Molecular Immunology 56 (2013) 213–221

Contents lists available at SciVerse ScienceDirect

Molecular Immunology

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

Review

Autoantibodies against complement components and functional consequences

Marie-Agnès Dragon-Durey[a,b,c], Caroline Blanc[a,d], Maria Chiara Marinozzi[a,b], Rosanne A. van Schaarenburg[e], Leendert A. Trouw[e,*]

[a] INSERM UMRS 872, Cordeliers Research Center, Paris, France
[b] Paris Descartes University, Paris, France
[c] Laboratoire d'Immunologie, Hôpital Européen Georges Pompidou, Paris, France
[d] Paris Diderot University, Paris, France
[e] Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

ARTICLE INFO

Article history:
Received 3 May 2013
Accepted 10 May 2013
Available online 20 June 2013

Keywords:
Complement
Autoantibodies
C1q
Factor H

ABSTRACT

The complement system represents a major component of our innate immune defense. Although the physiological contribution of the complement system is beneficial, it can cause tissue damage when inappropriately activated or when it is a target of an autoantibody response. Autoantibodies directed against a variety of individual complement components, convertases, regulators and receptors have been described. For several autoantibodies the functional consequences are well documented and clear associations exist with clinical presentation, whereas for other autoantibodies targeting complement components this relation is currently insufficiently clear. Several anti-complement autoantibodies can also be detected in healthy controls, indicating that a second hit is required for such autoantibodies to induce or participate in pathology or alternatively that these antibodies are part of the natural antibody repertoire.

In the present review, we describe autoantibodies against complement components and their functional consequences and discuss about their clinical relevance.

1. Introduction

The complement system is an important part of the immune defense (Ricklin et al., 2010). Traditionally placed in the innate immune system, complement plays an essential role in the host's defense against pathogens. More recent insight clearly indicates that complement components also play essential roles in instructing the adaptive immune response. In fact, over the past decade, complement or individuals complement components have been implicated in a wide variety of physiological processes such as clearance of dead cells (Trouw et al., 2008), pruning of nerve endings, gestation, lipid metabolism, tumor progression and tissue regeneration (Ricklin et al., 2010).

Next to all the good the complement system does to keep the host clear of pathogens and maintaining tissue integrity, complement activation is also involved in a wide array of diseases, either because of too much activation, too little regulation or both (Ricklin et al., 2010). At the far end of this spectrum complement components themselves are targeted by an immune response of the host resulting in an autoantibody response against complement components (Norsworthy and Davies, 2003; Trouw et al., 2001). The first reports on antibody responses against complement components describe the immunoconglutinins, autoantibodies that target autologous C3 and C4 solid-phase fragments (Lachmann, 1967). Immunoconglutinins have been reported to occur in Crohn's disease and in rheumatoid arthritis (RA) (Druguet et al., 1980) as well as systemic lupus erythematosus (SLE) (Durand and Burge, 1984; Nilsson et al., 1990).

In this review we will highlight the currently known anti-complement autoantibodies and describe their molecular and clinical consequences. Two autoantibodies will be particularly highlighted, anti-C1q autoantibodies and anti-factor H antibodies.

2. Antibodies directed against classical pathway components

2.1. Anti-C1q autoantibodies

The autoantibodies that target C1q mainly target epitopes that are present in the collagen like region (CLR) of C1q (Agnello et al., 1971; Antes et al., 1988). The antibodies are directed against a neo-epitope that becomes accessible once the C1q molecule is bound in the solid-phase. To discriminate anti-C1q

* Corresponding author at: Department of Rheumatology, C1R, Leiden University Medical Center, 2333ZA Leiden, The Netherlands. Tel.: +31 715235723.
E-mail address: L.A.Trouw@LUMC.nl (L.A. Trouw).

0161-5890/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.molimm.2013.05.009

Table 1
Targeted complement proteins.

