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Complement in renal transplantation: The road to translation

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ABSTRACT

Renal transplantation is the treatment of choice for patients with end-stage renal disease. The vital role of the complement system in renal transplantation is widely recognized. This review discusses the role of complement in the different phases of renal transplantation: in the donor, during preservation, in reperfusion and at the time of rejection. Here we examine the current literature to determine the importance of both local and systemic complement production and how complement activation contributes to the pathogenesis of renal transplant injury. In addition, we dissect the complement pathways involved in the different phases of renal transplantation. We also review the therapeutic strategies that have been tested to inhibit complement during the kidney transplantation. Several clinical trials are currently underway to evaluate the therapeutic potential of complement inhibition for the treatment of brain death-induced renal injury, renal ischemia-reperfusion injury and acute rejection. We conclude that it is expected that in the near future, complement-targeted therapeutics will be used clinically in renal transplantation. This will hopefully result in improved renal graft function and increased graft survival.

1. Introduction

Renal transplantation is the gold standard for patients with end-stage renal disease (Mange et al., 2001). In 2012 alone over 19.000 renal transplantations were performed in the European Union (Europe, 2014). Although an increasing number of kidney transplantations are performed, the success is critically dependent on the quality of the renal allograft. Renal graft quality, in turn, is determined by a variety of factors including: the donor, preservation conditions, ischemia times and subsequent reperfusion as well as the immunoreactivity of the recipient. Of major importance is the donor condition of the renal allograft. Kidneys are derived from living, deceased brain death (DBD) or deceased cardiac death (DCD) donors. Evidence showed that the origin of the donors is important for renal graft outcome, with better graft survival of kidneys obtained from living donors (Terasaki et al., 1995). After donation, the kidneys are preserved to keep them viable between time of procurement and transplantation. Organ preservation made huge progress over the last years, which creates potential to assess, recover or repair the kidney during preservation. The process of transplantation exposes the kidney to an unavoidable period of ischemia time and subsequent reperfusion, which is reported to have a major impact on short and long-term renal graft survival (Rabb et al., 1997; Takada et al., 1997). After transplantation, immunological tolerance is rare and the immunological response of the recipient to the graft affects outcome. This immune response is designed to cause rejection of the renal graft, with the involvement of both humoral and cellular mechanisms. All these factors influence renal transplant injury and therefore renal allograft function and survival. An important denominator in the pathophysiology of renal transplant injury is the complement system. Several studies have already demonstrated the relevance of the complement system in renal transplantation. The complement system, can be activated via three different pathways: the classical pathway (CP), the lectin pathway (LP) and the alternative pathway (AP) (Fig. 1). All pathways converge at the central complement component 3 (C3) by pathway specific C3-convertases. Once C3 is cleaved, the amplification loop facilitates the rapid generation of more

Abbreviations: ABMR, Antibody mediated rejection; aHUS, Atypical hemolytic syndrome; AP, Alternative pathway; DBD, Deceased brain dead; DCD, Deceased cardiac death; DSA, Donor specific antibodies; C1-INH, C1-inhibitor; C3, Complement component C3; CDC, Complement-dependent cytotoxicity; CL-11, Collectin-11; CP, Classical pathway; CR2, Complement receptor 2; Crry, Complement receptor 1-related gene/protein y; sCR1, soluble Complement Receptor 1; DAF, Decay accelerating factor; HMP, Hypothermic machine perfusion; IRI, Ischemia-reperfusion injury; LP, Lectin pathway; LPS, Lipopolysacharide; mAb, Monoclonal antibody; MAC, Membrane attack complex; MASP, Mannan-binding lectin serine protease; MBL, Mannose binding lectin; MCP, Membrane cofactor protein; NMP, Normothermic machine perfusion; RAG-1, Recombination activating gene-1; siRNA, small interfering RNA; UW, University of Wisconsin; Y-CVF, Yunnan-cobra venom factor

