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Review

# The amyloid precursor protein and its homologues: Structural and functional aspects of native and pathogenic oligomerization

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ABSTRACT

Over the last 25 years, remarkable progress has been made not only in identifying key molecules of Alzheimer's disease but also in understanding their meaning in the pathogenic state. One hallmark of Alzheimer pathology is the amyloid plaque. A major component of the extracellular deposit is the amyloid-β (Aβ) peptide which is generated from its larger precursor molecule, i.e., the amyloid precursor protein (APP) by consecutive cleavages. Processing is exerted by two enzymes, i.e., the β-secretase and the γ-secretase. We and others have found that the self-association of the amyloid peptide and the dimerization and oligomerization of these proteins is a key factor under native and pathogenic conditions. In particular, the Aβ homodimer represents a nidus for plaque formation and a well defined therapeutic target. Further, dimerization of the APP was reported to increase generation of toxic Aβ whereas heterodimerization with its homologues amyloid precursor like proteins (APLP1 and APLP2) decreased Aβ formation. This review mainly focuses on structural features of the homophilic and heterophilic interactions among APP family proteins. The proposed contact sites are described and the consequences of protein dimerization on their functions and in the pathogenesis of Alzheimer's disease are discussed.
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## Introduction

It became widely accepted that the proteolytic processing of APP is a central event in the onset of Alzheimer's disease. Following the initial ectodomain shedding of APP by ADAM10 (a disintegrin and metalloprotease, also known as α-secretase) or BACE1 (β-site APP cleaving enzyme, also β-secretase), the remaining membrane-bound C-terminal stubs are degraded by the γ-secretase complex. This process has been named regulated intramembrane proteolysis (RIP) (reviewed in De Strooper, 2010). The concerted action of BACE1 and γ-secretase leads to the generation of Aβ peptides. Soluble oligomers of Aβ are regarded as the toxic agent and are most likely responsible for neurodegeneration observed in Alzheimer's disease (Harmeier et al., 2009; Schmechel et al., 2003; Walsh et al., 2002). APP processing by the α-secretase creates the soluble APP ectodomain (sAPPα), which exerts neuroprotective activities (Furukawa et al., 1996; Mattson, 1997; Small et al., 1994). Insulin and insulin growth factor-1 (IGF-1) have been shown to increase α-secretase cleavage of APP as well as the ectodomain shedding of the APP-like proteins APLP1 and APLP2 in human neuroblastoma (SH-SY5Y) cells (Adlerz et al., 2007; Jacobsen et al., 2010). Accumulating evidence suggests that APP and its homologous proteins APLP1 and APLP2 are capable of forming homo- and heterodimers in living cells with a direct impact on APP processing and Aβ generation (Kaden et al., 2008, 2009; Munter et al., 2007). The APP family proteins are type I transmembrane proteins with a large, glycosylated extracellular domain and a short conserved cytoplasmic tail. For APP, dimerization likely occurs as early as in the endoplasmic reticulum and follows a zipper-like mechanism starting from the N to the C terminus involving multiple contact sites. Three different interaction sites are described in the literature, two reside in the ectodomain and one in the transmembrane sequence (TMS) (Beher et al., 1996; Kaden et al., 2008; Munter et al., 2007; Rossjohn et al., 1999; Soba et al., 2005; Wang and Ha, 2004). The physiological functions of APP are still not understood in detail, however, a functional role in cell development, cell–cell and/or cell–matrix interaction is likely. Oligomerization of cell surface receptors and activation in response to ligands is a common mechanism to transfer signals across the cell membrane. A proper signal recognition and such a transduction could not be verified for APP yet although it had been postulated when the full-length form of the molecule was first published (Kang et al., 1987). The Notch receptor is a substrate of the same set of proteases and the Notch intracellular domain (NICD) exhibits important signaling functions in neural development (for review see Woo et al., 2009). However, for Notch dimerization it could not be shown to be decisive for processing (Vooijs et al., 2004).

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## Structural features of APP and APLP

The APP family proteins contain different domains as shown in Fig. 1A. The linker domains are supposed to be unstructured and their main function is to ensure the flexibility of the other individual domains. In this review, we will discuss structural aspects and proposed functions of the E1 and E2 domains, the ectodomain as such, the transmembrane part and the cytoplasmic domain as the structures help to understand the dimerization processes important for Aβ generation.

## The E1 and E2 domains

The E1 domain of APP (residues 18–207) contains two independent folding units, the growth factor-like domain (GFLD, 28–123) and the copper-binding domain (CuBD, 127–188) (Barnham et al., 2003; Rossjohn et al., 1999; Small et al., 1994). The crystal structure of the APP GFLD revealed a highly charged basic surface that was supposed to interact with glycosaminoglycans and a hydrophobic surface that being important for ligand binding (Rossjohn et al., 1999). Furthermore, the crystal structure showed a highly flexible region consisting of an N-terminal loop formed by a disulfide bridge between cysteines 98 and 105 (Rossjohn et al., 1999). This so-called loop-region was described to possibly mediate dimerization (Rossjohn et al., 1999). Indeed, biochemical data revealed that the E1 domain itself can dimerize in solution and the self-interaction is gradually diminished by adding a small peptide mimicking the loop region (loop peptide) (Kaden et al., 2008; Scheuermann et al., 2001). Interestingly, the loop peptide decreased the generation of sAPPβ as well as Aβ40 and Aβ42 when the synthetic peptide was added to APP-expressing neuroblastoma cells (SH-SY5Y). This indicated a direct or indirect influence of dimerization on APP processing (Kaden et al., 2008). We could further show that the loop's disulfide bond is indispensable for the effects of the loop peptide, as peptide bearing serine residues instead of cysteines neither bound to APP nor diminished dimerization or influenced APP processing (Kaden et al., 2008).

