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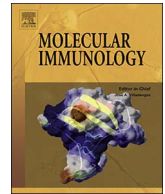
Review

C1q: A fresh look upon an old molecule

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A R T I C L E   I N F O

A B S T R A C T

Originally discovered as part of C1, the initiation component of the classical complement pathway, it is now appreciated that C1q regulates a variety of cellular processes independent of complement activation. C1q is a complex glycoprotein assembled from 18 polypeptide chains, with a C-terminal globular head region that mediates recognition of diverse molecular structures, and an N-terminal collagen-like tail that mediates immune effector mechanisms. C1q mediates a variety of immunoregulatory functions considered important in the prevention of autoimmunity such as the enhancement of phagocytosis, regulation of cytokine production by antigen presenting cells, and subsequent alteration in T-lymphocyte maturation. Furthermore, recent advances indicate additional roles for C1q in diverse physiologic and pathologic processes including pregnancy, tissue repair, and cancer. Finally, C1q is emerging as a critical component of neuronal network refinement and homeostatic regulation within the central nervous system. This review summarizes the classical functions of C1q and reviews novel discoveries within the field.

1. The complement C1q molecule: from early appearance in evolutionary time to recent recombinant expression

At the time of its discovery at the end of the 19th century complement was described as a heat-labile factor able to cooperate with antibodies to eliminate bacteria. By the mid-1920s complement was recognized as consisting of four components (C1 to C4, with names assigned in order of their discovery), and their isolation from serum was achieved in the early 1940s (Sim et al., 2016). The macromolecular nature of C1 as a complex of three protein entities, namely C1q, the recognition subunit, and its associated proteases C1r and C1s, was defined in the early 1960s, i.e. more than half a century ago (Lepow et al., 1963; Naff et al., 1964). The fact that C1q and the initiating proteins of the classical complement pathway were first discovered is likely related to the high concentrations of these proteins in serum, by comparison with the corresponding recognition proteins (mannan-binding lectin

(MBL), ficolins) and associated proteases (MBL-associated serine proteases) of the lectin complement pathway. From this point of view C1q can be considered undoubtedly as an old molecule.

In addition, C1q is also "old" in being present early in evolutionary time. An orthologue of vertebrate C1q proteins has been identified in amphioxus, the modern survivors of the ancient basal chordate lineage (Gao et al., 2014), well before the appearance of jaw vertebrates and adaptive immunity. C1q from Branchiostoma japonicum (BjC1q) possibly activates a primitive C1q-mediated complement system, through the binding of Ig-domain-containing amphioxus proteins as well as C4-activating proteases. BjC1q can also bind mammalian C1r and C1s proteases, as well as human IgG, and thus can replace human C1q to activate the human classical pathway. The C1q molecule further evolved with three different A, B and C subunits, possibly during the diversification of cartilaginous fishes, with clear sequence signatures characterizing their functional evolutionary diversification (Gao et al.,

2014; Tariq et al., 2015; Goshima et al., 2016). Although only one C1q, C1r, C1s protein sequence has been obtained from the liver transcriptome of a hammerhead shark, the presence of three C1q chains in the nurse shark has been reported at the protein level, suggesting that C1q could be expressed in extra-hepatic sites in sharks as in mammals (Goshima et al., 2016). A recent study details the C1q sequences in the Chinese goose and the corresponding evolutionary relationships of the three C1q subunits in duck, chicken, bird and alligator (Tariq et al., 2015).

1.1. C1q ultrastructure and polypeptide chain composition

Electron microscopy studies in the 1970s revealed the typical shape of C1q as resembling a bunch of flowers, with six peripheral globular regions each connected by fibrillar strands to a central bundle of fibers (Shelton et al., 1972; Svehag et al., 1972). In parallel, detailed biochemical studies revealed that C1q is a complex glycoprotein assembled from 18 polypeptide chains of three different types named A, B, and C of 29, 27, and 23 kDa, respectively. Each chain comprises an N-terminal collagen-like sequence and a C-terminal globular gC1q module, with disulfide bridges linking the N-terminal ends of the A and B chains and of two C chains (Reid and Porter, 1976). Each A-B dimer associates with a C chain, resulting in a basic subunit comprised of two disulfide-linked heterotrimeric collagen-like triple helices prolonged by globular domains (Fig. 1). Biochemical characterization of the C1q protein culminated in the determination of the amino acid sequences of the entire A and B chains and that of the collagen-like region of the C chain by N-terminal Edman sequencing (Reid, 1979; Reid et al., 1982). Both cDNA and genomic clones were isolated shortly afterwards for the A and B chains (Reid, 1985), and the isolation of the cDNA sequence of the C chain allowed completion of the entire derived amino acid sequence of the C1q molecule (Sellar et al., 1991). The three genes were found to be aligned 5′-3′ in the same orientation and in the order A-C-B on human chromosome 1p.

1.2. C1q functional domains

The presence of two distinct types of structures in the C1q molecule, *i.e.* the globular heads and the collagen-like fragments, allowed their isolation by limited proteolysis of C1q with collagenase and pepsin, respectively (Brodsky-Doyle et al., 1976; Hughes-Jones and Gardner, 1979). Functional studies showed that the globular regions are mainly responsible for target recognition, including binding to the Fc region of immunoglobulins (Hughes-Jones and Gardner, 1979), but also to bacterial and viral surface proteins, as well as altered self elements (apoptotic cells, amyloid and prion proteins) (Gaboriaud et al., 2011). The collagen-like regions mediate immune effector mechanisms, including complement activation through interaction with the C1r and C1s proteases (Siegel and Schumaker, 1983) and enhancement of phagocytosis through interaction with cell receptors (Bobak et al., 1987).

Isolation of the globular region of C1q allowed determination of its X-ray crystal structure, revealing a compact heterotrimeric assembly with a calcium ion bound at the top (Gaboriaud et al., 2003). Each of

the three gC1q modules exhibits distinct surface patterns of charged and hydrophobic residues, which likely endow them with a diversity of specific recognition properties. In addition, the compact structure of the trimer allows ligand binding through residues contributed by two or three chains, thereby broadening the recognition spectrum of C1q (Gaboriaud et al., 2003). This structure confirmed the structural homology between tumor necrosis factor (TNF) and gC1q-containing proteins, previously revealed in the crystal structures of the homo-trimeric gC1q domain of mouse adiponectin (Shapiro and Scherer, 1998) and collagen X (Bogin et al., 2002).

