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Fundamental role of C1q in autoimmunity and inflammation

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Abstract

C1q, historically viewed as the initiating component of the classical complement pathway, also exhibits a variety of complement-independent activities in both innate and acquired immunity. Recent studies focusing on C1q's suppressive role in the immune system have provided new insight into how abnormal C1q expression and bioactivity may contribute to autoimmunity. In particular, molecular networks involving C1q interactions with cell surface receptors and other ligands are emerging as mechanisms involved in C1q's modulation of immunity. Here, we discuss the role of C1q in controlling immune cell function, including recently elucidated mechanisms of action, and suggest how these processes are critical for maintaining tissue homeostasis under steady-state conditions and in preventing autoimmunity.

Keywords

C1q; Complement; Inflammation; Autoimmunity; SLE

Introduction

The first complement component, C1q, accomplishes a diverse range of complement-dependent and complement-independent functions in the immune response [1, 2]. It binds various ligands derived from self and non-self and modulates the functions of immune cells. It is well known that abnormal regulation of immune cells and break down of homeostasis cause autoimmune disease, including lupus. This review stresses the tolerogenic role of C1q and provides mechanistic insight into how genetic deficiency of C1q leads to systemic lupus erythematosus (SLE).

C1q structure and ligands

C1q is a 460 kDa macromolecule found circulating in blood. It is composed of 18 polypeptide chains (six trimers of C1qa, C1qb and C1qc). It contains an N-terminal triple-helical collagen-like region (C1q tail) and a C-terminal globular head region (gC1q) [3, 4]. The gC1q has similar structure to tumor necrosis factor (TNF) and belongs to the C1q/TNF

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

superfamily which is involved in inflammation [5]. The C1q tail has the repeating sequence G-X–Y (X is any amino acid and Y is proline or hydroxyproline) characteristic of collagen. C1q also belongs to the collectin family which includes mannose-binding lectin, surfactant protein A (SP-A), SP-D, and ficolin which are pattern recognition proteins of the innate immune system [6, 7].

C1q is one of the most highly positively charged proteins in human serum; based on this and other chemical features, C1q (especially its globular region) has been classified as a charged pattern recognition molecule recognizing a wide variety of both self and non-self-ligands [8–11]. C1q binds to molecules released from apoptotic and necrotic cells including phosphatidylserine, nucleic acids, and other damage-associated molecular patterns (DAMPs) [12, 13]. In addition, C1q can bind altered self-proteins including β-amyloid [14], prion [15, 16], oxidized low-density lipoprotein [17], DNA and heparin sulfate [18]. In response to infection, C1q binds to pathogen-associated molecular patterns (PAMPs) on viruses and bacteria including lipopolysaccharide [19, 20].

The role of C1q in apoptotic cell clearance: C1q and C1q receptors

The diversity of ligands for C1q relates in part to its domains, the gC1q and C1q tail regions, which bind specific cell surface receptors to regulate both innate and adaptive immunity. Most receptors described for the gC1q and C1q tail domains are involved in phagocytic uptake by macrophages, functioning in the clearance of dead and dying cells. This well-recognized role of C1q in innate immunity is aimed at preventing inflammation caused by the release of intracellular cytotoxic substances into the extracellular space [12, 21, 22]. A growing number of C1q receptors include gC1qR (p33 or C1qBP), CD91, CD35, α2β1, CD93 (C1qRp), calreticulin (CRT, cC1qR), β-integrin, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN, CD209), receptor for advanced glycation endproducts (RAGE) and leukocyte-associated immunoglobulin-like receptor 1 (LAIR-1, CD305) [23–27].

CD91 (low-density lipoprotein receptor-related protein 1) is a transmembrane protein that associates with the co-receptor calreticulin on the surface of macrophages and microglial cells [28, 29] to initiate the clearance of C1q-bound apoptotic cargo [22, 30]. Calreticulin, initially described as a molecular chaperone in the endoplasmic reticulum (ER), was the first receptor identified for the C1q tail and requires a conformational change in C1q in order to bind the C1q tail [31]. More recently, calreticulin has been shown to interact with both gC1q and C1q tail domains and to function as a phosphatidylserine recognition molecule on the apoptotic cell surface [32]. RAGE is a member of the Ig superfamily and belongs to the class of type I cell surface receptors expressed on all types of leukocytes. RAGE binds gC1q and enhances C1q-mediated phagocytosis [33]. The scavenger receptor Scarf1 has also been described as a C1q-dependent receptor for apoptotic cell clearance [34]. Scarf1-deficiency leads to spontaneous autoimmune disease and global activation of T cells, follicular helper T cells and B cells suggesting a role of Scarf1/C1q interactions in preventing autoimmunity. C1q also elicits macrophage expression of the Mer tyrosine kinase (Mer) which results in enhanced clearance of apoptotic debris [35].

