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Review

Pathogenic mechanisms in Alzheimer's disease

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Abstract

Alzheimer's disease is a progressive neurodegenerative disorder associated with aging and characterized by neurofibrillary tangles and amyloid plaques that deposit in the brain, triggering the neurodegenerative phenomena and leading to neuronal death. Amyloid plaques are primarily composed of β-amyloid peptides, which derive from the Amyloid Precursor Protein (APP) upon the consequential action of β- and γ-secretase. This review discusses recent literature on β- and γ-secretase, and on those cellular factors, like cholesterol and phosphorylation of APP, that are involved in aging and may affect the function of both β- and γ-secretase.

Keywords: Amyloid precursor protein; β-Secretase; γ-Secretase; Amyloidogenic processing

Contents

1. Introduction

Alzheimer's Disease is a progressive neurodegenerative disorder affecting the elderly population. It is characterized by the presence of lesions both at an intracellular and extracellular level, identified as the neurofibrillary tangles and the amyloid plaques, respectively. The origin and the role of the neurofibrillary tangles and amyloid plaques are quite different, although both lead to neurodegeneration.

Neurofibrillary tangles are composed of paired helical filaments, aggregates of phosphorylated protein tau that form when levels of phosphorylated tau are elevated in the cell (Grundke-Iqbal et al., 1986). Tau is a microtubule-associated protein that regulates cytoskeleton structure. When highly phosphorylated, tau is sequestered into paired helical filaments

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(Iqbal et al., 1994), and causes disruption of microtubules, that ultimately leads to cell death. Phosphorylation of tau by protein kinases such as the neuron-specific cyclin dependent kinase 5 (cdk5) precedes the formation of paired helical filaments that cause neurodegeneration (Cruz et al., 2003; Noble et al., 2003).

Importantly, paired helical filaments and neurofibrillary tangles are not a characteristic only of Alzheimer's disease, but are present in many different neurodegenerative diseases called tauopathies (Goedert et al., 1998; Spillantini et al., 1998; Spillantini and Goedert, 1998).

Amyloid plaques are deposits composed primarily of β-amyloid insoluble peptides of approximately 4 kDa generated from the precursor Amyloid Precursor Protein (APP), a type Ia transmembrane protein, characterized by a large NH2-terminal extracellular/cytosolic domain and a small intracellular/luminal COOH-terminal domain (De Strooper and Annaert, 2000; Nunan and Small, 2002). APP is processed following two different pathways, the so-called amyloidogenic and non-amyloidogenic processing, respectively. The non-amyloidogenic pathway involves the activity of α-secretase (metalloproteases such as the tumor necrosis alpha converting enzyme TACE and Adam10; Buxbaum et al., 1998; Parvathy et al., 1999; Parvathy et al., 1998) at a plasma membrane level. α-secretase activity cuts within the sequence of the β-amyloid peptide, at the residue aa 17 (for review see Nunan and Small, 2002). When APP undergoes the non-amyloidogenic processing, there is no release of intact β-amyloid peptide, and the generated stubs do not aggregate and do not have amyloidogenic activity.

In Alzheimer's disease pathology, the production of β-amyloid peptide is the result of APP amyloidogenic processing. This involves the activity first of β- then of γ-secretase, and requires the internalization of APP from the plasma membrane to the endosomes and the lysosomes (Koo and Squazzo, 1994; Koo et al., 1996; Perez et al., 1999). β-secretase, recently identified as the beta-site APP-cleaving enzyme BACE1 (Vassar et al., 1999), cuts APP at the beginning of the sequence of the β-amyloid peptide, generating an extracellular soluble stub called sβAPP and an intracellular COOH-term stub called C99.