1.3. Recombinant C1q and site-directed mutagenesis studies

Detailed investigation of the structure-function relationships of C1q required its production in a recombinant form. The first achievements consisted in bacterial expression of soluble fusion proteins of the individual gC1q domains (A, B and C) with maltose binding protein (MBP), which were purified by affinity chromatography on an amylose resin. Characterization of their interaction properties revealed that these domains have likely evolved as functionally autonomous entities with differential ligand-binding properties (Kishore et al., 2003). Site-directed mutagenesis revealed that the binding sites for a number of C1q target molecules, including IgG, IgM, pentraxins and bacterial components such as *Salmonella* lipopolysaccharides and *Klebsiella* outer membrane protein K36, are closely overlapping (Kojouharova et al., 2003; Kojouharova et al., 2004; Roumenina et al., 2006; Zlatarova et al., 2006; Roumenina et al., 2008), but differ from the binding sites for the viral glycoproteins gp41 of HIV-1 and gp21 of HTLV-1 (Kojouharova et al., 1998; Kishore et al., 2003).

Production of full-length recombinant C1q has been a major technical bottleneck for a long time, owing to the three chain structure, particular inter-chain disulfide pattern and numerous post-translational modifications of the molecule. For example, the collagen-like sequences of C1q contain the repeating Gly-X-Y triplet where X is often a proline residue and Y a hydroxyproline or hydroxylysine residue, the latter being frequently modified with glucosylgalactosyl disaccharide units (Reid, 1979; Pflieger et al., 2010). However, this challenge was achieved in 2013 with the production of the full-length recombinant protein in stably transfected mammalian 293-F cells (Bally et al., 2013). The recombinant C1q molecule is similar to serum-derived C1q, as judged from biochemical analysis and electron microscopy imaging, and retains the ability to associate with the C1r and C1s proteases, to recognize physiological C1q ligands including IgG and pentraxin 3, and to trigger complement activation. The production of recombinant C1q opened the way for deciphering the interaction properties of this protein by site-directed mutagenesis, as illustrated by the identification of the C1s-C1r-C1r-C1s–binding residues in the C1q collagen-like stems (Bally et al., 2013). The availability of recombinant C1q should allow engineering of C1q molecules lacking specific functions (*i.e.* complement activation or binding to a protein partner) which will represent unique tools to study the role of C1q in various cellular contexts.

The latest progress in recombinant C1q production was the generation of a single-polypeptide form of the human C1q globular region (C1q-scGR) (Moreau et al., 2016), based on a strategy previously used
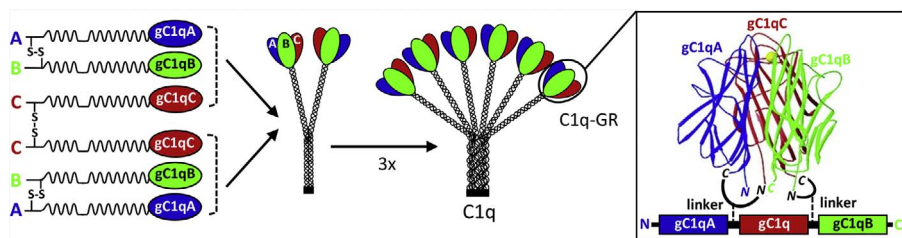
Fig. 1. Schematic representation of the assembly of the C1q molecule and of the recombinant single chain globular region. C1q is assembled from three polypeptide chains (A, B and C) each containing an N-terminal collagen-like sequence and a C-terminal globular gC1q module. A particular inter-chain disulfide pattern results in a basic subunit comprised of two heterotrimeric collagen-like stalks prolonged by globular domains (C1q-GR). Three subunits associate to yield the full-length protein with a typical shape of a bouquet of six flowers. The crystal structure of the trimeric C1q-GR shows that the N- and C- terminal ends of the 3 chains are in close proximity which allowed insertion of short linkers between the gC1qA-gC1qC and gC1qC-gC1qB modules to yield a recombinant single chain construct.

to produce a single-chain form of the homotrimeric globular domain of adiponectin, a protein structurally related to C1q (Ge et al., 2010). Indeed the crystal structures of the globular domains of mouse adiponectin (Shapiro and Scherer, 1998) and of C1q (Gaboriaud et al., 2003) revealed the close proximity of the N- and C-termini of the three gC1q modules at the base of the trimer (Fig. 1), allowing connection of adjacent monomers by short linkers. Physicochemical, structural, and functional characterization of the recombinant single chain fragment, produced at high yield in stably transfected 293-F cells, showed that its 3D-structure and binding properties were similar to those of the three-chain fragment generated by collagenase digestion of serum-derived C1q (Moreau et al., 2016).

This novel recombinant tool will allow more reliable assessment of the effects of single residue mutations in a heterotrimeric context as present in native C1q and the ability to test the hypothesis that recognition of certain ligands involves residues contributed by several subunits.

2. Classical functions: complement, phagocytosis and cytokine regulation

2.1. The classical complement pathway

Originally discovered as a part of C1, the classical complement pathway initiation complex C1qC1r$_2$C1s$_2$, C1q was quickly shown to have the recognition motif for the Fc portion of IgM and IgG. Appropriate binding of the C1q globular head domains to multiple Fc regions of antibody in an immune complex alters the conformation of the serine protease C1r, enabling autoactivation of C1r and then cleavage of C1s. C1r activation somehow involves conformational changes, since it is produced in a proenzyme form, with a collapsed binding site conformation (Gohara and Di Cera, 2011). Activated C1s, also a serine protease, then cleaves C4 and C2 to generate the classical complement C3 convertase, C4b2b and the C5 convertase, C4b2b3b. As such, this leads to the generation of chemotactic peptides C3a and C5a and thus recruitment of immune effector cells to the site of infection, and initiates antibody mediated killing of pathogens by the downstream complement components via the generation of membranolytic C5b-9 and/or opsonization of the pathogen by C3b (also iC3b, C4b and C1q) followed by complement receptor mediated ingestion and degradation by phagocytes. Evidence has since accumulated of antibody independent activation of C1 via C1q binding to other exogenous molecules such as lipid A and other constituents of bacteria and viruses indicating a primary role of C1 in protection from pathogens. In addition, endogenous substances such as apoptotic cells, beta sheet amyloid fibrils, pentraxins and others have been shown to bind C1q and activate C1 (reviewed in (Bohlson et al., 2007)). This diversity of possible interactions is derived from the 3 independently folded A, B, and C globular domains and combination of sites as indicated above. The outcome of these interactions depends on both the complement proteins present at the site as well as the ability of the activating substance to bind complement activation inhibitors (reviewed in (Sjoberg et al., 2009)).

