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Current and future implications of basic and translational research on amyloid-β peptide production and removal pathways

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ABSTRACT

Inherited variants in multiple different genes are associated with increased risk for Alzheimer's disease (AD). In many of these genes, the inherited variants alter some aspect of the production or clearance of the neurotoxic amyloid β-peptide (Aβ). Thus missense, splice site or duplication mutants in the presenilin 1 (PS1), presenilin 2 (PS2) or the amyloid precursor protein (APP) genes, which alter the levels or shift the balance of Aβ produced, are associated with rare, highly penetrant autosomal dominant forms of Familial Alzheimer's Disease (FAD). Similarly, the more prevalent late-onset forms of AD are associated with both coding and non-coding variants in genes such as SORL1, PICALM and ABCA7 that affect the production and clearance of Aβ. This review summarises some of the recent molecular and structural work on the role of these genes and the proteins coded by them in the biology of Aβ. We also briefly outline how the emerging knowledge about the pathways involved in Aβ generation and clearance can be potentially targeted therapeutically. This article is part of Special Issue entitled "Neuronal Protein".

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1. Introduction

The neuropathology of Alzheimer's disease (AD) is characterised by abnormal protein deposits. One of these protein aggregates is composed of hyperphosphorylated tau proteins, which assemble into intraneuronal neurofibrillary tangles (NFT) (Ballatore et al., 2007; Buée et al., 2000; Goedert, 2005; Lee et al., 2001; Terry, 1963). The second principal protein aggregate, composed of the amyloid β-peptide (Aβ), accumulates in the extracellular space of the brain as senile plaques (SP) and in perivascular deposits, where it gives rise to amyloid angiopathy (Glenner and Wong, 1984; Masters et al., 1985). However, the brains of AD patients often also exhibit an abnormal accumulation of other abundant proteins, including α-synuclein (in Lewy bodies) or TDP43 (Josephs et al., 2014). It is clear that the pathological accumulation of both tau and Aβ is important and necessary components of the disease process. However, the exact functional relationship between these two processes remains the topic of intense research (Vossel et al., 2010; Ittner et al., 2010). This review will focus upon the biology of the Aβ peptide.

1.1. Production of AB

Aβ is a cleavage product of the amyloid precursor protein (APP). APP, a type I transmembrane protein (Figs. 1, 2), can shed its extracellular N-terminal domain (sAPP) through two independent proteolytic cleavage pathways. The enzymatic entities that lead to Aβ cleavage are broadly referred to as secretases. In the stoichiometrically predominant pathway (Ray et al., 2011), APP is initially subject to α-secretase cleavage, which can be executed by one of several members of the ADAM (a disintegrin and metalloproteinase domain) protease family, including ADAM10, ADAM17, ADAM9 and ADAM19 (Esch et al., 1990; Sisodia et al., 1990; Asai et al., 2003; Fahrenholz et al., 2000; Fuwa et al., 2007; Lammich et al., 1999). ADAM10 is the dominant α-secretase in the brain and recently two rare mutations in ADAM10 were identified which were suggested as predisposing for late-onset Alzheimer's disease (Suh et al., 2013). However, other groups have yet to confirm these findings. The α-secretase-dependent pathway is referred to as the non-amyloidogenic pathway because it cleaves the APP molecule close to the outer face of the cell membrane between residues in the centre of the Aβ peptide, thereby precluding the subsequent formation of intact Aβ peptides.

The alternative and less abundant sheddase reaction is mediated by β-secretase (BACE), which cleaves APP at the N-terminal boundary of the Aβ peptide domain, located in extracellular proximity to the plasma membrane at a site seventeen residues N-terminal to the canonical α-secretase cleavage site (Figs. 1, 2). β-Secretase cleavage requires prior re-cycling of APP from the cell surface (Haass et al., 1992; Lai et al., 1995; Vassar et al., 2014), a process which likely involves clathrin-mediated endocytosis of the full length APP by proteins such as PICALM, BIN1 and CD2AP. Following endocytosis, APP is targeted to specific subcellular compartments by intracellular vesicular protein sorting receptors. These interactions with sorting receptors, including SORL1 determine whether the full-length APP holoprotein is redirected to the retromer compartment, or allowed to drift into the late endosomal compartment (Rogaeva et al., 2007; Bhalla et al., 2012; Lane et al., 2012; Seaman, 2012; Vardarajan et al., 2012)).

