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Featured Article

Peripheral complement interactions with amyloid β peptides in Alzheimer's disease: Erythrocyte clearance of amyloid β peptides

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Abstract

Introduction: Although amyloid β peptide (Aβ) is cleared from the brain to cerebrospinal fluid and the peripheral circulation, mechanisms for its removal from blood remain unresolved. Primates have uniquely evolved a highly effective peripheral clearance mechanism for pathogens, immune adherence, in which erythrocyte complement receptor 1 (CR1) plays a major role.

Methods: Multidisciplinary methods were used to demonstrate immune adherence capture of Aβ by erythrocytes and its deficiency in Alzheimer's disease (AD).

Results: Aβ was shown to be subject to immune adherence at every step in the pathway. Aβ dose-dependently activated serum complement. Complement-opsonized Aβ was captured by erythrocytes via CR1. Erythrocytes, Aβ, and hepatic Kupffer cells were colocalized in the human liver. Significant deficits in erythrocyte Aβ levels were found in AD and mild cognitive impairment patients.

Discussion: CR1 polymorphisms elevate AD risk, and >80% of human CR1 is vested in erythrocytes to subserve immune adherence. The present results suggest that this pathway is pathophysiologically relevant in AD.

Keywords: Alzheimer's disease; Amyloid β peptide; Complement; Complement receptor 1; Immune adherence; Blood; Erythrocyte; Human

1. Background

Multiple studies have made clear that amyloid β peptide (Aβ) can move from the brain to the peripheral circulation [1–3] and from the peripheral circulation to the brain [4,5]. As such, the disposition of circulating Aβ may be pathophysiologically important. For example, failure to clear Aβ from blood could lead to an unfavorable concentration gradient for the movement of Aβ out of the brain [3]. Moreover, the propensity of fluid-phase Aβ to form insoluble fibrils and to activate complement and other inflammatory mediators could well play a role in the colocalization of inflammatory mediators with the vascular abnormalities that are observed in Alzheimer's disease (AD) reviewed in the study by Grammas et al. [6,7]. Mackic

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et al. [8,9] have provided critical data on serum and organ levels of Aβ after its intravenous (IV) inoculation into the bloodstream of nonhuman primates (NHPs). However, the mechanisms by which Aβ is purged from the circulation in primates still remain unclear.

Originally elucidated by Nelson et al. [10] in 1953, complement-dependent, erythrocyte-mediated clearance of circulating immune complexes ("immune adherence") has been investigated in detail for more than 60 years and is now considered a primary mechanism for pathogen removal in humans reviewed in the study by Birmingham et al. [11,12]. Fig. 1 illustrates some of the major steps in this pathway, several points of which may be worth emphasizing.

First, in humans, immune adherence hinges on the expression of complement receptor 1 (CR1) by erythrocytes, a phenomenon that is unique to primates. Subprimate erythrocytes do express complement receptors (e.g., Crry), but not CR1, so that their capacity to capture complement-opsonized immune complexes appears to be significantly limited compared with human immune adherence mechanisms [19].

Second, polymorphisms in the CR1 gene have been consistently shown to be among the top genetic risk factors for AD [20–24], and >80% of human CR1 is devoted to the erythrocyte compartment [11,12]. Taken together with the unique expression of CR1 by primate erythrocytes, these findings make erythrocytes perhaps the most parsimonious site for CR1 to impact AD risk.

Third, although human erythrocytes only express some 200 to 1500 CR1 molecules per red cell [11], the sheer number of erythrocytes ($2–3 \times 10^{13}$) in the bloodstream, compared with circulating and fixed macrophages, makes this an extremely powerful and efficient pathway for pathogen clearance. For example, pathogens experimentally infused into NHPs that have been immunized against the pathogen are typically eliminated by immune adherence mechanisms in 10 to 20 minutes [25].

Fourth, immune adherence research has focused on the clearance of immune complexes [11,12]. However, both our research [15,16] and that of others [14,17] have shown that Aβ, like certain bacterial and viral antigens [13], does not require immune complex formation to activate complement or to be bound by complement opsonins that serve as ligands for immune adherence. Thus, Aβ (and other antibody-independent complement activators) may have been overlooked as a substrate for immune adherence pathways.