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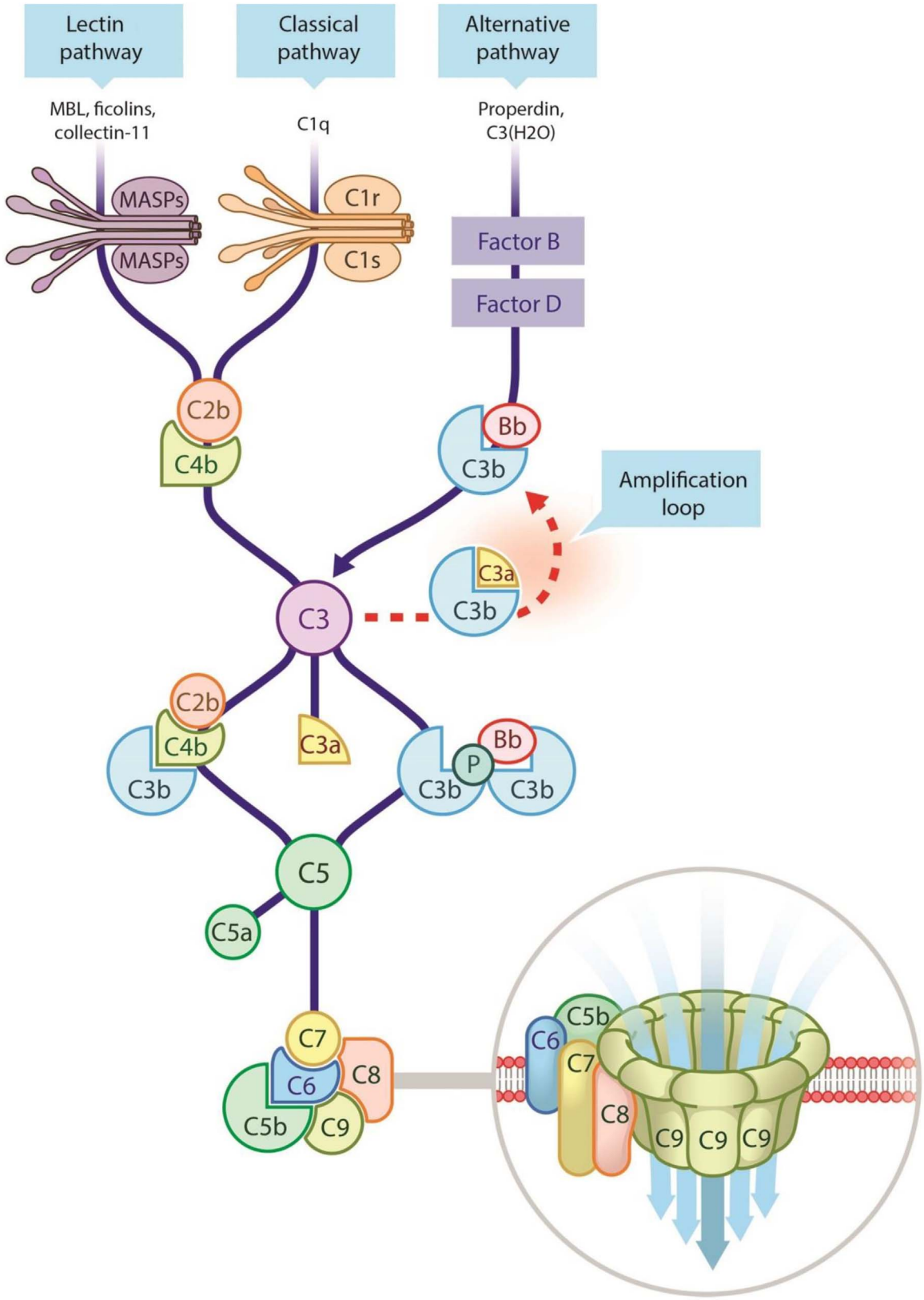

Fig. 1. Schematic overview of the complement system.
The complement system is activated via the classical (CP), lectin (LP) or alternative pathway (AP). The LP is initiated by mannose-binding lectin (MBL), ficolins or collectins, which bind to carbohydrate ligands found on pathogens, stressed or apoptotic cells. Furthermore, other molecules like IgA are also able to activate complement via the LP. The CP is initiated by C1, a complex consisting of recognition molecule C1q and the serine proteases C1r and C1s. The CP is activated when C1 binds to immune complexes, cellular debris, altered-self and apoptotic cells or different pentraxins like CRP. The AP is continuously activated in small amounts by the hydrolysis of systemic C3. The subsequently formed C3b interacts with factor B and D to form C3bBb, a C3-convertase, which cleaves additional C3 molecules. Once C3 is cleaved, the amplification loop facilitates the rapid generation of more C3 convertase (C3bBb) and more C3b, which can then attach to foreign surfaces. C3bBb is stabilized by properdin, which increases the C3 activation potential of C3bBb. Ultimately, activation of all three pathways leads to the formation of the C3- and C5-convertase, thereby generating the membrane attack complex (MAC) or C5b-9. Additionally, complement activation also leads to the formation of opsonins (e.g. C3b, iC3b and C3d) and anaphylatoxins (e.g. C3a and C5a) who exe.