2.2. Enhancement of phagocytosis

In the late 1980s, a role for C1q that was independent of complement activation emerged with the observation that immobilized C1q, in the absence of C1r and C1s, triggered an enhancement of FcγR-mediated phagocytosis when targets were coated with a sub-optimal concentration of antibody (Bobak et al., 1987). This observation suggested that C1q may be beneficial during early stages of an immune response, or in the immunocompromised conditions that may correspond to limited antibody production. The activity required the collagen-like tail of C1q (Bobak et al., 1987), and extended to enhancement of CR1-mediated phagocytosis (Bobak et al., 1988). Moreover, the

enhancement of phagocytic function was shared with structurally similar "defense collagens" including SP-A and MBL (Tenner et al., 1989; Tenner et al., 1995). C1q stimulated enhanced phagocytic function when it was either immobilized on a substrate, or within a soluble immune-complex (IC) (Webster et al., 2001).

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the generation of autoantibodies (reviewed in (Beurskens et al., 2015)) and IC deposition leading to chronic inflammation and tissue/organ destruction. C1q-deficiency in humans results in development of SLE or an SLE-like syndrome (Manderson et al., 2004; Stegert et al., 2015) consistent with a role for C1q in clearance of IC. In addition, either complete genetic C1q deficiency in mice, or a lower production of C1q by murine peritoneal macrophages, has been linked to the presence of autoantibodies and murine lupus nephritis (Botto et al., 1998; Miura-Shimura et al., 2002). Therefore, C1q may be beneficial in facilitating clearance of IC in vivo thus limiting pathology associated with SLE both indirectly, via activation of the classical complement pathway and deposition of C3b (the ligand for CR1), or directly via enhanced phagocytosis of IC. However, an additional role of C1q in the clearance of apoptotic cells was highlighted when C1q knock out mice displayed a deficit in clearance of peritoneally injected apoptotic cells and enhanced glomerulonephritis (Botto et al., 1998). Apoptotic cells are considered the source of auto-antigen in SLE, and C1q binds to surface blebs on apoptotic human keratinocytes (Korb and Ahearn, 1997) via the globular head region (Navratil et al., 2001). Studies over the last 15 years confirmed that C1q enhances phagocytosis of a variety of apoptotic cells by multiple cell types both in vitro and in vivo (reviewed in (Galvan et al., 2012a)). Interestingly, most recently Elkon and colleagues, using an inhibitor of C1s, demonstrated that C1q facilitates apoptotic cell engulfment independent of classical pathway activation (Colonna et al., 2016).

2.3. Programmed engulfment of apoptotic cells

C1q triggers immediate responses from phagocytes resulting in enhanced phagocytosis of a variety of targets (e.g. IC, antibody and complement- opsonized targets and apoptotic cells) as discussed above, and this phenomenon has been the subject of much investigation. However, over the last decade we have begun to appreciate the role of C1q in programming responses from phagocytic cells resulting in enhanced phagocytic capacity and alternation in pro-inflammatory cytokine synthesis (reviewed in (Bohlson et al., 2014)). Analysis of gene expression profiles in C1q-stimulated mouse bone marrow derived macrophages (BMDM) identified multiple pro-phagocytic genes that were upregulated by C1q. Among these genes, Mer tyrosine kinase and its ligand Gas6 were upregulated in C1q-stimulated BMDM, and C1q-dependent enhanced engulfment of apoptotic cells required de novo Mer expression in vitro since Mer-deficient macrophages failed to respond to C1q with enhanced engulfment of apoptotic cells (Galvan et al., 2012b). Unlike the immediate signal for enhanced phagocytosis which is mediated by the collagen-like tails of C1q, and conserved with MBL, programmed efferocytosis required the full-length C1q molecule and was not shared with MBL. While primary human macrophages failed to upregulate Mer expression following prolonged stimulation with C1q alone (Hulsebus et al., 2016), human monocytes and dendritic cells cultured with the combination of C1q and HMGB1 upregulated Mer, suggesting a conserved pathway in mouse and human cells (Son et al., 2016). These data are consistent with the observation that there is a reduction in the expression of pro-engulfment genes in macrophages from patients with SLE (Majai et al., 2014). Future studies should reveal the contribution of C1q to expression of pro-engulfment genes in vivo.

Table 1
Main features of C1q receptors.

Names (CD number) Family	Cellular expression	Ectodomain composition	C1q region recognized	Main protein ligands /partners	C1q-mediated biological response
gC1qR, C1qBP, p33, p32	Mitochondrial protein	"doughnut-like" trimer	gC1q	DC-SIGN, CRT β_1 integrin	Regulation of DC differentiation (trimolecular complex with DC-SIGN)
cC1qR, calreticulin, CRT	ER lectin-like chaperone	Lectin-like + "arm"	cC1q gC1q	MBL, ficolins, LRP1, CD59	Eat-me signal for apoptotic cells phagocytosis
CR1 (CD35) Regulator of complement activation	Erythrocytes, leukocytes, DCs	4 long homologous repeats of CCP modules	cC1q	C3b, C4b MBL, ficolins	Possible role in the clearance of immune complexes
LRP1, α_2M receptor (CD91) LDL receptor	MΦs, DCs, non-professional phagocytes	4 clusters of LA, WTD and EGF-like modules	cC1q gC1q	Lipoproteins, ECM proteins, CRT, CR3, protease-inhibitor complexes	Uptake of apoptotic cells
$\alpha_2\beta_1$ β_1 integrin	leukocytes, platelets	α-β heterodimer	cC1q	Collagen, laminin MBL, SP-A, CRT	Activation of peritoneal mast cells
CR3, Mac1, $\alpha_M\beta_2$ (CD11bCD18) β_2 integrin	Specific MΦ populations, DCs	α-β heterodimer	?	iC3b, sRAGE, LRP1, collagen	Apoptotic cells clearance (trimolecular complex with RAGE)
SREC-I, SCARF1, SR-F1 Scavenger receptor	Macrophages, DCs, endothelial cells	7 EGF-like modules	?	oxLDL, HSP, CRT, SRF-2 ectodomain	Apoptotic cells clearance
Megf10, SR-F3 Scavenger receptor	Astrocytes, myosatellite cells	EMI + 15 EGF-like modules	?	amyloid-β peptide (Aβ42)	Apoptotic cells clearance by astrocytes
RAGE, SR-J Ig superfamily receptor	Leukocytes, DCs, endothelial cells, neurons	3 IgG-like modules (V-C1-C2)	gC1q	HMGB1, AGE, PS, CR3,	Apoptotic cells clearance (trimolecular complex with CR3) Differentiation of monocytes to M2-like macrophages (tetramolecular complex with LAIR-1 and HMGB1)
LAIR-1 (CD305) Inhibitory Ig-like immune receptor	Myeloid and lymphoid immune cells	Ig-like module (C2)	cC1q	MBL, SP-D, collagens)	Restriction of DC differentiation and activation Differentiation of monocytes to anti-inflammatory M2-like MΦs (tetramolecular complex with RAGE and HMGB1)
Siglec-3 (CD33) Inhibitory Ig-like immune receptor	Myeloid immune cells	2 IgG-like modules (V-C2)	gC1q	CD14	Restriction of DC differentiation and activation (trimolecular complex with LAIR-1)
DC-SIGN (CD209) C-type lectin receptor	Most immune cells, Macrophages, DCs, PMNs	Tetramer; neck + C-lectin domain	gC1q	ICAM-3, gC1qR	Regulation of DC differentiation (trimolecular complex with gC1qR)

