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# Complement-mediated inflammation and injury in brain dead organ donors

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ABSTRACT

The importance of the complement system in renal ischemia-reperfusion injury and acute rejection is widely recognized, however its contribution to the pathogenesis of tissue damage in the donor remains underexposed. Brain-dead (BD) organ donors are still the primary source of organs for transplantation. Brain death is characterized by hemodynamic changes, hormonal dysregulation, and immunological activation. Recently, the complement system has been shown to be involved. In BD organ donors, complement is activated systemically and locally and is an important mediator of inflammation and graft injury. Furthermore, complement activation can be used as a clinical marker for the prediction of graft function after transplantation. Experimental models of BD have shown that inhibition of the complement cascade is a successful method to reduce inflammation and injury of donor grafts, thereby improving graft function and survival after transplantation. Consequently, complement-targeted therapeutics in BD organ donors form a new opportunity to improve organ quality for transplantation. Future studies should further elucidate the mechanism responsible for complement activation in BD organ donors.



## 1. Introduction

Organ transplantation is the optimal treatment for the majority of patients with end-stage organ failure. Since the first successful transplantation more than a half-century ago, considerable progress has been made in surgical techniques, availability of donors, alloimmunity, organ preservation and patient and graft survival. However, the demand for donor organs remains to exceed the number of grafts available for transplantation (Bendorf et al., 2013). This disparity has forced many transplant centers to use suboptimal donors with decreased organ quality (Ojo et al., 2004). Therefore, current research focuses on strategies to improve organ quality and thereby graft function before and after transplantation. Potential therapeutic options include pharmacological interventions in the donor prior to organ retrieval (Westendorp et al., 2011). For kidney, liver and lung transplantation, grafts are retrieved from living, deceased brain dead (BD) and deceased cardiac death (DCD) organ donors. The majority of donor hearts are retrieved from BD organ donors, however, DCD organ donors might form a significant contribution to transplant numbers in the near future (Wittwer and Wahlers, 2008). This review will focus on the effect of the complement system on organ quality in BD donors, with particular emphasis on the kidney.

## 2. Brain death and organ donation

Brain death, a term created in 1959 by two French doctors, consists of an irreversible coma without reflexes but with intact systemic circulation (Mollaret and Goulon, 1959). Later, a committee at Harvard Medical School proposed to add this irreversible coma to the death criterion ("A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death.," 1968). This act created the legal basis for the procedure to obtain organs for transplantation from deceased patients who are BD. Nowadays, BD organ donors continue to form the main source of organs for transplantation. However, organs retrieved from BD organ donors give inferior results compared organs retrieved from living donors (Terasaki

*Abbreviations:* ACTH, adrenocorticotropic hormone; ADH, anti-diuretic hormone; AP, alternative pathway; BD, brain dead/brain death; C1-INH, C1 esterase inhibitor; CD59, membrane attack complex-inhibitory protein; CP, classical pathway; CR1, complement receptor 1; CR2, complement receptor 2; DAMPs, damage-associated molecular patterns; DCD, deceased cardiac death; IgG, immunoglobulin G; IgM, immunoglobulin M; IL-6, interleukin 6; IL-1beta, interleukin 1beta; KIM-1, kidney injury marker 1; LP, lectin pathway; LPS, lipopolysaccharide; MBL, mannose-binding lectin; MAC, membrane attack complex; PAMPs, pathogen-associated molecular patterns; sC5b-9, soluble C5b-9; $T_3$, triiodothyronine; TGF-beta, tumor growth factor beta.

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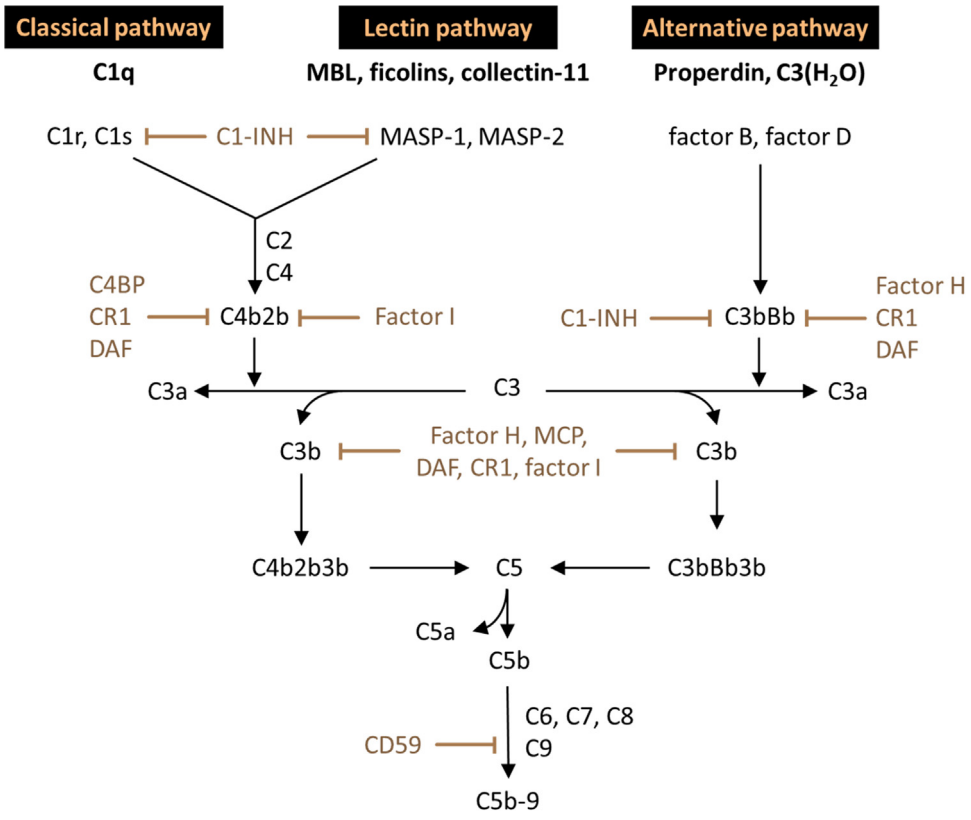


