Immunobiology 217 (2012) 162–168

Contents lists available at ScienceDirect

Immunobiology

journal homepage: www.elsevier.de/imbio

Factor H as a regulator of the classical pathway activation

Uday Kishore [a,*], Robert B. Sim [b,*]

[a] Centre for Infection, Immunity and Disease Mechanisms, Biosciences, School of Health Sciences and Social Care, Brunel University, Uxbridge UB8 3PH, London, UK
[b] Department of Pharmacology, University of Oxford, Mansfield Road, Oxford OX1 3QT, UK

ARTICLE INFO

Article history:
Received 31 May 2011
Received in revised form 29 June 2011
Accepted 18 July 2011

Keywords:
Factor H
Complement
Classical pathway
Phospholipid
Lipid A
Apoptotic cell

ABSTRACT

C1q, the first subcomponent of the classical pathway, is a charge pattern recognition molecule that binds a diverse range of self, non-self and altered self ligands, leading to pro-inflammatory complement activation. Although complement is required for tissue homeostasis as well as defence against pathogens, exaggerated complement activation can be damaging to the tissue. Therefore, a fine balance between complement activation and inhibition is necessary. We have recently found that factor H, a polyanion recognition molecule and soluble regulator of alternative pathway activation in blood and on cell surfaces, can directly compete with C1q in binding to anionic phospholipids (cardiolipin), lipid A and *Escherichia coli* (three known activators of the classical pathway) and acts as a direct down regulator of the complement classical pathway. This ability of factor H to dampen classical pathway activation is distinct from its role as an alternative pathway down-regulator. Thus, by directly competing for specific C1q ligands (exogenous as well as endogenous), factor H is likely to be involved in fine-tuning and balancing the C1q-driven inflammatory processes in autoimmunity and infection. However, in the case of apoptotic cells, C1q-mediated enhancement of uptake/adhesion of the apoptotic cells by monocytes was reduced by factor H. Thus, factor H may be important in controlling the inflammation, which might arise from C1q deposition on apoptotic cells.

© 2011 Elsevier GmbH. All rights reserved.

Introduction

The complement system is a major contributor to humoral immunity, mediating many activities that contribute to host defence, homeostasis and immunological tolerance. Complement activation initially involves recognition of a wide range of target ligands that can be derived from self, non-self and altered self. Target recognition can trigger three complement activation pathways via C1q (classical pathway), Mannan-binding lectin (MBL) and ficolins (the lectin pathway), and C3, factors H and B and properdin (the alternative pathway). C1q binds, as the C1 complex ($C1q + C1r_2 + C1s_2$), mainly via charge interactions to IgG- or IgM-containing immune complexes, or directly to a non-Ig ligand such as DNA, Gram-negative bacteria, retrovirus, amyloids and prions, anionic phospholipids and synthetic substances (reviewed in Sim et al. 2007; Nayak et al. 2010).

Complement activation by the alternative pathway occurs when C3, factor B and properdin interact with particulate matter such as bacterial and fungal cell wall constituents, IgG immune complexes, or a wide variety of other compounds and surfaces (Sim and Malhotra 1994; Ferreira et al. 2010). Conversely, complement factor H binding to surfaces and/or to C3b on surfaces inhibits activation of the alternative pathway (Carreno et al. 1989). MBL and ficolins, serum proteins with structural similarity to C1q, bind mainly via nonionic interactions to glycans and other targets, leading to activation of the lectin pathway via the MBL-associated serine protease 2 (MASP-2) which is homologous to C1r and C1s (Fig. 1) (Wallis et al. 2010).

C1 is made up of three glycoproteins, C1q, C1r and C1s. C1r and C1s are serine proteases that become activated when C1q binds to a target. C1q is a 460 kDa glycoprotein composed of 18 polypeptide chains (6A, 6B and 6C) and is present in human serum at a concentration of about 115 mg/L (Reid and Porter 1976). The A, B and C chains combine to form six equivalent subunits each consisting of a collagen-like “stalk” at the N terminus of the molecule and a carboxyl-terminal heterotrimeric globular (gC1q) domain. The six subunits associate to form a structure resembling a bunch of six tulips (Kishore et al. 2004a,b). The C1r and C1s subcomponents of C1 bind the collagen region of C1q. Binding of C1q to ligands brings about a conformational change in the collagen region that activates C1r and C1s (Dodds et al. 1978). C1q binds to IgG and IgM-containing immune complexes via its gC1q domains. The majority

Abbreviations: CL, cardiolipin; MBL, mannan-binding lectin; PI, phosphatidylinositol; PA, dipalmitoylphosphatidic acid; PG, phosphatidylglycerol; PS, phosphatidylserine; PE, dimyristoylphosphatidylethanolamine; PC, phosphatidylcholine; MASP, MBL-associated serine protease; SAP, serum amyloid protein; SLE, systemic lupus erythematosus; ghA, ghB and ghC, globular head regions of C1q A, B and C chains, respectively.