New insights into tolerogenic functions of C1q

Aside from facilitating phagocytosis, C1q regulates immune cell differentiation, cytokine secretion and macrophage polarization toward a tolerogenic phenotype [36, 37]. Recent studies related to C1q-facilitated phagocytosis reveal that aside from clearance of apoptotic debris, C1q-mediated uptake of apoptotic lymphocytes by human macrophages and DCs actively promotes tolerogenic activity (Fig. 1a, [38]). In this case, C1q-exposed macrophages and DCs exhibit a reduced capacity to produce pro-inflammatory cytokines, diminished ability to promote inflammatory type T helper (Th) 1/Th17 responses as well as a tendency toward sustaining regulatory T cells. The ability of C1q to engage in molecular complexing at the cell surface is also emerging as an important regulatory function. In immature monocyte-derived DCs (moDCs), C1q, DC-SIGN and gC1qR form a trimolecular complex on the plasma membrane which is presumed to modulate DC differentiation and function through DC-SIGN-mediated signaling pathways [26].

LAIR-1 (CD305) is a transmembrane protein containing two immunoreceptor tyrosine inhibitory motifs (ITIM) and is an ubiquitous collagen receptor expressed on a variety of immune cells [39, 40]. Recently, we identified LAIR-1 as the first known inhibitory receptor for C1q [25, 41]. Binding of C1q's collagen tail to LAIR-1 on monocytes leads to phosphorylation of LAIR-1 ITIMs, recruitment of SHP-1, and interruption of downstream signal transduction associated with the production of pro-inflammatory cytokines and monocyte-derived DC growth factors. We also showed that binding of C1q to LAIR-1 on plasmacytoid (p) DCs restricts the production of type I interferons, which are important in antiviral defenses and sustaining moDC differentiation [25] (Fig. 1b, c). Similar to C1q, surfactant protein D (SP-D) possesses an N-terminal helical collagen domain and was recently found to also engage LAIR-1 and restrict myeloid cell activity [42].

Thus, growing understanding of distinct interactions between C1q and cell-associated receptors with endogenous and exogenous stress molecules has provided insight into how C1q-facilitated uptake of apoptotic cells and signal transduction may help censor damaging inflammation and autoimmunity [38, 43]. Which molecular interactions with C1q (either devoid of or containing immunogenic cargo) predominate in distinct anatomical locations and physiological settings remains an important area of study.

Genetic and functional deficiency of C1q in SLE

Systemic lupus erythematosus (SLE) is an autoimmune disease that involves profound abnormalities in both the myeloid and lymphoid cell compartments. In SLE, C1q deficiency may result either from genetic defects or C1q-targeted autoantibodies [23, 44]. The observation that SLE develops in approximately 90 % of patients genetically deficient in C1q introduced the concept that, aside from its role in activating the complement cascade, C1q functions to prevent autoimmunity [45]. Studies of C1q−/− mice revealing a spontaneous lupus-like disease characterized by the development of antinuclear antibodies and glomerulonephritis associated with failure to clear apoptotic bodies provided some insight into a complement-independent role [46]. Moreover, associations between single nucleotide polymorphisms (SNPs) in C1q and specific clinical phenotypes have been

reported [47, 48]. Based on these observations, possible explanations of C1q deficiency contributing to the development of SLE are the following: (1) impaired apoptotic cell clearance [46] consistent with the increased presence of apoptotic cells in lymph nodes and tissues of SLE patients and C1q−/− mouse models [49, 50]; (2) abnormal development of self-reactive B cells with specificities toward multiple autoantigens [51]; (3) lack of tolerogenic activity on monocytes/macrophages and DCs [52, 53]; and (4) failure to control monocyte to DC differentiation [25, 54].

In SLE, C1q deficiency may occur as a result of autoantibodies to C1q. Anti-C1q antibodies were initially identified in pathogenic immune complexes in SLE patients [55, 56]. They have been linked to lupus nephritis, a severe manifestation of SLE, and are present in 30–50 % of lupus patients [57, 58]. While antibodies to both gC1q and C1q collagen tail have been identified, the consequence of blocking C1q domains on its biological activity is not firmly established. In the kidney, anti-C1q antibodies may participate in lupus pathogenesis by contributing to the formation of immune complexes. Impairment of C1q's role in promoting tolerance could also result from anti-C1q antibodies interfering with the ability of C1q to promote the uptake of apoptotic debris or immune complexes. Anti-C1q antibodies (notably to the C1q tail) might also contribute to SLE by blocking the interaction of the C1q tail with its inhibitory receptor, LAIR-1 on monocytes, pDCs and B cells, all of which are profoundly abnormal in SLE.

C1q in the central nervous system (CNS)

In the brain, C1q has been ascribed an important role in shaping neuronal architecture by participating in synaptic pruning, a process whereby functional neuronal synapses are produced during development [59, 60]. In addition, there is evidence to substantiate that C1q guards against neural inflammation in the brain [2]. C1q-mediated complement-dependent and complement-independent activities are both associated with synaptic pruning, which involves uptake by macrophage-like microglia cells in the brain [59, 60]. C1q−/− mice fail to produce normal synaptic connectivity in the neocortex, suggesting that C1q is involved in synaptic pruning during the development of the central nervous system (CNS) [59]. Moreover, sustained defects in synapse elimination in C1q knockout mice lead to neurodegenerative disease [61]. In the C1q−/− model of epilepsy, the failure of synaptic pruning induces increased dendritic length, branching and density of dendritic spines [62]. Based on these collective findings, C1q has a key role in shaping neuronal connectivity by directing the uptake of unwanted synapses into microglia for clearance.