Target protein	Associated diseases	Predisposal condition	Isotype	Epitopes identified	Functional consequence	References
C1q	SLE	–	IgG	CLR and globular region		Reviewed in Trendelenburg (2005), Seelen et al. (2003)
	Sd Mac Duffy (HUVS)	–	IgG			Wisnieski and Naff (1989)
C1s	SLE	–	IgG	NK	Increased C1s activity, low C4	He and Lin (1998)
C1-inhibitor	Acquired angioedema	Lympho-proliferative disorders (more rarely SLE)	Any isotype, depending on the monoclonal gammopathy	Reactive center	C1-inhibitor inactivation (clivage)	Geha et al. (1985), Cicardi et al. (1996), Mandle et al. (1994)
MBL	SLE	–	IgG and IgM	NK	NK	Seelen et al. (2003), Takahashi et al. (2004), Mok et al. (2004)
Ficolin-3	SLE	–	IgG	NK	NK	Inaba et al. (1990)
FH	HUS	CFHR1 complete deficiency	IgG3 and IgG1, 1 case IgA	C-term part, C and N term parts at onset	CFH neutralization (immune complexes formation), default of cell membranes protection	Dragon-Durey et al. (2005, 2010), Strobel et al. (2010)
	C3GP	Lympho-proliferative disorders	IgG, free λ light chain	N-term part	Default of FH cofactor activity	Meri et al. (1992), Jokiranta et al. (1999), Brackman et al. (2011), Lorcy et al. (2011), Nozal et al. (2012), Goodship et al. (2012), Bridoux et al. (2011)
	RA, SLE	–	IgG	NK	NK	Foltyn et al. (2012)
	NSCLC	–	IgG	NK	NK	Amornsiripanitch et al. (2010)
FI	HUS	–	IgG	NK	Low experimental evidence	Kavanagh et al. (2012)
C3 alternative pathway C3bBb (C3Nef)	C3GP, APLD	–	IgG	C3bBb neoepitope	Fluid and solid phase C3bBb stabilization, resistance to regulation	Spitzer et al. (1969), Davis et al. (1977), Ohi et al. (1992), Paixao-Cavalcante et al. (2012), Misra et al. (2004)
C4 alternative pathway C3bBb (C4Nef)	SLE, post infectious GN, meningitidis	–	IgG	NK	C4b2a stabilization, resistance to regulation	Daha and van Es (1980), Halbwachs et al. (1980), Gigli et al. (1981), Miller et al. (2012)
FB +/ C3	C3GP	–	IgG	Bb, C3b/C3c	Solid phase C3bBb stabilization, resistance to regulation	Strobel et al. (2010), Chen et al. (2011)
CR1	SLE	–	–	–	Low CR1 expression	Wilson et al. (1985), Cook et al. (1986)
CR2	RA	–	–	–	B cell activation	Barel et al. (1986)
CR3	SLE, RA, HIV	–	–	–	Neutropenia, susceptibility to infection	Hartman and Wright (1991), Rubinstein et al. (1999)

SLE: systemic lupus erythematosus; HUVS: hypocomplementemic urticarial vasculitis syndrome; RA: rheumatoid arthritis; HUS: hemolytic uremic syndrome; C3GP: C3 glomerulopathies; NSCLC: non-small cell lung carcinoma; APLD: acquired partial lipodystrophy; GN: glomerulonephritis; NK: not known.

autoantibodies binding to C1q from immunecomplexes binding to C1q a high salt containing buffer should be used, the anti-C1q autoantibodies will still bind whereas the low-avidity interaction between immunecomplexes and C1q is disrupted (Kohro-Kawata et al., 2002). Later assays were developed that used purified CLR so that high salt buffer was no longer needed. Recently a novel test based on linear peptides was reported (Vanhecke et al., 2012). By now, anti-C1q autoantibodies have been reported to occur in a wide variety of diseases, as reviewed in Seelen et al. (2003a), Siegert et al. (1992) and Trendelenburg (2005). Anti-C1q autoantibodies are also present in healthy individuals and the percentage increases with age ranging from 4% up to 18% in the elderly (Siegert et al., 1993) (Tables 1 and 2).

IgG anti-C1q autoantibodies have a extremely high prevalence in hypocomplementaemic urticarial vasculitis syndrome (HUVS), where up to 100% of the cases are reported to be positive for