* Corresponding authors. Tel.: +44 1895 266362; +44 1895 274348.
E-mail addresses: uday.kishore@brunel.ac.uk, ukishore@hotmail.com (U. Kishore), bob.sim@bioch.ox.ac.uk (R.B. Sim).

0171-2985/$ – see front matter © 2011 Elsevier GmbH. All rights reserved.
doi:10.1016/j.imbio.2011.07.024

of the non-Ig ligands also bind via the gC1q domain (Ghai et al. 2007; Nayak et al. 2010, in press).

Factor H, a single polypeptide chain protein of 155 kDa, is composed of 20 complement control protein (CCP) modules (Ripoche et al. 1988). Its concentration in human sera can be between 150 and 750 mg/L. It prevents the assembly of and dissociates the alternative complement pathway C3 convertase, C3bBb, and acts as a cofactor for factor I-mediated cleavage of C3b (Sim et al. 1993). The discrimination between activators and nonactivators of the alternative pathway is determined by binding of factor H to surfaces and to surface-associated C3b (Carreno et al. 1989; Meri and Pangburn 1990). The interaction of factor H with surface charge clusters and C3b is of major importance in the activation and regulation of complement. Factor H binds directly to many microorganisms and parasites where it is thought to down regulate complement alternative pathway activation (Díaz et al. 1997; Kraiczy and Würzner 2006).

In this article, we summarise recent evidence emerging from our laboratory that factor H can compete with C1q for binding to certain ligands such as anionic phospholipids and lipid A and down regulate the classical pathway. In addition, factor H can bind apoptotic cells independently of C1q and dampen C1q-mediated phagocytosis of apoptotic cells by monocytes.

C1q binding to cardiolipin and complement activation is inhibited by factor H

In addition to offering resistance to infection and clearance of invading pathogens, complement is also involved in the recognition and clearance of altered or damaged host cells (apoptotic and necrotic host cells). C1q has been shown to bind to subcellular particles such as mitochondria (Peitsch et al. 1988) and chromatin (Sim and Malhotra 1994), which are exposed during cell necrosis. C1q is centrally involved in the uptake and clearance of apoptotic cells (Korb and Ahearn 1997; Ogden et al. 2001). Charge molecular patterns exposed on apoptotic and necrotic cell surface (altered self) such as anionic phospholipids (e.g. cardiolipin found abundantly in mitochondrial membranes) bind C1q and activate the classical pathway (Kovacsovics et al. 1985; Bradley et al. 1999). Furthermore, factor H is known to bind anionic surfaces (e.g. synthetic polyanions) (Carreno et al. 1989) as well as cardiolipin (Kertesz et al. 1995).

To examine if factor H can interfere with C1q binding to anionic phospholipids and alter classical pathway activation, we recently surveyed C1q and factor H binding to anionic phospholipids (Tan et al. 2010). In radioimmunoassay, C1q bound to all five anionic phospholipids: PG, PI, PA, PS and CL (and also to non-anionic PE) presented on solid phase as well as in multilamellar liposomes (very high binding to CL). Factor H also bound to liposomes containing CL (and also PA, PS, PG and PI) in a manner qualitatively similar to C1q. All the anionic phospholipids activated the classical pathway, but negligibly the alternative pathway. Factor H competed directly with C1q for binding to anionic phospholipids and acted as a direct regulator of the complement classical pathway, as evident from C4 activation by anionic phospholipids using human sera in which the C1q: factor H molar ratio was adjusted over a wide range (Fig. 2) (Tan et al. 2010). A factor H homologue, β2-glycoprotein-1 (Yu et al. 1997; Ferluga et al. 1998), also strongly inhibited C1q binding to cardiolipin. Recombinant globular domains of C1q A (ghA), B (ghB) and C (ghC) chains (Kishore et al. 2003) bound anionic phospholipids similarly to native C1q, confirming that C1q binds anionic phospholipids via its globular head regions (Tan et al. 2010). Thus, the competition between factor H and C1q for binding to cardiolipin is caused by both proteins binding to CL at the same or overlapping sites. It is worthwhile to report here that in normal human serum (NHS) at physiologic ionic strength, immunoglobulins do not interfere with C1q binding to phospholipids. This activity of factor H is likely to be important in preventing excessive (inflammatory) classical pathway activation by anionic phospholipids, such as phosphatidylserine (PS) and cardiolipin, exposed on necrotic cell debris, e.g. mitochondria (Peitsch et al. 1988), or on cells altered by bacterial and spider venom sphingomyelinases (Tambourgi et al. 2002, 2007). PS and cardiolipin are exposed on apoptotic cell surfaces (Martin et al. 1995; Sorice et al. 2000), although they may not be the major binding sites for C1q or factor H on these cells.