2.4. Anti-inflammatory role of C1q parallels clearance of immune complexes and apoptotic cells

As discussed above, C1q has been shown to play a role in enhancing phagocytosis of IC and apoptotic cells, likely to be critical in the prevention of chronic inflammation and autoimmunity. In tissue where C1q can be synthesized in the absence of C1r and C1s in response to injury (Bensa et al., 1983; Fonseca et al., 2011), this would facilitate rapid clearance of pro-inflammatory IC or cellular debris. In addition, however, C1q decreases proinflammatory cytokine release and promotes production of anti-inflammatory mediators in macrophages, dendritic cells and microglia (Bohlson et al., 2014), consistent with silent clearance of cell debris, and provides a checkpoint for induction of an immune response to cell antigens. Specifically, while enhancing clearance, C1q bound to apoptotic cells directed human monocyte-derived macrophages (HMDM) ingesting these apoptotic cells towards a less inflammatory state, characterized by induction of gene expression and protein secretion of the anti-inflammatory cytokines IL-27 and IL-10, as well as decreasing inflammasome activity and the secretion of mature IL-1β (Benoit et al., 2012). This anti-inflammatory function of C1q skews the adaptive immune system towards a more regulatory state and a limited induction of an immune response to the autoantigens being ingested. Importantly, in a mixed-leukocyte reaction, human macrophages ingesting C1q-coated apoptotic cells added to allogeneic or autologous T cells significantly and substantially decreased Th17 and Th1 subset proliferation, and demonstrated a trend towards increased Treg proliferation relative to macrophages ingesting apoptotic cells without C1q. Similarly, C1q-polarized dendritic cells decreased autologous Th17 and Th1 proliferation relative to dendritic cells ingesting apoptotic cells in the absence of C1q (Clarke et al., 2015). These data

are consistent with the suppressive effect of C1q on dendritic cell maturation (Castellano et al., 2007) and that of Lu and colleagues (Teh et al., 2011) demonstrating that primary human monocytes differentiated to dendritic cells in the presence of immobilized C1q showed reduced induction of allogeneic Th1 and Th17 cells. Thus, C1q-polarized phagocytic cells regulate T effector cell activation, essentially "sculpting" the adaptive immune response to avoid autoimmunity while clearing dying cells. While there have been some studies suggesting the possibility of a direct C1q interaction with T cells, more definitive investigations are needed (reviewed in (Clarke and Tenner, 2014)). The recent confirmation of the predominant role of C1q (rather than C1 activation and C3b deposition) on clearance and immunosuppression of apoptotic cells should direct therapeutic intervention in SLE and other autoimmune diseases (Colonna et al., 2016).

C1q-dependent immunoregulatory functions have also been observed in IC clearance via different mechanisms. Interestingly, in the human system, C1q-bound to ICs markedly shifted IC binding to monocytes and away from plasmacytoid DCs (pDCs), thereby reducing the expression of the majority of IFNα-response genes induced by ICs (Santer et al., 2010; Santer et al., 2012) and characteristic of the IFN signature associated with SLE progression (Baechler et al., 2003). In the mouse, Ossendorp and colleagues have reported that C1q enhances uptake of IC in splenic dendritic cells, and thereby promotes cross presentation to CD8+ T cells (Ho et al., 2017). Further studies are needed to determine the contributions of these activities to regulating the immune response.

3. Interaction with cell surface proteins: old and new receptors

The interaction of C1q with the lymphocyte surface was suggested

in the early 1970s (Dickler and Kunkel, 1972) and subsequently demonstrated for most cells of the peripheral blood under various conditions, as well as cells involved in tissue repair and wound healing including platelets, fibroblasts, endothelial cells, mast cells, and epithelial cells (reviewed by (Kouser et al., 2015)). Deciphering which are the key molecules involved in these different contexts remains under investigation. Rather than "one C1q receptor or even receptor complex", it is now proposed that different complexes of surface molecules act in concert upon engagement of C1q to induce function relevant to the microenvironment, either to maintain homeostasis, or to respond to infection or other challenges in tissue. Apart from historical C1q-binding proteins, cC1qR (CRT) and gC1qR, which lack transmembrane domains, known C1q receptors might be grouped according to the nature of their extracellular domains: (i) large multimodular ectodomains involved in interaction with multiple ligands (CR1, LRP1 and the recently identified scavenger receptors SR-F1 and SR-F3); (ii) integrins (α_2-β_1 and CR3/α_M-β_2); (iii) Ig-like receptors (RAGE, LAIR-1 and CD33) and (iv) the lectin receptors DC-SIGN and DC-SIGNR. Another important feature of C1q receptors lies in the existence of soluble counterparts, arising from gene alternative splicing (soluble RAGE and DC-SIGN isoforms), gene duplication (LAIR-2), or proteolytic ectodomain shedding (as reported for CR1 and LRP1). These soluble proteins might act as decoy receptors by competing with cell surface receptors for ligand binding and preventing subsequent signal transmission, thereby playing a role in regulation of C1q-mediated cellular functions. The main features of C1q receptors are summarized in Table 1 and we will address a few of these below.

