; Ricklin et al., 2010). Complement controls homeostasis and multiple reactions in the vertebrate organism including defense against microbial infections (Diaz-Guillen et al., 1999; Mastellos and Lambris, 2002; Nordahl et al., 2004; Ricklin et al., 2010). In consequence defective control of the spontaneous self amplifying cascade or regulation is associated with numerous human disorders (Ricklin and Lambris, 2007; Skerka and Zipfel, 2008; Zipfel et al., 2006). Understanding the exact action and regulation of this sophisticated homeotic cascade system is relevant to understand disease pathology of various complement associated human disorders. Furthermore this knowledge is relevant for a better diagnosis and appropriate therapy. At present diagnosis of C3 glomerulopathy is primarily based on the kidney biopsy, and histological, immmunohistological and electron microscopical evaluation (D'Agati and Bomback, 2012; Fakhouri et al., 2010; Medjeral-Thomas et al., 2014a,b; Sethi et al., 2012b). The challenge is to define the actual cause of

the diverse glomerular changes or damages, to define how C3 deposition results in the reported glomerular changes, the location of the cell damage and the formation of deposits.

Identifier

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