With advanced age, C1q levels are dramatically increased (as much as 300-fold) in mouse and human brains, including in areas of synapses [63]. In support of the idea that complement-mediated synapse elimination plays a role in neurodegenerative disease, C1q activates the complement cascade in Alzheimer's disease (AD) [63, 64], a disease associated with advanced age and massive synapse loss [65]. C1q binds amyloid-β (Aβ), a misfolded protein associated with AD, to activate complement-dependent destruction of neurons [66, 67]. Complement-independent functions of C1q in AD are also suggested by interactions with C1q receptors. RAGE is one of the several known receptors for Aβ and C1q [33] and may drive inflammation associated with the progression of neurodegenerative disorders by

activating the pro-inflammatory Jak-STAT and NF-kB signaling pathways [68, 69]. Thus, C1q/Aβ and RAGE complexes may regulate neuronal inflammation. C1q has also been shown to improve neuronal viability and neurite outgrowth and prevent Aβ-induced neurotoxicity in vitro [70]. Intact C1q but not gC1q, C1q tails or heat-inactivated C1q is required for neuroprotection [71, 72]. Thus, while particular physiological settings in the brain or peripheral tissue may be associated with C1q-mediated activation of the complement cascade, in the absence of other complement components, C1q complement-independent functions may operate. Given that LAIR-1 is expressed in the brain [73], it is tempting to speculate that LAIR-1/C1q partnering contributes to guarding against unwarranted inflammatory activity in this tissue.

Conclusion

C1q has long been considered an innate immune molecule. Its complement-independent functions on immune and non-immune cells serve to highlight a critical role in maintaining homeostasis. C1q's interaction with novel receptors linked to immune tolerance and prevention of autoimmunity and neuronal inflammation are fascinating areas for further investigation.

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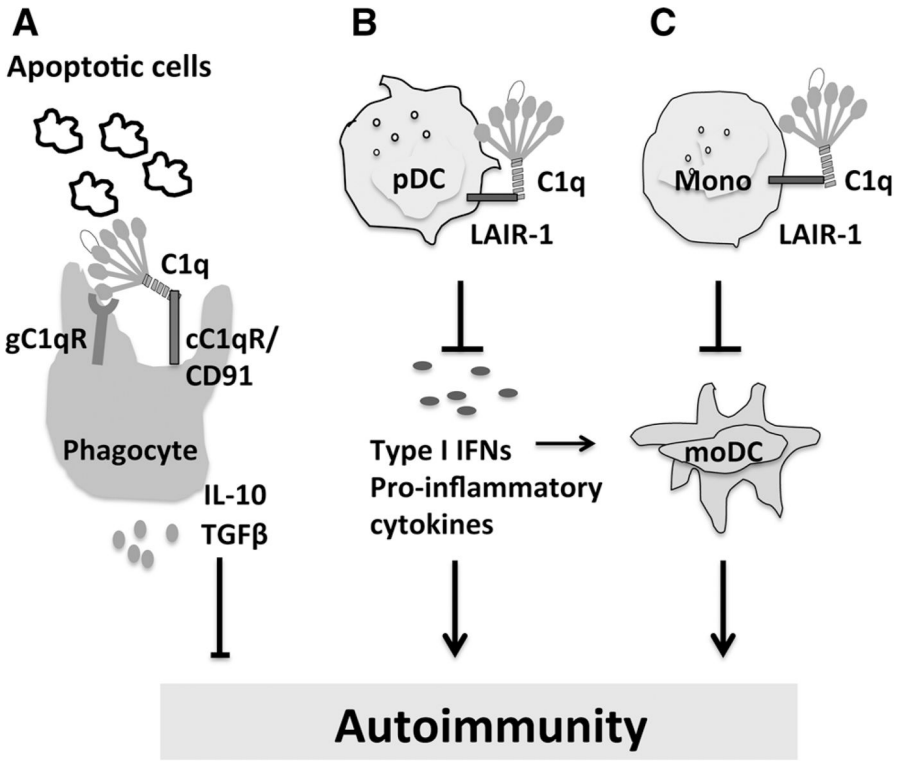

Fig. 1.

C1q has a fundamental suppressive role in immune homeostasis. **a**. In well-described apoptotic cell clearance pathways, C1q interacts with a variety of gC1q and C1q tail receptors on phagocytic cells, leading to modulation of cytokine production/inflammatory responses. **b** and **c**. Interaction between the C1q collagen tail and LAIR-1 prevents the production of type I IFNs and inflammatory cytokines by pDCs and monocytes and inhibits DC differentiation and activation either during steady state or inflammation. *PDC* plasmacytoid DC, *Mono* monocyte, *moDC* monocyte-derived dendritic cell