3.1. cC1q and gC1q receptors

Paradoxically, the first two C1q binding proteins that were described as receptors for the collagen-like and the globular regions of C1q (cC1qR/collectin receptor/calreticulin (CRT) and gC1qR, respectively) (Malhotra et al., 1993; Ghebrehiwet et al., 1994) turned out to be multifunctional, primarily intracellular proteins located in the endoplasmic reticulum (cC1qR/CRT) and in mitochondria (gC1qR/p33), but which were detected at the surface of a wide variety of cells. Since both proteins lack a transmembrane domain or lipid anchor, they need to function in association with other surface molecules. (Ogden et al., 2001; Vandivier et al., 2002; Ghiran et al., 2003) (Hosszu et al., 2012). There are however contradictory reports and definitive experiments remain to be done to establish functional correlates of these protein interactions (see below). In addition, the term cC1qR, although historical, is probably no longer appropriate since it has been demonstrated that cC1qR is identical to CRT and also binds to the globular regions of C1q (Kovacs et al., 1998; Paidassi et al., 2011).

3.2. Receptors involved in C1q enhancement of phagocytosis

Identification of the receptor(s) required for C1q-dependent phagocytosis has remained enigmatic despite years of investigation. Monoclonal antibodies reactive with CD93, a transmembrane glycoprotein expressed on phagocytic cells, inhibited C1q-dependent enhanced phagocytosis (Guan et al., 1994; Steinberger et al., 2002). However, CD93 did not bind directly to C1q (McGreal et al., 2002), and mice deficient in CD93, though deficient in clearance of apoptotic cells in vivo, responded to C1q with enhanced phagocytic function in vitro (Norsworthy et al., 2004). Similarly, antibodies against CRT inhibited C1q-dependent engulfment (Ogden et al., 2001). CRT has been localized to the plasma membrane of multiple cell types, including apoptotic cells and cancer cells, where it functions as an "eat me" signal. While CRT-dependent engulfment of apoptotic cells required expression of LRP1/CD91 on the phagocyte (Gardai et al., 2005), LRP1/CD91 was not required for C1q-dependent enhancement of FcγR-mediated phagocytosis, nor was it required for C1q-dependent engulfment of apoptotic cells in the presence of serum (Lillis et al., 2008). These data

suggest that multiple receptors or multi-molecular complexes may regulate C1q-dependent phagocytic function, as discussed further below.

3.3. Multimodular endocytic and scavenger receptors

CR1 is known as a receptor for complement fragments C4b and C3b (immune adherence receptor) and a regulator of complement activation, (reviewed in (Krych-Goldberg and Atkinson, 2001)). C1q has been shown to interact with CR1 LHR-D in vitro (Klickstein et al., 1997), but the contribution of the C1q-CR1 interaction in immune adherence remains to be fully elucidated.

LRP1, a large, 600-kDa multifunctional endocytic receptor of the LDL receptor family, has been shown to interact with C1q in vitro (Duus et al., 2010a) but as mentioned above, at least the ability of C1q to enhance engulfment of apoptotic cells or antibody-coated targets is not impaired by the lack of CD91/LRP (Lillis et al., 2008). Both CR1 and LRP1 have been shown to interact with other defense collagens such as MBL and ficolins in vitro (Duus et al., 2010b; Jacquet et al., 2013), suggesting binding of these receptors to the conserved collagen-like regions of the defense collagens.

The class F scavenger receptors SR-F1 (*alias* SCREC-I/SCARF1) and SR-F3 (*alias* Megf10) have been suggested to play a crucial role in the C1q-dependent engulfment of apoptotic cells and in preventing autoimmunity (Ramirez-Ortiz et al., 2013; Iram et al., 2016). SR-F1 has been described as an endocytic receptor for CRT (Berwin et al., 2004), but no interaction was detected using isolated proteins (Ramirez-Ortiz et al., 2013). It has also been shown to interact through its ectodomain with the related scavenger receptor SRF-2 (Ishii et al., 2002), but the possible role of this interaction in the context of C1q binding remains to be investigated. Recessive mutations in Megf10/SR-F3 result in a rare disease characterized by early-onset myopathy, respiratory distress and dysphagia (EMARDD), and cells expressing EMARDD mutations are defective at engulfment of apoptotic cells and internalization of C1q (Iram et al., 2016). However, the role of C1q in progression of EMARDD and the protein domains involved in C1q-SR-F1 or −SR-F3 interaction remain to be determined.

3.4. Integrins $\alpha_2\beta_1$ and $\alpha_M\beta_2$

Integrin $\alpha_2\beta_1$ is known as a receptor for extracellular matrix components, including collagen and laminin. It has been shown to interact with CRT at the surface of various cells, including platelets (Elton et al., 2002) and with C1q and other members of the collectin family such as MBL and SP-A. The C1q-$\alpha_2\beta_1$ interaction has been suggested to play a role in mast cell activation and cytokine secretion and to involve the collagen-like part of C1q and the integrin inserted (I) domain, similar to that involved in collagen binding (Edelson et al., 2006).

Integrin $\alpha_M\beta_2$ (or CR3) is a phagocytic integrin that plays an essential role in the uptake of target particles (e.g. microorganisms and apoptotic cells) opsonized with complement C3 fragments (reviewed in (Ehlers, 2000)), as well as is essential for the generation of superoxide by human neutrophils triggered by immobilized C1q (Goodman et al., 1995). CR3 has been shown to interact extracellularly with C1q receptor components including LRP1 (Ranganathan et al., 2011) and RAGE, and directly with C1q (Ma et al., 2012). Since the collagen domain of C1q is sufficient for the CD18-dependent induction of superoxide in neutrophils, and CR3 has recently been reported to bind collagens in vitro (Lahti et al., 2013), it is possible that the interaction of CR3 involves the collagen-like region of C1q, but this has not yet been biochemically determined.

3.5. Ig-like receptors RAGE, LAIR-1 and CD33

RAGE is a multi-ligand receptor for endogenous danger signals such as AGEs, HMGB1 and DNA, and participates in apoptotic cell clearance

by acting as a phosphatidylserine (PS) receptor (reviewed in (Sorci et al., 2013). It was shown recently to bind to the globular regions of C1q and to enhance C1q-mediated phagocytosis of apoptotic cells, a process proposed to involve a ternary complex with the CR3 receptor (Ma et al., 2012).