The CuBD (amino acids 127–188/124–189) consists of an α-helix that is tightly packed on a triple-stranded β-sheet (Barnham et al., 2003; Kong et al., 2007). At the copper-binding site, Cu(II) can be reduced to Cu(I), leading to the oxidation of the cysteine residues 144/158 and formation of an intramolecular disulfide bond

(Multhaup et al., 1996,1998). This was further supported by structural data showing a tetrahedral or square plane coordination for Cu(II) or Cu(I), respectively (Barnham et al., 2003; Kong et al., 2007). Interestingly, Hesse et al. could show that Cu(II) can inhibit the homophilic binding of an APP fragment to rat APP *in vitro* (Hesse et al., 1994). Later it was described that treatment of Chinese Hamster Ovary (CHO) cells with copper led to a stimulation of α-secretase cleavage (Borchardt et al., 1999). Recently, the structure of the whole APP E1 domain was resolved with a resolution of 2.7 Å (Dahms et al., 2010) showing that the two subunits of the E1 domain, the GFLD and CuBD form a rigid entity and do not consist of two independent folding units connected by a flexible linker as earlier suggested (Gralle et al., 2006). Interestingly, the residues that form the structural network between the GFLD and CuBD are conserved between APP and APLP2 but are not conserved between APP and APLP1. This led to the assumption that the E1 domain of APLP1 has an individual substructure (Dahms et al., 2010), which is in excellent agreement with our data published on the specific features of APLP1 (Kaden et al., 2009), which are discussed below (see chapter entitled APP protein family).

The E2 domain (amino acids 365–570) is the largest subdomain of the APP ectodomain and consists of six α-helices. Wang et al. published the X-ray structure of an E2 antiparallel dimer (Wang and Ha, 2004), showing that the N-terminal double stranded coiled coil structure of the first monomer packs against the C-terminal triple stranded coiled coil structure of the second monomer (Wang and Ha, 2004). This structural feature supports earlier data of Hesse et al. (1994), who found that the collagen-binding site in the E2 domain may be involved in APP–APP interactions (Beher et al., 1996). However, in contrast to Wang et al., Dulubova et al. found that the E2 domain does not dimerize in solution (Dulubova et al., 2004). Of note, the fragment analyzed by Dulubova et al. was much shorter (amino acids 460–576) and lacked the N-terminal double stranded helices of the fragment used by Wang et al. (amino acids 365–566), which may explain the contrasting data of the dimerization state. However, somewhat puzzling is the fact that the E2 domain of *C. elegans* APL-1 was recently also found as a monomer in solution by the same group (Hoopes et al., 2009). This could be due to differences in the human and worm sequences, but could also reflect the fact that dimers are preferentially crystallized over monomers since monomeric proteins can form non-physiological dimers in crystals and then oligomerization may be an artifact of the crystallization conditions (Hoopes et al., 2009). Additional experiments by using more convenient methods need to be performed to clarify the physiological relevance of the oligomeric state and orientation of the E2 domains of APP, its orthologs APPL and APL-1, and its homologous proteins APLP1 and APLP2.

## The ectodomain

There are only few data on the structure of the APP ectodomain as a whole and most are based on small angle X-ray scattering (SAXS) modeling. Conflicting data about dimerization exist for soluble APP generated by ADAM10 cleavage (sAPPα). While we found the APP ectodomain (sAPPα) purified from *Pichia pastoris* dimerizes in solution by cross-linking and size-exclusion chromatography, others only described sAPP monomers, or rather found dimers only in the presence of heparin (Gralle et al., 2002, 2006; Gralle and Ferreira, 2007; Kaden, 2007). This discrepancy could be due to differences in methods and buffers used for purification. Our data further show that the ectodomains of APLP1 and APLP2 were not only dimeric but can also form tetramers in solution, further supporting the hypothesis of self interactions in the APP protein family (Kaden, 2007).

The ectodomains of APP and APLPs possess multiple binding sites for metal ions and components of the extracellular matrix substantiating possible functions of the APP family proteins in cell–matrix interactions. These ligands include copper, zinc, collagen and heparan sulfate that all influence each other in their binding strength (Beher et al., 1996; Breen et al., 1991; Bush et al., 1993; Multhaup et al., 1996; Small et al., 1994). Interestingly, APP and APLP2 can bind heparan sulfate in their E1 and E2 domains, whereas APLP1 has only one binding site in the E2 domain, again emphasizing the differences between the E1 domain of APP or APLP2 and APLP1 (Bush et al., 1994; Multhaup et al., 1994, 1995). Furthermore, there might be a functional relationship between the heparan sulfate and copper ion binding activities of APP/APLP2 in their modulation of the heparan sulfate degradation in glypican-1 as the rate of autoprocessing of glypican-1 is modulated by APP and APLP2 in neurons and by APLP2 in fibroblasts (Cappai et al., 2005).

## The transmembrane region and the Aβ sequence

The Aβ peptide encompasses the N-terminal juxtamembrane region (28 amino acid residues) as well as half of the TMS (Fig. 1B).

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