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Reduced CD59 expression is associated with high membrane attack complex (MAC) levels in neurons of Alzheimer's disease

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Abstract

Complement proteins, including C1q, factor B, and the membrane attack complex (MAC), have been reported to be activated and play important roles in Alzheimer's disease (AD) brain. However, it remains controversial whether the expression of CD59, which regulates the terminal complement pathway and thus prevents the formation of lytic MAC, is upregulated or deficient in the AD brain. In this study, we used double immunofluorescence labeling to demonstrate that neurons in AD brains lacked CD59, whereas CD59 was present almost all neurons in the low pathology control (LPC) brains. In the high pathology control (HPC) brains, 20 – 45% of neurons were positive for CD59. We also observed that many neurons in the AD brains were positive for MAC, whereas almost all neurons in the LPC brains lacked MAC. In the HPC brains, 10% or fewer neurons were positive for MAC. These results indicate that labeling of MAC in neurons is associated with deficient CD59 expression in neurons in AD brains. Moreover, the changes in CD59 (55 – 80% reduction) and MAC (10% or fewer positive) in neurons observed in HPC individuals, who are an intermediate subset between the AD and LPC stages, indicate that changes in CD59 start to occur in the early stage of AD. These changes likely precede the completion of terminal complement activation in the brain, although it is uncertain whether reduced expression of CD59 or production of MAC occurs earlier. Tottori J. Clin. Res. 9(1), XX-XX, 2017

Keywords: neuroinflammation, complement proteins, membrane attack complex (MAC), CD59, Alzheimer's disease (AD)

Introduction

Numerous inflammatory mediators have been identified in AD brains but not detected in elderly individuals without dementia [1]. Mounting evidence suggests that neuroinflammation is involved in the pathogenesis of AD [2,3]. In particular, the complement system has been shown to play important roles. While both the classical and alternative complement pathways contribute to the pathogenesis of AD [4], evidence is lacking for a direct involvement of the lectin pathway [5]. Complement proteins such as C1q, factor B, and the MAC (C5b–9) have been immunohistochemically identified in β-amyloid (Aβ)-positive plaques and in phosphorylated tau (p-tau)-positive tangles in the AD brain [6–9]. In addition, Aβ and p-tau have been reported to activate the complement system in AD [10–12] in a unique manner that is Aβ- and p-tau-mediated and antibody-independent, the effect of which lead to neurodegeneration in AD [10,13].

Several defense or regulatory proteins control complement activation [13,14], and these fall into two distinct groups. The first group comprises inhibitors of the complement pathways