LAIR-1 is an inhibitory collagen receptor involved in the control of various phases of the immune response (reviewed by (Meyaard, 2008)). LAIR-1 and its soluble homologue LAIR-2 have been shown to interact with C1q and related proteins, including MBL and surfactant protein D, through their collagen-like regions (Olde Nordkamp et al., 2014a,b). LAIR-1 engagement by C1q inhibits DC differentiation and activation either during steady state or inflammation and is suggested to help maintain monocyte tolerance (Son et al., 2012; Son and Diamond, 2015). In addition, C1q was reported recently to suppress the HMGB1-polarization of monocytes and maintain an anti-inflammatory M2-like macrophage, a pathway mediated through a complex with both RAGE and LAIR-1 and depending on the relative levels of C1q and HMGB1 (Son et al., 2016).

CD33 is an inhibitory immunoreceptor of the sialic acid Ig-like lectin (Siglec) family of receptors able to promote sialic acid-dependent cell adhesion (Crocker et al., 2007). C1q was reported recently to crosslink CD33 and LAIR-1, thereby triggering phosphorylation of CD33/LAIR-1 inhibitory motifs (Son et al., 2017). While LAIR-1 interacted with the collagen-like tail of C1q, CD33 bound to the globular head region. Taken together, these data suggest that full length C1q concurrently crosslinks multiple inhibitory receptors to regulate myeloid cell activation.

3.6. C-type lectin receptors DC-SIGN and DC-SIGNR

DC-SIGN is a C-type lectin receptor involved in multiple functions including adhesion, pathogen recognition and antigen presentation (Garcia-Vallejo and van Kooyk, 2013). Interactions between neutrophils and DCs are mediated through interaction of DC-SIGN with CR3 (Ludwig et al., 2006). DC-SIGN and the related protein DC-SIGNR were reported recently to bind to C1q globular heads (Hosszu et al., 2012; Pednekar et al., 2016). In addition, C1q and gC1qR were shown to associate with DC-SIGN on the surface of immature DCs and to regulate DC differentiation and function. Interestingly, SIGN-R1, a DC-SIGN homolog expressed on mouse splenic marginal zone macrophages, was shown to enhance apoptotic cells clearance through interaction with C1q and subsequent complement activation (Prabagar et al., 2013). The SIGNR1-C1q interaction has been proposed to involve the primary carbohydrate binding site in SIGN-R1 and the polysaccharides ending in a 2,6 sialic acid present in the globular domain of the C1q A chain (Silva-Martin et al., 2014), whereas binding of C1q to DC-SIGN was Ca^{2+}-dependent and inhibited by mannan, suggesting the involvement of C1q mannose residues (Hosszu et al., 2012).

4. C1q- recent advances and novel findings

4.1. Expression of C1q at tissue level

While plasma C1q can be produced by the Kupffer cells (macrophages of the liver), it is now known that the bone marrow myeloid cells can completely rescue C1q deficiency (Petry et al., 2001) and that many tissue myeloid cells can be induced to produce C1q, including mast cells and chondrocytes (Bradley et al., 1996; van Schaarenburg et al., 2016). As described above, C1q has long been recognized as initiator of the classical pathway of complement (C) activation and its tissue deposition when co-localized with C4 and C3 was usually regarded as an indication of local C activation (Ricklin et al., 2010; Merle et al., 2015). However, increasing evidence collected over recent years suggests that local presence of C1q should not necessarily be considered a marker of C activation as it is not always associated with C4 deposition (Kouser et al., 2015). In addition, while plasma containing

circulating C1q as part of C1 complex (Ziccardi and Tschopp, 1982) may represent a possible source of tissue-bound C1q in cases of breached vasculature, it is increasing evident that C1q can be synthesized and secreted locally by various cell types, including macrophages, dendritic cells, fibroblasts, and mast cells that are ubiquitously distributed throughout the body (Ghebrehiwet et al., 2012). In addition, other cells selectively localized in specific tissues and organs such as microglial cells, glomerular and tubular cells, osteoclasts, and trophoblasts contribute to local production of C1q (Fonseca et al., 2017; Xavier et al., 2017). Although C1q is likely to be secreted in limited amount at the extravascular sites, recent evidence suggests that locally synthesized C1q is involved in the regulation of multiple cellular functions in addition to the cellular control of innate and adaptive immunity, as described above.

4.2. Role of C1q in the pathophysiology of pregnancy

Interest in placenta as site of C involvement was prompted several years ago by the recognition that this newly formed tissue connecting the developing embryo to the mother undergoes profound changes to allow successful embryo implantation and regular progression of pregnancy. These changes include extensive tissue remodeling that occurs primarily in the maternal decidua and is associated with an inflammatory process. The inflammation that develops during embryo implantation is sustained by cytokines and chemokines released by decidual cells and hormonal changes and is compatible with a successful pregnancy (Bulla et al., 2012). The cell debris formed as a result of tissue remodeling and the inflammatory process contribute to trigger C activation. Analysis of term and preterm placenta performed in the eighties and the early nineties revealed the presence of both early and late C components in the stroma of villi around the vessels, in the perivillous deposits of fibrin. C1q was also detected in maternal decidua in areas of fibrinoid necrosis localized in the basal plate and fibrinogen deposits in the wall of uteroplacental arteries (Girardi et al., 2006). More recent studies have highlighted the contribution of C1q to tissue remodeling in placenta acting predominantly on extravillous trophoblasts that depart from the cell columns of the anchoring villi and invade the maternal decidua reaching the inner third of the myometrium. A large number of these cells surrounds the uterine spiral arteries forming cell cuffs and contributes together with decidual NK cells to the extensive vascular remodeling characterized by loss of the musculoelastic structure of the vessel wall replaced by fibrinoid material (Bulla et al., 2012). As a result of these structural changes, the arteries transform into large vessels with markedly reduced resistance that favors unrestricted blood flow in the intervillous space (Bulla et al., 2005; Pijnenborg et al., 2006 Pijnenborg et al., 2006). The extravillous trophoblasts were found to express the messages for the three chains of C1q when they start invading the decidua (Agostinis et al., 2010). The molecule secreted from these cells, which are widely distributed in decidual tissue, binds to the extracellular matrix and, by interacting with cell surface-expressed receptor for the globular head of C1q and the associated $\alpha_4\beta_1$ integrin, delivers an activation signal and promotes trophoblast migration. The relevance of these findings to pregnancy outcome is supported by the impaired labyrinth development and the vessel remodeling observed in pregnant C1q-deficient mice compared to wild-type mice (Agostinis et al., 2010). Moreover, the absence of C1q predisposes these mice to manifest clinical and laboratory signs of preeclampsia including hypertension, albuminuria, reduced expression of VEGF, increased level of circulating VEGF receptor1 (sFlt-1), and increased fetal loss (Singh et al., 2011). Interestingly, trophoblasts surrounding unremodeled spiral arteries found in a substantial number in pre-eclamptic placentae and considered as a characteristic feature of this clinical condition, fail to express C1q (Agostinis et al., 2011).

