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Review

The relative importance of local and systemic complement production in ischaemia, transplantation and other pathologies

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Abstract

Besides a critical role in innate host defence, complement activation contributes to inflammatory and immunological responses in a number of pathological conditions. Many tissues outside the liver (the primary source of complement) synthesise a variety of complement proteins, either constitutively or response to noxious stimuli. The significance of this local synthesis of complement has become clearer as a result of functional studies. It revealed that local production not only contributes to the systemic pool of complement but also influences local tissue injury and provides a link with the antigen-specific immune response. Extravascular production of complement seems particularly important at locations with poor access to circulating components and at sites of tissue stress responses, notably portals of entry of invasive microbes, such as interstitial spaces and renal tubular epithelial surfaces. Understanding the relative importance of local and systemic complement production at such locations could help to explain the differential involvement of complement in organ-specific pathology and inform the design of complement-based therapy. Here, we will describe the lessons we have learned over the last decade about the local synthesis of complement and its association with inflammatory and immunological diseases, placing emphasis on the role of local synthesis of complement in organ transplantation.

Keywords: Local synthesis of complement; C3; Inflammatory and autoimmune diseases; Infectious disease; Ischaemia/reperfusion injury; Allograft rejection; Strategy for therapy

1. Introduction

Research in the last two decades has generated substantial information about the extrahepatic synthesis of complement and its association with inflammatory and immunological diseases. With the generation of complement deficient animals and employment of bone marrow (BM) or organ transplantation, the role of local production of complement is becoming clearer in several disease models, including tissue reperfusion injury, immune complex glomerulonephritis, humoral immunity, and cell mediated allograft rejection. The results show that local production and activation of complement makes a significant contribution to local tissue inflammatory injury and also enhances the adaptive immune response. There have been several excellent review articles regarding the role of local synthesis of complement in organ-specific disease, including renal disorders, diseases of the central nervous system, systemic lupus erythematosus, autoimmune diseases including arthritis, and bacterial infection (Andrews et al., 1995b; Zhou et al., 2001; Gasque et al., 2000; Laufer et al., 2001; Chowdhury et al., 2004). The focus of the present article is on its role in transplantation.

2. The complement system in disease

The complement system can be divided into a set of trigger pathways, enzymatic and effector components, receptors and regulators, many of which have been detailed elsewhere (Walport, 2001a, b). With regard to disease pathogenesis, in addition to the well established effector mechanism of membrane pore formation (C5b-9), recent attention has focussed on the interaction between the soluble (C3a and C5a) or membrane bound (C4b, iC4b, C4d, C3b, iC3b and C3dg) products, and their corresponding receptors [C3aR, C5aR, CR1–4 and the newly

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discovered CRIg (Helmy et al., 2006)] which are expressed on both tissue-resident cells and migratory leukocytes. Complement receptors on cells with immune function are of particular interest, as they appear to underpin an important link between the innate and adaptive arms of the immune response. For example, complement receptors CR1 and CR2 that are present on B cells and follicular dendritic cells recognise C3b and C3dg-opsonised antigen, augmenting the retention of antigen and facilitating the antigen-specific B cell response in secondary lymphoid tissue (Fearon and Carroll, 2000). Receptors C3aR and C5aR, found on both myeloid and non-myeloid cells, apart from their known effector functions in the innate response [reviewed by (Gerard and Gerard, 2002; Guo and Ward, 2005)], appear to regulate the function of antigen presenting cells (APC) and consequently can adjust the T cell response [reviewed by (Kohl, 2006)].