The resulting membrane bound C-terminal fragments (CTF) of APP, generated by either α-secretase or by β-secretase cleavage activities, then undergo a secondary intramembrane endoproteolysis, designated γ-secretase cleavage, by a membrane-bound, multimeric protein complex, known as the presenilin complex (often also casually termed the "γ-secretase complex"). The presenilin complex is composed of four proteins (Edbauer et al., 2003): presenilin 1 (Sherrington et al., 1995) or presenilin 2 (Rogaev et al., 1995; Finckh et al., 2000), nicastrin (Yu et al., 2000), aph-1 and pen-2 (Francis et al., 2002) (see below). γ-Secretase cleavage products of APP-CTF are then extruded from the plasma membrane into the intracellular compartment (amyloid intracellular domain — AICD) or into the extracellular compartment (Aβ from the BACE pathway; p3 from the α-secretase pathway) (Figs. 1, 2).

During the last decade, molecular biological studies, and more recently, structural biology studies, using both negative stain electron microscopy and cryo-electron microscopy methods, have begun to shed light on how the presenilin complex completes the process of Aβ peptide production via a series of cleavages (termed γ, ε, ζ site cleavages) within the transmembrane domain of APP (Fig. 1). The presenilin complex recruits substrates by docking them at a putative initial substrate docking site on the surface of the complex (Kornilova et al., 2005). The substrates are then drawn into a water-accessible cavity inside the complex, allowing hydrolysis of the scissile peptide bond in the transmembrane domain (Li et al., 2014; Lu et al., 2014) (Fig. 3). Some insights into how this might be achieved have been acquired from analysing the effects of binding of peptide-like γ-secretase inhibitor compounds such as Compound E (Li et al., 2014). These studies suggest both that the structure of the complex is quite labile, and that it may exist in several different conformational states. Shifting between these different activity/conformational states is regulated by various (often reciprocal) long-range allosteric interactions (Elad et al., 2014; Li et al., 2014). For instance, we have shown that binding of substrate to the Initial Substrate Docking Site opens up a presenilin complex binding epitope for the peptidomimetic inhibitor Compound E. However, the subsequent occupancy of this peptidomimetic inhibitor binding site has a reciprocal effect on the Initial Substrate Docking Site, causing it to close. We have proposed that this represents the mechanism of a lateral gate that protects the hydrophilic catalytic site but allows intermittent access of substrate transmembrane domains. Specifically, we propose that binding of the substrate to the Initial Substrate Docking Site results in "opening up" a translocation pathway from the surface of the complex to the catalytic pocket. Subsequent occupancy of the translocation pathway (containing the Compound E binding site) causes the allosteric closure of the Initial Substrate Docking Site, allowing the substrate to access the catalytic pocket while protecting

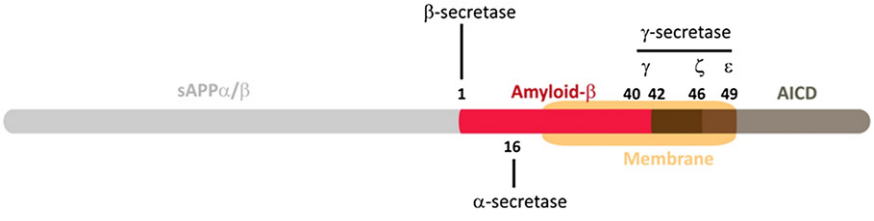

Fig. 1. Schematic of the APP holoprotein showing the location of the transmembrane domain (orange) and the relative sites of cleavage by α-secretase, β-secretase and γ-secretase, which respectively generate: soluble sAPPα and APP-CTFα; soluble sAPPβ and APP-CTFβ; and Aβ and the amyloid intracellular domain (AICD).