A distinct group of extravillous trophoblasts enters the lumen of the spiral arteries and migrates upward like metastatic cells acquiring an endothelial cell phenotype that allows the endovascular trophoblasts to

adhere and partially replace the endothelium. (Bulla et al., 2005). C1q plays an important role in this process acting as a molecular bridge between endovascular trophoblasts and decidual endothelial cells. These are the only endothelial cells that synthesize and express C1q on the cell surface under physiological conditions (Bulla et al., 2008). The ability of both cells to produce C1q and to express the receptors for C1q favors a cross interaction between the two cell types.

4.3. Contribution of C1q to tissue repair

Wound healing is probably the best studied example of tissue regeneration and proceeds through three successive phases comprising blood clotting and inflammation, proliferation characterized by granuloma tissue formation and angiogenesis, and tissue remodeling (Sun et al., 2014). C1q has been shown to act at a later stage of the regeneration process and to favor wound healing stimulating angiogenesis in a C activation-independent manner (Bossi et al., 2014). Immunohistochemical analysis of the granulation tissue formed in the proliferation phase revealed strong C1q staining of the vessel endothelium and the surrounding stroma in the lesional skin in the absence of C4 and C3. The endothelial cells of newly formed vessels, unlike the cells of normal skin, were found to express the messages for the three chains of C1q and to synthesize the molecule detected on the cell surface. By interacting with the receptor for the globular head (gC1qR), C1q proved to be effective in stimulating proliferation and migration of endothelial cells and in inducing vessel formation evaluated both in vitro by the tube formation assay and ex-vivo by the rat aortic ring assay. The proangiogenic activity of C1q was further supported by the observation that the mean vascular density in the wound was significantly reduced in C1q-/- mice compared to wild-type animals and was restored to normal after topical application of C1q (Bossi et al., 2014).

C1q has been shown to have a different effect on skeletal muscle regeneration after injury causing impaired tissue repair in aged wild-type mice that was not seen in C1q deficient mice and that this effect was due to C1q-dependent activation of the canonical Wnt pathway involved in the regulation of mammalian aging (Naito et al., 2012). Although the contribution of the classical pathway downstream of C1 activation was excluded by the failure of C3-deficiency to prevent the impairment of C1q-induced muscle regeneration, the finding that the activation of Wnt signaling was inhibited by C1-inhibitor or a neutralizing antibody to C1s suggests that C1s is also involved in this process (Naito et al., 2012). The same group has subsequently shown that inhibition of the angiotensin II receptor suppresses C1q synthesis in injured muscles and enhanced recovery of muscle function (Yabumoto et al., 2015), providing potential for therapeutic application if these results translate to humans.

4.4. Effect of C1q on cancer development

Tumor growth is largely dependent on the intrinsic properties of cancer cells as well as on several factors, including the C system, that may either control or promote its progression (Markiewski et al., 2008; Macor et al., 2015). C1q has recently attracted special attention for its potential contribution to regulation of tumor growth following the detection of substantial amounts of this C component in the tumor microenvironment (Bulla et al., 2016). Analysis of tissue specimens obtained from solid tumors including colon, lung, breast, pancreatic carcinoma and melanoma revealed C1q deposition on the vascular endothelium, and in the stroma, mesenchymal cells, and mononuclear cells surrounding the tumor mass at the edge of tumor invasion. Interestingly, the cancer cells failed to express C1q in all tumors examined. A syngeneic model of melanoma developed in C57BL/6 mice showed prolonged survival of tumor-bearing mice and slower tumor growth in C1q-deficient mice compared to wild-type mice. The slower cancer progression observed in the absence of C1q was associated with

reduced vascular density and was unrelated to local recruitment of suppressor cells that favor tumor expansion by inhibiting the immune response (Bulla et al., 2016). Similar results were obtained using a syngeneic mouse model of lung carcinoma. In vitro experiments showed that surface-bound C1q was able to promote adhesion, proliferation and migration of the melanoma cells used for the tumor model and to protect them from apoptosis. Although the ligands for C1q on cancer cells that mediate its biological effects were not identified, gC1qR was hyper-expressed in several human tumors (Dembitzer et al., 2012), and is likely to be one of them.

It is important to emphasize that not all cancer cells respond to C1q in the same way. Hong et al. (Hong et al., 2009) showed that C1q induced apoptosis and growth suppression of the human prostate DU145 cells as a result of direct activation of the tumor suppressor WW-domain containing oxidoreductase (WOX1). Interestingly, analysis of prostate tissue revealed that C1q was present in normal prostate while it was hypo-expressed in benign prostatic hyperplasia (BPH) and prostate cancer further supporting the contribution of C1q to the control of cell proliferation. In addition, C1q was reported to induce a pro-apoptotic effect on an ovarian cell line, SKOV3, acting via a TNF-α induced apoptosis pathway that involves upregulation of Bax and Fas (Kaur et al., 2016). Although these in vitro data were obtained analyzing cell lines under experimental conditions that do not reflect the complex tumor microenvironment, recent in vivo findings confirmed the protective activity of C1q against the mammary carcinoma that develops spontaneously in BALB-neuT mice (Bandini et al., 2016). C1q-deficient BALB-neuT mice manifested an accelerated tumor growth associated with an increased number of intra-tumoral vessels compared to wild-type neuT mice. The difference in tumor progression between C1q-deficient and WT mice was attributed to a reduced activation of WW domain containing oxidoreductase (WWOX) in C1q-deficient mice. Unfortunately, no attempt was made to reverse the accelerated progression of tumor in C1q-deficient mice by administration of C1q or bone marrow transplantation.

