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Parallel findings in age-related macular degeneration and Alzheimer's disease

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ABSTRACT

Age is a common risk factor for Alzheimer's disease (AD) and age-related macular degeneration (AMD). Because of the increasing age of the population, these two age-related diseases have recently received a great deal of attention. In addition to age as a risk factor, AD and AMD have many characteristics in common. An important characteristic common to both diseases is the presence of amyloid β (Aβ) in the senile plaques of the AD brain and in the drusen of AMD patients. We have focused on the role of Aβ as a key regulator of the progression from drusen to AMD, and our results have shown that Aβ causes an imbalance of angiogenesis-related factors in the retinal pigment epithelial (RPE) cells. Mice that lack the Aβ-degrading enzyme neprilysin develop RPE degeneration, and the sub-RPE deposits that are formed have features similar to those of AMD in humans. These data suggest that a common pathogenic mechanism might exist between AMD and AD. Thus, therapeutic approaches that have targeted Aβ in patients with AD can also be applied to AMD. In this review, we summarise recent findings on the shared characteristics and perspectives between AMD and AD, beginning with the mechanism of Aβ deposition and including a discussion of Aβ-targeted therapeutic approaches for both AD and AMD.

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1. Introduction

Age is a risk factor common to both age-related macular degeneration (AMD) of the eye and Alzheimer's disease (AD) of the brain. There has been considerable interest in these two diseases because of the increasing number of patients suffering from both conditions in our ageing population. According to the 2002 World Health Organization report, AMD is among the most common causes of blindness, particularly irreversible blindness, in the world (Gehrs et al., 2006). In the United States alone, 1.75 million individuals are affected by AMD, and 7 million people are at risk of developing AMD (Friedman et al., 2004). In Japan, the age-standardised, 9-year cumulative incidence of early AMD was 10.0%, and for late AMD, it was 1.4% in individuals ≥40-years-of-age (Yasuda et al., 2009).

AD is the most common form of dementia in many countries, accounting for 50%–56% of cases at autopsy and in clinical series. The prevalence of AD doubles every 5 years after 65 years of age, with a diagnosis of 1275 new cases/100,000 persons/year for persons over 65 (Hirtz et al., 2007). As the population ages, the number of cases will approach 13.2 to 16.0 million in the USA by mid-century (Hebert et al., 2003). These data suggest that the development of methods to prevent and treat both AMD and AD is essential for maintaining a good quality of life.

The retina is an integral part of the central nervous system (CNS), and like other regions of the brain, it is derived from the neural tube, a precursor of the CNS. An important feature common to both the brain and the retina is that both have blood-tissue barriers. Because of their common origin and anatomical features, AMD and AD have many parallel characteristics. For example, amyloid β (Aβ), a peptide of 39–43 amino acids, is the main constituent of senile amyloid plaques in the brains of AD patients and is also deposited in the drusen of eyes with AMD. It has been more than 25 years since it was first hypothesised that the neurodegeneration in AD might be caused by the deposition of Aβ in plaques in brain tissue (Glenner and Wong, 1984), which came to be known as the "amyloid hypothesis". The results of studies that have been performed to test the amyloid hypothesis are gaining interest among researchers who study AMD. This is also true in our laboratory.

In this review, I will summarise the parallel characteristics and perspectives of AMD and AD beginning with the mechanism of Aβ deposition and concluding with a discussion of Aβ-targeted therapies for both AD and AMD.

2. Molecular similarities between drusen and senile plaques in the brain

Extracellular deposits are a common pathological hallmark of both AMD and AD. In AMD, the deposits are called drusen, and in AD, the deposits in the brain are referred to as senile plaques. Drusen lie between the RPE and Bruch's membrane, and these subepithelial drusen are classified ultrastructurally into two types – basal laminar and basal linear. Both types are strongly associated with AMD (Green and Harlan, 1999). The presence of large and confluent drusen is a significant risk factor for developing choroidal neovascularisation (CNV), a complication in the advanced stage of the wet type of AMD. The Macular Photocoagulation Study Group

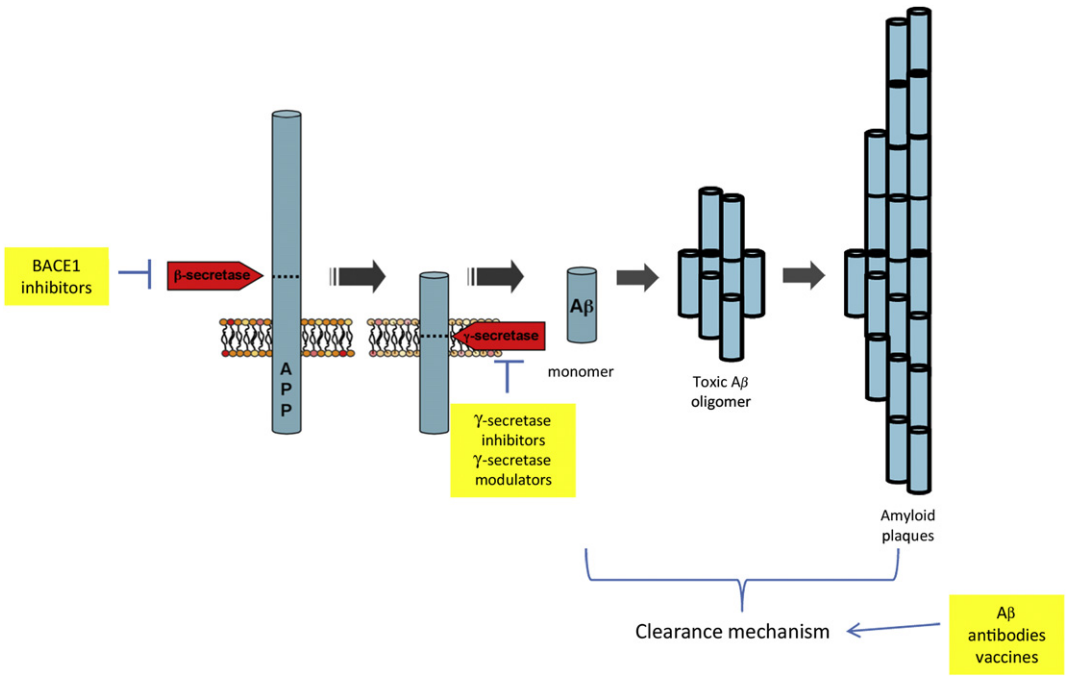

Fig. 1. The amyloid cascade and major therapeutic approaches targeting amyloid β (Aβ). The transmembrane amyloid precursor protein (APP) is sequentially cleaved by two proteases, β-secretase (also known as β-site APP cleaving enzyme 1; BACE1) and γ-secretase, to release various isoforms of the Aβ peptide. The most aggregation-prone form, $Aβ_{1-42}$, aggregates to form toxic oligomers and is deposited in amyloid plaques. The targeting approaches are coloured yellow. A major therapeutic effort is aimed at reducing $Aβ_{1-42}$ production with BACE1 inhibitors and with γ-secretase inhibitors and modulators. A different class of therapeutics aims to enhance the clearance of Aβ. Most of these are therapeutic antibodies or vaccines are directed at soluble monomeric Aβ and/or oligomers and/or plaques.