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Review

Signaling effect of amyloid-β_{42} on the processing of AβPP

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ABSTRACT

The effects of amyloid-β are extremely complex. Current work in the field of Alzheimer disease is focusing on discerning the impact between the physiological signaling effects of soluble low molecular weight amyloid-β species and the more global cellular damage that could derive from highly concentrated and/or aggregated amyloid. Being able to dissect the specific signaling events, to understand how soluble amyloid-β induces its own production by up-regulating BACE1 expression, could lead to new tools to interrupt the distinctive feedback cycle with potential therapeutic consequences. Here we describe a positive loop that exists between the secretases that are responsible for the generation of the amyloid-β component of Alzheimer disease. According to our hypothesis, in familial Alzheimer disease, the primary overproduction of amyloid-β can induce BACE1 transcription and drive a further increase of amyloid-β precursor protein processing and resultant amyloid-β production. In sporadic Alzheimer disease, many factors, among them oxidative stress and inflammation, with consequent induction of presenilins and BACE1, would activate a loop and proceed with the generation of amyloid-β and its signaling role onto BACE1 transcription. This concept of a signaling effect by and feedback on the amyloid-β precursor protein will likely shed light on how amyloid-β generation, oxidative stress, and secretase functions are intimately related in sporadic Alzheimer disease.

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Amyloid-β: functions and dysfunctions

The amyloid-β peptide (Aβ) is generated following the sequential cleavage of its precursor, the amyloid-β protein precursor (AβPP) by β- and γ-secretase in the amyloidogenic pathway. The non-amyloidogenic pathway, primed by a first cleavage of AβPP by α-secretase, whose identity is still vague, leads to the production of non-amyloidogenic C-terminal fragment peptide C83 (Selkoe, 2001; Vassar, 2004). The best candidates to α-secretase function are members of the ADAM family of disintegrin and metalloproteases

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(Kojro and Fahrenholz, 2005): recent data show how the different expression and integrity of these proteases can modulate the phenotype of Alzheimer disease (AD) mice models (Schmitt et al., 2006; Schroeder et al., 2009). The β-secretase is known to be the β-site AβPP cleaving enzyme I, BACE1 (Hussain et al., 1999; Sinha et al., 1999), a 501 amino acid aspartyl protease widely expressed in brain that fulfills most of the requirements expected for a candidate β-secretase (Lin et al., 2000; Vassar et al., 1999). The γ-secretase is a multimeric, high molecular weight complex with proteolytic activity, formed by a minimum of four molecules: presenilin 1/2 (PS1/2), Nicastrin, Pen-2 and Aph-1 (De Strooper et al., 1999; Haass and De Strooper, 1999; Selkoe, 2001).

Amyloid-β functions

As much as a cellular and molecular function for AβPP and its derivatives has been searched for, no clear physiological roles have been fully characterized, and they often mingle with the toxic effects of Aβ. The similarity of AβPP to NOTCH and to its processing strengthens the idea that AβPP and its derivatives may have a signaling role.

Aβ is the subject and object of pathways leading to cell death or survival, where it could play a role not just as a toxic compound, but as a functional signaling intermediate. TrkA is a member of the tyrosine kinase family receptors. Upon binding to its ligand, i.e., NGF, the intracellular C-terminal portion of TrkA phosphorylates and activates the Src homology 2 domain containing protein, which leads to MAPK activation and stimulation of cell growth. It also activates the PLCγ pathway which also leads to MAPK activation as well as PI3K which leads to AKT activation and inhibition of apoptosis (Gomez and Cohen, 1991; Qian et al., 1998; Sawada et al., 2000; Ulrich et al., 1998). Its expression seems reduced in brains of AD patients (Marinelli et al., 1999), more than the physiological age-related switch between TrkA and p75NTR would predict. In this picture, BACE1 stabilization and increased Aβ production seem to be a consequence of aging (Costantini et al., 2006). On the other end, Aβ strikes the production of NGF, activation of the TrkA/p75NTR pathways and MAPT (tau) hyperphosphorylation (Bulbarelli et al., 2009). p75NTR, a low affinity receptor for NGF, acts via binding with Trk receptors and mostly leading to cell death and apoptosis (Harrington et al., 2004), and its blockade has been shown to halt Aβ-induced NGF-dependent cell death (Yaar et al., 2008, 2007). The apparent nonsense could be explained by, and interplay between, neurons and activated NGF-secreting astrocytes, attempting to survive in an amyloid milieu: in "old" hippocampal neurons expressing p75NTR, this would lead to cell death (Saez et al., 2006) and Aβ could be a regulator of the process.

One of the downstream consequences of p75NTR signaling is the activation of NFKB, via p38/MAPK and JNK: although mostly considered to be a surviving pathway (Bui et al., 2002), some authors have proposed that NFKB activation could strike apoptosis in neuroblastoma cells via p53 (Costantini et al., 2005). Furthermore, inflammation and up-regulation of Il-6, IL-1, and TNF-α through microglia activation and Aβ also contributes to NFKB activation (Dudal et al., 2004; Jin et al., 2008; Pan et al., 2009).