These contradictory data on the effect of C1q on tumor growth in the in vivo studies may be explained by differences in mouse strains, type of tumors and tumor models used. However, two important points should be considered when translating the murine data to cancer patients. One is that C1q has been detected in the microenvironment of growing solid tumors and its expression has been associated with cancer invasion and metastatic foci (Bulla et al., 2016). More importantly, analysis of gene expression in human breast cancer by Winslow and colleagues (Winslow et al., 2015) revealed an increased expression of the genes for the three chains of C1q associated with a poor prognosis suggesting that C1q was not protective and was able to promote tumor growth. Given the conflicting results obtained by different groups, further studies are warranted to define the role of C1q in cancer development.

4.5. C1q in the nervous system

With exciting new discoveries of critical roles for classical complement pathway in pruning of neuronal synapses, the influence of the complement system in central nervous system has been substantially expanded (Stephan et al., 2012). How complement impacts disease progression is clearly complex, with evidence of both complement-dependent detrimental and protective effects (reviewed in (Wyss-Coray and Rogers, 2012)).

C1q expression is upregulated following neuronal injury, during aging and early in neurodegenerative disorders such as Alzheimer's disease (reviewed in (Veerhuis et al., 2011)). Similar to its activities in the periphery, C1q enhances the uptake of apoptotic neurons and neuronal blebs by microglia, the primary phagocytic cell of the central nervous system. More rapid ingestion by microglia of apoptotic neurons or neuronal blebs should prevent toxic intracellular contents (such as high concentrations of glutamate) from being released thereby

preventing excitotoxic damage to surrounding neurons. C1q either immobilized or bound to apoptotic neurons also suppresses the LPS-induced production of proinflammatory cytokines IL-1α, IL-1β, IL-6 and TNF-α, all suggesting anti-inflammatory/homoeostatic role for C1q in the brain (Fraser et al., 2010), and predicting neuroprotection.

In an unexpected discovery, it was observed that in vitro C1q, in the absence of other complement components, induces gene expression critical for neuronal survival and neurite outgrowth (Pisalyaput and Tenner, 2008; Benoit and Tenner, 2011) and protection against oligomeric and fibrillar Aß-induced neuronal death (Benoit et al., 2013). Microarray analysis demonstrated that C1q up-regulates genes involved in membrane and cytoskeleton processes, in growth of neurites and cholesterol metabolism, and in the regulation of the expression of neurotrophic factors (Benoit and Tenner, 2011). The transcriptional programs stimulated by C1q in nutrient stressed or Aß-injured neurons share some pathways (Benoit and Tenner, 2011; Benoit et al., 2013). A common signaling event is the phosphorylation and nuclear translocation of the transcription factor CREB. CREB is a transcription factor vital for long-term memory and synaptic plasticity, neurogenesis (Tchantchou et al., 2009; Li et al., 2011) and induction of neurotrophic factors in the CNS (Colangelo et al., 1998), thus suggesting mechanisms by which the C1q-induced neuroprotection may occur.

However, as injury increases, synthesis of most other complement factors is also increased. Interestingly, in the presence of other complement components the removal or loss of sialic acid on neuronal membranes results in binding of C1 via C1q, activation of complement, deposition of C3b on the neurons and subsequent ingestion of those membranes by microglia via CR3, the receptor for C3b/iC3b (Linnartz et al., 2012). How CD33, a sialic acid binding negative regulator of the immune system that is expressed on human microglia and that can interact with C1q (as described above), influences this activity, if at all, remains to be defined (reviewed in (Linnartz-Gerlach et al., 2014)). It is firmly established both in vitro and in vivo that fibrillar (beta sheet fibrils) Aβ (fAß) which accumulate in Alzheimer's disease (AD) can activate both the alternative and the classical complement pathways in the absence of antibody. Thus, in the AD brain both activators and the complement proteins are present leading to the colocalization of C1q, C3b/iC3b and C4b to nearly 100% of the fibrillar amyloid plaques (vs. diffuse plaques) in AD in humans and in mouse models of AD. In addition, activated microglia and astrocytes and the complement membranolytic complex C5b-9 have been detected in the areas containing the fibrillar plaques in AD (Webster et al., 1997) as reviewed in (Veerhuis et al., 2011), suggesting a detrimental outcome of complement activation in neurodegenerative diseases.

Innovative studies by Stevens, Barres and colleagues, beautifully demonstrated that activation of the early components of the classical complement pathway, C1, C4 and C3 during normal development contributes to synaptic pruning esssential for proper neuron circuit construction (Stevens et al., 2007). In contrast to the predominant synthesis of C1q in the adult brain by microglia (Fonseca et al., 2017), here C1q was produced by the neurons in a TGFß and activity dependent fashion (Bialas and Stevens, 2013). Subsequently, these investigators and others have further uncovered that excessive complement-mediated synapse elimination is associated with neuronal degeneration (Williams et al., 2016) and with cognitive loss in diverse mouse models of aging and neurological disorders (Shi et al., 2015; Hong et al., 2016; Lui et al., 2016; Vasek et al., 2016). Substantial suggestions of correlates in the human diseases including not only neurodegenerative diseases such as AD and frontal temporal dementia (Hong et al., 2016; Lui et al., 2016), but also cognitive loss experienced by some after West Nile Virus infection (Vasek et al., 2016)and perhaps psychiatric disorders such as schizophrenia (Sekar et al., 2016), suggest contributions of these processes to human disease.

It remains to be determined what are the contributions of complement mediated excessive synaptic pruning, C5a induced microglial polarization, and other complement mediated functions to the cognitive

loss seen in these diseases as well as the neuroprotective pathways that appear to be modulated by complement and/or C1q alone. This should enable selective targeting and/or modulation of complement activation products or their receptors as an effective strategy for retaining the neuroprotective, anti-inflammatory and phagocytic functions of complement, while dampening proinflammatory induced damage.

In summary, the C1q molecule continues to surprise and intrigue complement biologists as novel activities are discovered. Being evolutionarily ancient, it has been selected to be structurally diverse and capable of complexing with multiple binding partners in solution and on cell membranes to influence local and systemic activities. While there are many disorders where C1q-targeted therapies may be possible, a comprehensive understanding of downstream consequences of modulating this multifunctional protein will be critical for success in the clinic.

Conflict of interest

The authors report no conflict of interest.

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