Seminars in Immunology 28 (2016) 250–259

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Complement—here, there and everywhere, but what about the transplanted organ?

R.M. Montero, S.H. Sacks*, R.A. Smith

MRC Centre for Transplantation, Division of Transplant Immunology and Mucosal Biology, NIHR Comprehensive Biomedical Research Centre, King's College London, Guy's & St Thomas' NHS Foundation Trust, United Kingdom

ARTICLE INFO

Article history:
Received 15 March 2016
Received in revised form 20 April 2016
Accepted 26 April 2016
Available online 11 May 2016

Keywords:
Complement
Kidney transplantation
Mirococept
Therapeutics

ABSTRACT

The part of the innate immune system that communicates and effectively primes the adaptive immune system was termed "complement" by Ehrlich to reflect its complementarity to antibodies having previously been described as "alexine" (i.e protective component of serum) by Buchner and Bordet. It has been established that complement is not solely produced systemically but may have origin in different tissues where it can influence organ specific functions that may affect the outcome of transplanted organs. This review looks at the role of complement in particular to kidney transplantation. We look at current literature to determine whether blockade of the peripheral or central compartments of complement production may prevent ischaemic reperfusion injury or rejection in the transplanted organ.

We also review new therapeutics that have been developed to inhibit components of the complement cascade with varying degrees of success leading to an increase in our understanding of the multiple triggers of this complex system. In addition, we consider whether biomarkers in this field are effective markers of disease or treatment.

Contents

* Corresponding author.
E-mail address: steven.sacks@kcl.ac.uk (S.H. Sacks).

http://dx.doi.org/10.1016/j.smim.2016.04.007
1044-5323/

1. Introduction

1.1. What is complement?

The complement system was first recognised as a fundamental part of the innate immune system in the late 1890s. It initiates and maintains host defence by combining recognition molecules, proteolytic enzymes, receptors and foreign or altered internal products. The complement system comprises of 35–40 components and regulators that are soluble or membrane bound and catalyse the breakdown of converting enzyme complexes or convertases that lead to the formation of membrane attack complex (C5b, C6, C7, C8 and C9 (C5b-C9)). Activation of the complement cascade has been described to use three pathways; the classical, lectin and alternative pathways (Fig. 1). The classical pathway is triggered by antigen-antibody immune complexes arising from immune surveillance molecules (e.g. IgG, IgM, C-reactive protein) leading to activation of C4, C2 and C3. The lectin pathway is initiated by collectins (e.g. mannose binding lectin, MBL) and ficolins, which bind to carbohydrate ligands on the surface of pathogens. This subsequently leads to the formation of C4b, C2a—the C3 convertase complex similar to the classical pathway. In contrast, the alternative pathway is activated by either spontaneous hydrolysis of C3 or by C3b binding to the activated surface thus amplifying the cascade, using Factors B, D and P to form the alternative C3 convertase C3bBb.

Initiation of the complement cascade results in the deposition of C3 onto the activating surface. Cleavage of C3 forms C3a and C3b with the latter triggering formation of C5 convertase. C5 is cleaved leading to formation of C5b-C9. The anaphylatoxins (C3a and C5a) are potent pro-inflammatory molecules that are chemoattractant and activate leucocytes via C3aR and CD88 (C5aR1). Opsonins (C3b, inactive C3b (iC3b) and degradation product C3d) remain covalently bound to target surfaces facilitating transport and removal of the targeted cells or immune complexes. Formation of C5b-9 in the targeted cell membrane results in direct lysis of the pathogen causing cell activation, injury and death [1]. The complement system is regulated by a number of inhibitors and regulators to prevent local destruction of tissues. CD35 (CR1), CD46 (MCP), CD55 (DAF), C4BP (C4b-binding protein) and Factor H are all members of the same family of complement regulatory proteins that have similar structures with varying number of subunits that are encoded on chromosome 1 and inhibit the functions of the converting enzyme complexes that cleave C3 and C5. In addition, CD59 inhibits the formation of C5b-C9. Complement regulators have a number of functions that are described in Table 1. Dysregulation of the complement regulators has increasingly been described in a number of diseases such as age-related macular degeneration, systemic lupus erythematosus (SLE), spinal cord injuries, atypical haemolytic uraemic syndrome (aHUS), arthritis, autoimmune heart disease and paroxysmal nocturnal hemoglobinuria (PNH) [2–7]. Complement has also been described to be important in priming the adaptive immune system whereby C3a and C5a released by local complement activation act as cofactors for stimulation of antigen presentation whilst enhancing activation of naïve alloreactive T cells [8–12].

1.2. Peripheral and central complement production

An intra and extravascular pool of complement has previously been described whereby hepatic synthesis mainly maintains the intravascular pool. In contrast the extravascular pool arises from peripheral or local tissue cellular activity from tissue-resident and migratory cells such as antigen presenting cells (APCs), T cells and tubuloepithelial cells in the kidney [13,14]. It has been argued that C3 could be maintained in the central compartment due to its 180 kDa size; however it is ill-understood as to whether retention of this large complement molecule in the central compartment is due to size alone [15,16]. Other circulating complement factors including C2, C4 and Factor B can similarly be generated in tissue-resident cells. Animal studies have previously described the important role of central and peripheral pools of C3 with uncontrolled locally produced complement resulting in effective and rapid complement mediated tissue damage [15]. C3 arising from the transplanted kidney following an ischaemic insult has been described to be dependent on the cold ischaemic time prior to surgery with deposited C3 levels peaking approximately 48 h following the surgery, though in patients it has been reported that complement activation may begin in the organ donor [17,18]. This results in significant damage to the tubuloepithelial cells that are susceptible to hypoxic damage. Tubuloepithelial cells are the main source of local complement in the kidney, however all cellular compartments of the kidney are able to synthesise complement, based on in vivo and ex vivo analysis [19]. Improving our understanding in this area and of the inter-individual variations that confer disease susceptibility will allow us to deliver targeted specific personalised medicine to prevent the decline in allograft function [20]. The remainder of this review will focus on the role of complement in kidney transplantation, which is the most common type of solid-organ transplantation performed.

2. Kidney transplantation

The complement system has provided a natural barrier to xenotransplantation for many years, with damage to pig organs arising from exposure to human serum [21,22]. Studies in allotransplantation have also highlighted the importance of complement in alloantibody-mediated rejection. Subsequently it became apparent that peripheral complement also plays a central role determining how the donor organ responds to the stress of transplantation [23]. Further work has identified how alloimmune priming and cell-mediated rejection are complement-dependent. In this review, we shall focus on the role of complement in several of these functions that are relevant to current clinical practice.

2.1. Ischaemia-reperfusion injury

Ischaemia-reperfusion (IR) injury is thought to be the main contributor to the development of delayed graft function (DGF). DGF occurs in a third of all deceased donor organs rising to 50% in circulatory deceased donors [24]. This has led to an increase in reperfusion machine studies to determine whether the injury sustained may decrease with normothermic or hypothermic perfusion [25,26]. IR injury arises from a combination of tissue hypoxia, mitochondrial damage, ATP depletion and free oxygen radicals on reperfusion, leading to damage of the endothelium and epithelium. This induces cellular inflammation via toll-like receptors, cytokines, chemokines and complement. Complement activation both initiates and propagates tissue damage not only in kidney transplantation but also in other major transplanted organs such as the heart, lung, liver and pancreas [27–32].