The complement system is activated through three main pathways, namely the classical, alternative, and mannose binding lectin (MBL) pathways. The convergence point of all three pathways is the assembly of C3 convertases that cleave C3 into C3a and C3b, subsequently forming C5 convertases that cleave C5 releasing C5a and resulting in C5b-9 formation. The activation of each pathway requires certain components and activating proteins. For example, activation of the classical pathway requires immune complexes, MBL mediated complement activation is dependent on the classical pathway components (C4 and C2), and C3 is required for the formation of C5 convertase (Walport, 2001a, b). In the past few years, evidence has emerged for several bypass pathways of complement activation, both at the level of C3 and C5. These include the findings that mannose binding lectin can activate C3 in the absence of C2 or C4; that the coagulation pathway component, thrombin can directly activate C5 independent of C3; and that a mannose receptor (SIGN-R1) can directly bind to C1q and assemble C3 convertase independently of either antibody or factor B (Selander et al., 2006; Huber-Lang et al., 2006; Kang et al., 2006). The discovery of these bypass pathways suggests that complement activation, particularly under pathological conditions, is likely to involve a more diverse set of innate molecules and signatures than at first thought, such as amyloid-β, oxidatively modified low density lipoproteins, photooxidation products of A2E (Bradt et al., 1998; Wieland et al., 1999; Zhou et al., 2006a). Therapeutic strategies to reduce complement mediated inflammatory and immune responses may need to take these activators and bypass pathways into account.

3. Local synthesis of complement in a variety of tissues/organs/cells

The liver is the primary site for the synthesis of circulating complement proteins, with the exception of few components (i.e. C7, C1q and factor D). However, as shown in the past two decades, in both animals and man, extrahepatic synthesis of a wide range of soluble proteins of the complement system [i.e. C1 (r.s.q), C2–9, factor B (fB), factor D (fD), factor H (fH), factor I (fI) and properdin)] occurs in a variety of organs/tissues and cells, either constitutively or response to various stimuli (i.e. infectious or non-infectious) (Table 1). This local production can significantly contribute to the systemic pool of complement, with up 5% of the total circulating C3 derived during bone marrow engraftment and a basal contribution of about 5% of the total circulating C3 by a single transplant kidney (Naughton et al., 1996; Tang et al., 1999b). These findings indicate that extrahepatic synthesis generates a basal pool of complement at potential sites of pathogen invasion or tissue stress, such as the kidney. Furthermore, several complement components are mainly synthesised at extrahepatic sites. For example, C1q is mainly synthesised in brain microglia, monocytes, macrophages and immature dendritic cells (Schafer et al., 2000; Schwaeble et al., 1995; Castellano et al., 2004); fD is predominantly synthesised in fat tissue (Choy et al., 1992), and C7 is synthesised in both myeloid and other specialised cells (e.g. monocytes, macrophages, endothelial cells, fibroblasts and CNS cells) (Hetland et al., 1986; Colten et al., 1979; Lappin et al., 1992; Garred et al., 1990; Gasque et al., 1995). The prodominantly local synthesis of these molecules seems to have singificant biological functions. The tissue synthesis of C1q plays an important role in the clearence of immune complexes locally (Moosig et al., 2006), as apopotosis and clearance of apoptotic cells occurs in different tissue compartments (e.g. dermis, lymphnode, many organs) where circulating C1q may not be sufficiently available, and therefore local synthesis of C1q in the micro-environment could serve the removal of apoptotic material. Local production of fD and C7 has an important implication in regulating local complement activation, as C7 is often the limiting factor for termininal complement complex generation [reviewed by (Wurzner, 2000)], and fD is required for the activation of the alternative pathway.

As indicated in the Table, myeloid cells including monocytes and macrophages, and now dendritic cells (DC), also have the capacity for complement synthesis. Murine BM derived DCs can express a range of complement components and activators, recent evidence suggesting that cell autonomous production of C3 is required for full functional development of APCs as effective triggers of specific T cell responses (Peng et al., 2006; Zhou et al., 2006b). Likewise, the synthesis of several complement components and regulators has been found in human monocyte derived DCs (Castellano et al., 2004; Reis et al., 2006), though the functional relevance is at present unclear.

In addition to complement components, hepatic and extrahepatic tissues also synthesise various cell surface complement receptors and regulators, depending on location. There have been several excellent review articles on this subject (Song, 2004; Gasque et al., 2000; Nangaku, 1998; Bajtay et al., 2006), which we will not duplicate here. In general, complement receptors expressed on local tissues/cells can interact with effector molecules generated by local complement activation, exerting their biological functions (e.g. opsonophagocytosis, cell activation). The expression of regulators and the altered expression of regulators upon stimulation can down-regulate or up-regulate local complement activation. Thus, in addition to soluble complement proteins, local synthesis of cell surface regulators plays an important role in local inflammation mediated by local production and activation of complement.