Factor H regulates the classical pathway activation triggered by C1q binding to lipid A

We recently examined interactions of C1q and factor H with lipid A, a well-characterized activator of the classical pathway (Tan et al. 2011). C1q (as well as recombinant ghA, ghB and ghC) and factor H both bound to immobilized lipid A, lipid A liposomes and intact *Escherichia coli* (TG1 strain). Factor H competed with C1q for binding to these targets. Furthermore, increasing the factor H: C1q molar ratio in serum diminished C4b fixation, reinforcing the notion that factor H has an additional complement regulatory role of down-regulating classical pathway activation. Thus, under physiological conditions, factor H may dampen bacterially-driven inflammatory responses, thereby fine-tuning and balancing the inflammatory response in infections with Gram-negative bacteria.

The human complement system plays a major role in resistance against microbial infections via antibody-dependent and antibody-independent mechanisms. Complement is known to recognize lipopolysaccharide (LPS), which is the main amphiphilic component of the outer layer of Gram-negative bacteria. LPS is typically composed of three regions: lipid A (a highly conserved structure), core polysaccharide, and O-specific polysaccharide (Rietschel et al. 1994). Toxicity of LPS is associated with the lipid component (lipid A) while immunogenicity is associated with the polysaccharide components. The lipid A region of LPS binds to C1q leading to the activation of C1 (Cooper and Morrison 1978; Arvieux et al. 1984; Loos and Clas 1987; Clas et al. 1989). The polysaccharide region, according to its composition, may stimulate alternative and lectin pathway activation through lipid A-independent mechanisms (Morrison and Kline 1977; Jack and Turner 2003; Shang et al. 2005). Complement activation results in the generation of proinflammatory anaphylatoxins (C3a, C4a and C5a) and subsequent recruitment of neutrophils and macrophages. In addition, C3b and iC3b opsonise both Gram-negative and Gram-positive bacteria (Joiner et al. 1986), which is the major anti-bacterial defence mechanism. Excessive stimulation can also result in the serious-life threatening symptoms of septic shock (Bone 1991).

Factor H competed out C1q binding more effectively using purified lipid A compared with whole bacterial cells. These results suggest that, on *E. coli*, C1q and factor H share overlapping binding sites, but that C1q and factor H have other distinct, unshared binding sites. C1q or the C1 complex has been reported to bind to several candidate molecules on Gram-negative bacteria. These include porins or outer membrane proteins from *Aeromonas*, *Klebsiella*, *Salmonella* and *Brucella* species (Latsch et al. 1992; Alberti et al. 1996; Eisenschenk et al. 1999; Merino et al. 2005) as well as lipid A and LPS components such as polyribosylribitolphosphate from *Haemophilus influenzae* (Bunse and Heinz 1993). Alternatively, C1q can bind via its collagen-like region (CLR) to targets such as a 51/57 kDa protein from *E. coli* (van den Berg et al. 1996) and also the LPS component 2-keto-3-deoxyoctonic acid (KDO) from *E. coli* (Zohair et al. 1989) without the involvement of complement activation. There are well-known factor H-binding target ligands on Gram-negative bacteria (Kraiczy and Würzner 2006; Zipfel et al.

Download English Version:

https://daneshyari.com/en/article/10941090

Download Persian Version:

https://daneshyari.com/article/10941090

Daneshyari.com