**Fig. 1.** Activation and regulation of the complement system.
Schematic view of complement activation and regulation. In the classical pathway (CP), C1q recognizes immune complexes as well as other molecules (e.g. CRP), inducing the formation of the classical pathway C3 convertase (C4b2b) through cleavage of C2 and C4 by C1r and C1s. In the lectin pathway (LP), MBL, ficolins or collectin-11 recognize carbohydrates as well as other molecules (e.g. IgA), binding actives the MASP-1 and MASP-2, forming the same C3 convertase as the CP. The C3-convertase of the LP or CP, activates C3, thereby generating its active fragments C3a and C3b. In the alternative pathway, the activation of plasma protein C3 occurs via the spontaneous hydrolysis of C3 in C3($H_2O$) or via surface interactions of properdin with certain cell surfaces (e.g. LPS). Subsequently, binding of factor B creates the AP C3 convertase (C3bBb), which cleaves more C3 into C3b and thereby amplifies the complement response. Increased levels of C3b results in the generation of C5 convertases, which cleaves C5 in C5a, a powerful anaphylatoxin, and C5b. Next, C5b binds to the surface and interactions with C6–C9, forming the membrane attack complexes (MAC/C5b-9). Soluble and membrane-bound complement inhibitors regulate complement activation. C1-Inhibitor (C1-INH) regulates the activity of recognition complexes, while C4b-binding protein (C4BP) control activation at the C4 level of the CP and LP. Factor H and factor I act on the C3 and C5 convertase. In addition, the membrane-bound inhibitors complement receptor 1 (CR1) and membrane cofactor protein (MCP) act as co-factors for factor I, whereas decay accelerating factor (DAF) accelerates the decay of C3 convertases. The membrane-bound regulator CD59 can prevent the formation of the MAC on surfaces.

et al., 1995). This is the consequence of a cascade of events occurring in BD organ donors as a result of the cerebral injury and herniation of the brain stem. The pathophysiology of BD is complex and characterized by hemodynamic changes, hormonal dysregulation and immunological activation (Bos et al., 2007). First, the rise in intracranial pressure triggers the Cushing reflex, leading to a catecholamine storm followed by a stabilization period (Keil et al., 1995). Ultimately, a state of hypoperfusion is reached, leading to ischemic damage of potential grafts (Nagareda et al., 1993). Next to the catecholamine's, other hormonal deregulations take place such as decreased secretion of insulin, anti-diuretic hormone (ADH), triiodothyronine ($T_3$) and adrenocorticotropic hormone (ACTH) (Novitzky et al., 2006). Lastly, BD causes a systemic and local inflammatory response consisting of complement and endothelial activation, cytokines, and chemokines release and the influx of leucocytes into the organs (Bos et al., 2007; Bouma et al., 2009; Damman et al., 2008; Watts et al., 2013). BD therefore closely resembles systemic inflammatory response syndrome (SIRS). However, the cause of this immune activation is not well understood.

## 3. Brain death induced complement activation

The traditional view of the complement system has profoundly changed over time: the simple view of a heat-labile component of serum that is important for host defense has shifted to the current view of a complex system that contributes substantially to homeostasis (Ricklin et al., 2010). In short, the complement system can be activated via three pathways: the Lectin Pathway (LP), the Classical Pathway (CP), and the Alternative Pathway (AP). Carbohydrates activate the LP, antibody–antigen complexes the CP and microbial surfaces the AP (Fig. 1). This results in the formation of the C3- and C5-convertases and the generation of anaphylatoxins such as C3a and C5a. Subsequently, terminal pathway activation leads to the formation of the membrane attack complex (C5b-9 or MAC). The role of complement in diseases is complex; complement activation has the potential to be tremendously damaging to host tissues, whereas complement deficiencies promote the development of autoimmunity. Nonetheless, there is increasing evidence that the complement system plays an important role in tissue damage associated with BD.

### 3.1. Complement component C3

A pathogenic role for the complement system in BD was first demonstrated in rodents. Early evidence emerged from a study by Kusaka et al., demonstrating the presence of complement deposition in kidneys of BD rats (Kusaka et al., 2000). At the time of transplantation, no complement deposition was seen in kidneys of either BD organ donors or controls. However, as early as 1-h

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