Our laboratory first suggested that immune adherence might play a role in peripheral Aβ clearance and that

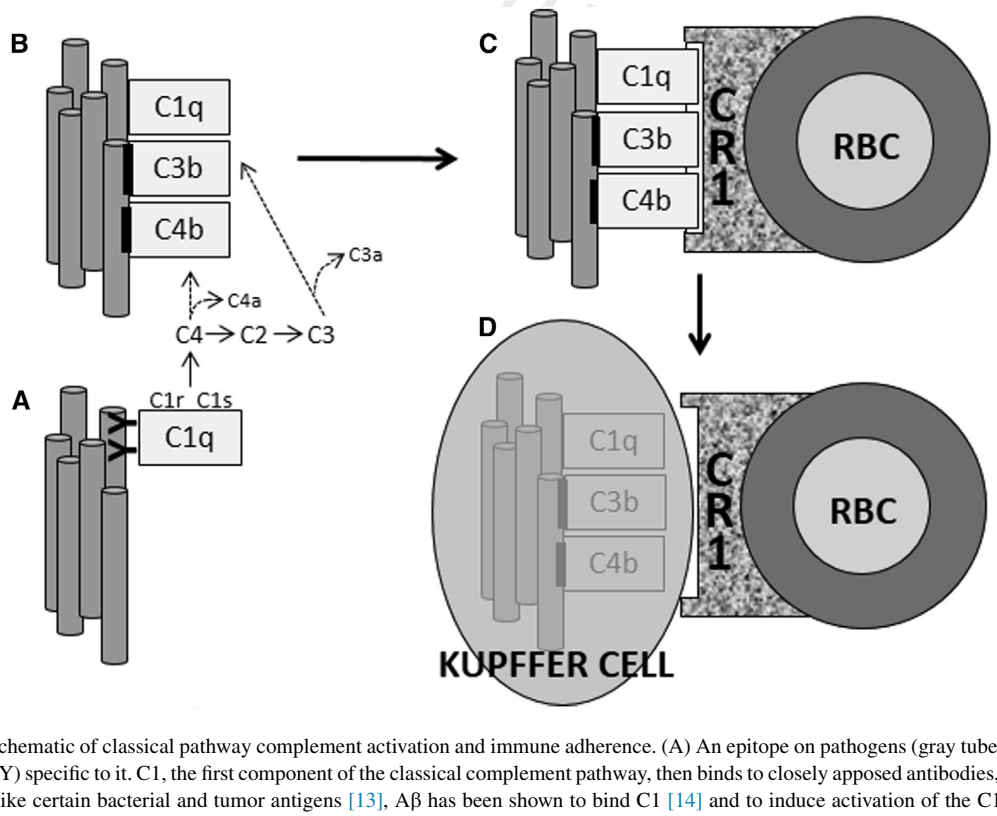

Fig. 1. Simplified schematic of classical pathway complement activation and immune adherence. (A) An epitope on pathogens (gray tubes) is bound by circulating antibodies (YY) specific to it. C1, the first component of the classical complement pathway, then binds to closely apposed antibodies, forming an immune complex. Notably, like certain bacterial and tumor antigens [13], Aβ has been shown to bind C1 [14] and to induce activation of the C1r and C1s proteases without antibody mediation [14–17]. (B) C1s-mediated activation of the classical complement pathway ensues, including generation of C4b, C3b, and iC3b, which become covalently fixed to the antigen (black bars). C1q also remains bound to the antigen. The antigen and/or immune complex is therefore said to be "opsonized" by complement. (C) Primate (but not subprimate) erythrocytes (RBCs) express cell-surface CR1, which has C4b, C3b, and C1q as ligands. Antigen/complement complexes thus become bound to erythrocytes. (D) Erythrocytes then ferry the complex through the bloodstream until they reach specialized macrophages, Kupffer cells, lining the hepatic sinusoids. Kupffer cells recognize the complement tag via cell-surface CR1 receptors and strip off and degrade the opsonized antigen [11,12,18]. Abbreviations: Aβ, amyloid β peptide; CR1, complement receptor 1. Q1