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C1q binding and complement activation by prions and amyloids

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Abstract

C1q binds to many non-self and altered-self-materials. These include microorganisms, immune complexes, apoptotic and necrotic cells and their breakdown products, and amyloids. C1q binding to amyloid fibrils found as extracellular deposits in tissues, and subsequent complement activation are involved in the pathology of several amyloid diseases, such as Alzheimer's disease. Prion diseases, such as scrapie also involve formation of amyloid by polymerization of the host prion protein (PrP). Complement activation is likely to contribute to neuronal damage in the end stages of prion diseases, but is also thought to participate in the initial infection, dissemination and replication stages. Infectious prion particles are likely to bind C1q and activate the complement system. Bound complement proteins may then influence the uptake and transport of prion particles by dendritic cells (DCs) and their subsequent proliferation at sites such as follicular DCs.

Keywords: Alzheimer; Amyloid; C1q; Prion; Scrapie; Transmissible spongiform encephalopathy

Introduction

The complement protein C1q binds to a very wide range of non-self and altered-self-materials. These include bacteria, viruses, immune complexes, apoptotic and necrotic cells and their breakdown products. Amyloid proteins are another group of altered-self-materials to which C1q binds. Amyloids, or amyloid fibrils, are the result of the refolding of various proteins from their normal folded functional forms into fibril-like polymers. The refolded protein monomers in amyloid fibrils take up a repetitive structure based on cross-beta structure, i.e. beta sheets at right angles to the long axis of the fibril (Dobson, 2005). Such fibers contain regular repeat structures, and it is easily envisaged that they form surface repetitive patterns, which may be suitable for recognition by pattern recognition receptors such as C1q.

Abbreviations: Aβ, amyloid β peptide; AD, Alzheimer's disease; APP, amyloid precursor protein; BSE, bovine spongiform encephalopathy; CJD, Creutzfeld–Jacob disease; FBD, familial British dementia; FDD, familial Danish dementia; PrP, prion protein; PrP^{C}, prion protein cell-surface form; PrP^{Sc}, prion protein (scrapie) amyloid form; TSE, transmissible spongiform encephalopathy

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Amyloids

Amyloid fibers form in many tissues, and are associated with inflammatory tissue damage. The central nervous system (CNS) is particularly prone to accumulating protein aggregates inside neurons and extracellularly. Several neurodegenerative diseases, which are characterized by neuronal cell loss in different parts of the brain, are associated with CNS inflammation and the presence of different forms of amyloids and aggregates, and microglial activation. For example, in Alzheimer's disease (AD), which is characterized by adult-onset, slowly progressive dementia, the neuropathological features include neuronal loss and extracellular deposition of amyloid plaques (senile plaques). The amyloid plaques arise by extracellular deposition of aggregated amyloid β peptide (Aβ), a cleavage product of neuronal amyloid precursor protein (APP) (Zhang et al., 2000; Kimberly et al., 2003). Cleavage can yield two different small cleavage products, Aβ1–40 or Aβ1–42, and subsequent accumulation and aggregation of these products in brain are the hallmarks of AD (Selkoe, 2001). Aβ1–42 has a greater tendency to aggregate and is more neurotoxic than Aβ1–40 and more correlated with the disease.

In regions of the brain which have dense accumulations of plaques and tangles in AD, C1q mRNA level is increased up to 80-fold compared to control levels (Yasojima et al., 1999). Moreover, an increase in the generation of reactive oxygen species has been demonstrated in neurons incubated with purified C1q (Luo et al., 2003). This increase may mediate neuronal injury during AD. The expression level of C1q B chain mRNA and the number of C1q-positive plaques in brain sections from AD were significantly greater than in control cases. Immunohistochemical analysis showed that the number of C1q-positive plaques correlated with the expression level of the C1q gene demonstrating that C1q within senile plaques is endogenously produced in the AD brain (Tooyama et al., 2001). Previously, C1q was thought to interact with Aβ1–42 via a specific region on the collagen region of A chain (Jiang et al., 1994), but more recently it has been shown that C1q interacts with fibrils of Aβ1–42 through the globular head of C1q (gC1q) (Tacnet-Delorme et al., 2001), with specific involvement of ghB module (B-chain globular region) (Kishore et al., 2003). C1q-Aβ interaction stimulates macrophage phagocytosis (Webster et al., 1997; Guan et al., 1994). Therefore, C1q is an important mediator of Aβ-induced inflammatory reaction through complement activation and Aβ phagocytosis.

In transgenic mice carrying mutations in APP or presenilin genes, an up-regulation of C1q has been noted that co-localises with fibrillar Aβ (Matsuoka et al., 2001). (Presenilins 1 and 2 modulate Aβ formation and aggregation (Scheuner et al, 1996)). A C1q knockout mouse ($Q^{-/-}$) was crossed with a transgenic AD mouse model bearing a mutation in APP in order to ascertain the role of C1q in AD. At older ages, the APP and APP/$Q^{-/-}$ mice developed comparable total amyloid in the frontal cortex and hippocampus. The level of activated glia surrounding the plaques, however, was significantly lower in the APP/$Q^{-/-}$ mice. In another murine model of AD containing transgenes for both APP and mutant PS1 (APP/PS1), a similar reduction of pathology was seen in APP/PS1/$Q^{-/-}$ mice (Fonseca et al., 2004).

Sarvari et al. (2003) screened a chemical library to find compounds which would inhibit binding of C1q (in vitro) to Aβ, and also examined the effect of C1-inhibitor in modulating classical pathway-mediated damage to rat hippocampal cells They found that complement inhibition at the C1 level abrogates complement-mediated Aβ cytotoxicity. This highlights the importance of the classical pathway and its recognition molecule C1q in the pathology of AD. Selected compounds from the chemical library targeted the Aβ binding site on C1q and protected complement-sensitive neurons against Aβ-mediated complement lysis. Compounds which inhibited C1q binding to Aβ at the μM level included benextramine and tamoxifen. The Aβ binding site on C1q was shown to be distinct from the IgG-Fc binding site, but overlapped with the binding site(s) for CRP and myelin basic protein.

In familial British dementia (FBD) and familial Danish dementia (FDD), which are associated with neurodegeneration and cerebrovascular amyloidosis with a neuropathological picture similar to AD, the pathology involves two accumulating amyloid peptides (ABri in FBD and ADan in FDD) (Rostagno et al., 2002). These are proteolytic fragments of a mutated precursor membrane-anchored molecule BriPP encoded by the gene, Bri2 (also known as ITM28). The Abri and Adan peptides specifically bind to C1q with high affinity and form stable complexes. In addition, C1q has been shown to be associated with Aβ plaques in Down's syndrome brain. Neurons in the hippocampus and entorhinal cortex, and less frequently in frontal cortex, are C1q positive in Down's syndrome. In this syndrome, C1q-positive neurons are also associated with activated microglia (Head et al., 2001).

Prion diseases

Prion diseases such as Creutzfeld–Jacob disease (CJD) in humans, scrapie in sheep, and bovine spongiform encephalopathy (BSE) in cattle (transmissible spongiform encephalopathies: TSEs) are also diseases of amyloid formation (for reviews, see Unterberger et al., 2005; Mabbott and MacPherson, 2006). Like AD, these are neurodegenerative disorders, characterized by extracellular accumulations of the protease-resistant