The MAPK pathway is often involved in Aβ-driven signaling, as downstream of Aβ-RAGE interaction (Yan et al., 2009), TrkA/p75NTR, insulin receptor (Townsend et al., 2007), and many more: in general, the MAPK signaling seems activated in AD (Lagalwar et al., 2006, Lee and Das, 2008; Zhu et al., 2002) and correlates strongly with the oxidative stress in AD models (Tamagno et al., 2003).

Intracellular Aβ accumulation, which may commence way before extracellular, seems to be involved in various types of cellular damage, such as mitochondrial toxicity, proteasome impairment, and synaptic damage; p53 expression can also be activated by intracellular Aβ (Ohyagi et al., 2005), leading to apoptosis, and has been reported to be up-regulated in AD pathological regions (Hooper et al., 2007) and in Down's syndrome (de la Monte, 1999), although when mutant PS1 is overexpressed, p53 up-regulation seems to depend more on failure of proteasomal degradation than on a transcriptional mechanism (Dudal et al., 2004).

Other signaling pathways that are somehow related to Aβ generation involve NOTCH, which is processed intramembranously by the same PS1-dependent γ-secretase activity, competes with AβPP for this processing, and interacts with AβPP itself on the plasma membrane (Berezovska et al., 2001; Oh et al., 2005). Wnt is involved in correct cell development and axon guidance together with β-catenin, APC, and GSK3β, and its pathway has been found to be deregulated in AD, by PS mutants and by Aβ itself (Boonen et al., 2009; Magdesian et al., 2008).

As a final example of the complexity of Aβ physiological role, it has been shown that neuronal activity modulates the production and secretion of Aβ (Nitsch et al., 1993); in turn, Aβ can depress this neuronal activity, via glutamatergic receptors, creating a negative feedback loop (Kamenetz et al., 2003; Shemer et al., 2006) that would act as a sort of synaptic homeostasis mechanism, preventing excitotoxicity. As reported in the next paragraphs, this modulation can become detrimental to neurons as quality and quantity of Aβ vary.

Amyloid-β dysfunctions

According to the amyloid cascade hypothesis of AD, Aβ is considered to be the primary motor of neuronal degeneration, although the pathway leading to neuronal death is very complicated and involves numerous steps (Hardy and Allsop, 1991). In particular, although debated until now, neurofibrillary tangles composed of hyperphosphorylated protein tau are considered a secondary event in the disease progression, a consequence of Aβ toxicity and Aβ plaque formation (Verdile et al., 2004). Amyloid plaques, one of the defining neuropathological characteristics of AD, are neither specific of this condition (Armstrong et al., 1996; Dickson et al., 1992; Yamaguchi et al., 1998) nor properly "pathogenic", as they have now come to be considered an end stage of amyloid deposition, representing an inactive reservoir of species that are in equilibrium with the smaller, putatively neurotoxic assemblies (Hardy and Selkoe, 2002). Although neuronal degeneration occurs in proximity of the amyloid plaques, some studies have suggested that intermediate Aβ aggregates such as protofibrils or simple oligomers are also involved in AD pathogenesis and even appear to be the more dangerous species. Furthermore, in patients dying with AD, there is a relatively weak correlation between the severity of dementia and the density of fibrillar amyloid plaques (Dickson et al., 1995; Katzman, 1986; Terry et al., 1991). More attention has thus been focused on the early stages of amyloid production and on its "maturation" from small soluble molecules, to oligomers and into more and more complex high molecular weight aggregates.

Aβ is a physiological cell product, mainly generated as a 40 amino acid peptide ($A\beta_{1\text{-}40}$), while only about 10% as a longer $A\beta_{1\text{-}42}$ peptide. The latter peptide is proportionally increased in patients affected by AD, both in familial and sporadic cases, and has a greater propensity to aggregate and form oligomers and fibrils (Burdick et al., 1992; Haass et al., 1992; Jarrett et al., 1993; Kumar-Singh et al., 2006). The conformational change from an α-helix into a well-organized β-sheet structure is a well-known characteristic of Aβ aggregation (Xu et al., 2005). A major role in the aggregation is played by the C-terminus of Aβ and by the hydrophobic core in the group of residues 17–21 (Tycko, 2003). This is in line with the pathogenic role of $A\beta_{42}$ and other shorter x-42 peptides which maintain a full-length C-terminus. The Aβ pool is also composed by many different N- and C-terminal truncated peptides, identified both in plaques and away from plaques, in soluble forms and in biological fluids (Hardy and Selkoe, 2002; Russo et al., 1997, 2000). It has been pointed out how N-terminal truncated peptides, in particular the pyroglutamate-3-42 peptide, are enriched in AD