Subsequently, γ-secretase cuts C99 at residues 40/42/43 of the β-amyloid sequence, generating intact β-amyloid peptides. The identity of γ-secretase has been a matter of studies over the years. Presenilins (PS1 and PS2) were first identified as the proteins acting as γ-secretase (Wolfe et al., 1999c); more recently, it was discovered that presenilins are part of a tetrameric complex comprised of the proteins nicastrin, Aph1 (anterior pharynx-defective phenotype) and Pen 2 (presenilin enhancer) that altogether regulate the production of β-amyloid peptides (for review see De Strooper, 2003; Haass, 2004).

It has been recently proposed that other factors contribute to β-amyloid formation. Among these are levels of cholesterol in the cells (for review see Puglielli et al., 2003) and APP phosphorylation (for review see da Cruz e Silva and da Cruz e Silva, 2003; Pastorino and Lu, 2004a).

Here we review the recent knowledge on the mechanisms that are at the basis of β- amyloid peptide production, from β- and γ-secretase, to those cellular factors, like cholesterol and APP phosphorylation that may affect their activity and may have an impact on the identification of new therapeutic targets for the treatment of Alzheimer's disease.

2. Beta secretase

2.1. BACE1

BACE1 has been identified by several groups as the β-secretase able to cleave APP and to regulate the production of β-amyloid in vitro (Hussain et al., 1999; Vassar et al., 1999; Yan et al., 1999). Experiments in vivo confirmed that this enzyme is primarily responsible for initiating the amyloidogenic processing of APP. Specifically, brains of BACE1 knockout mice (Cai et al., 2001) had no detectable levels of β-amyloid peptides and did not show accumulation of APP C-terminal fragments C99/C89 (Cai et al., 2001; Pastorino et al., 2004b), whereas brains of BACE1 transgenic mice were characterized by increased levels of β-amyloid and accumulation of the C-terminal fragments (Bodendorf et al., 2002).

BACE1 is an aspartyl protease that cleaves APP at the residue KM-D at the beginning of the sequence of β-amyloid peptides. It is a type 1 membrane protein characterized by a large extracellular domain, where two aspartic residues involved in β-secretase activity reside (Hussain et al., 1999), and by a short intracellular domain containing a sorting sequence (DISLL) that was shown to be involved in the trafficking of the protein. In particular, the LL domain was found to regulate the internalization of the protein from the plasma membrane to the endosomal compartment (Huse et al., 2000; Pastorino et al., 2002), where it localizes (Vassar et al., 1999), and to the lysosomes where BACE1 is degraded (Koh et al., 2005). Furthermore, the residue S was shown to be phosphorylated by CKII (Walter et al., 2001; Pastorino et al., 2002), regulating the trafficking of the protein between the endosomes and the Golgi, most likely through the interaction of BACE1 with GGA1 (Golgi-localized gamma-ear-containing ARF-binding GGA protein 1; Shiba et al., 2004; von Arnim et al., 2004).

Since BACE1 co-localizes to endosomes and requires an acidic pH for its activity (Vassar et al., 1999), it is supposed that the endosomes are the cellular compartment where BACE1 is mostly active. Interestingly, endosomal dysfunction has been linked to Alzheimer's disease and neurodegeneration (Nixon, 2005), and it was previously reported that β-secretase cleavage of APP occurs upon internalization (Koo and Squazzo, 1994; Koo et al., 1996; Perez et al., 1999). It cannot be excluded that BACE1 is active also in intracellular compartment distinct from the endosomes; in fact, BACE1 recycles from the endosomes to the *trans*-Golgi network (Walter et al., 2001), and localizes and is active within the lipid rafts, invaginations of the membrane rich in cholesterol and other lipids (Abad-Rodriguez et al., 2004; Cordy et al., 2003; Ehehalt et al., 2003; Riddell et al., 2001) in proximity of membrane structures. In addition, Kalvodova et al. (2005) showed that, when reconstituted in vitro in large uni-lamellar vesicles, BACE1 is particularly active in those vesicles enriched in cholesterol. Altogether, these data suggest that BACE1, being active in structures enriched in cholesterol, could link cholesterol to β-amyloid production