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Research report

Amyloid precursor protein processing and bioenergetics

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ABSTRACT

The processing of amyloid precursor protein (APP) to amyloid beta (Aβ) is of great interest to the Alzheimer's disease (AD) field. Decades of research define how APP is altered to form Aβ, and how Aβ generates oligomers, protofibrils, and fibrils. Numerous signaling pathways and changes in cell physiology are known to influence APP processing. Existing data additionally indicate a relationship exists between mitochondria, bioenergetics, and APP processing. Here, we review data that address whether mitochondrial function and bioenergetics modify APP processing and Aβ production.

1. Introduction

Aβ associates with and is believed by many to cause Alzheimer's disease (AD), and thus is central to major therapeutic initiatives. Well before the advent of positron emission tomography (PET) – based amyloid imaging, Aβ plaques were known to deposit within brains of cognitively normal individuals (Bennett et al., 2006; Dickson et al., 1992; Price and Morris, 1999). PET-based Aβ imaging in living subjects advanced the field by enabling longitudinal measurements of Aβ plaque accumulation. These studies showed brain Aβ fibril deposition increases prior to the onset of cognitive decline, and profoundly slows during the clinically active stages (Burns and Swerdlow, 2013; Jack et al., 2013). Therefore, plaque deposition may precede cognitive decline by 1–2 decades and Aβ fibril accumulation essentially plateaus before overt clinical symptoms manifest. Why fibrillary Aβ accumulation begins, accelerates, and decelerates to the point that little additional accumulation occurs prior to symptom onset is unknown.

Studies depicting connections between mitochondrial dysfunction and Aβ suggest potential leads to these questions. Amyloid Precursor Protein (APP) and Aβ reportedly co-localize with mitochondria (Devi et al., 2006; Hansson Petersen et al., 2008). Aβ inhibits respiratory chain function, and Aβ toxicity appears reduced in cells that lack functional respiratory chains (reviewed in (Swerdlow, 2012)). Altering mitochondrial function also changes APP processing, and can increase or decrease the production of amyloidogenic derivatives (Canevari et al., 1999; Casley et al., 2002a; Gabuzda et al., 1994; Gasparini et al., 1997; Khan et al., 2000; Leuner et al., 2012; Onyango et al., 2010; Pereira et al., 1998;

Abbreviations: ABAD, Aβ binding alcohol dehydrogenase; AD, Alzheimer's disease; ADAM, A Disintegrin and metalloproteinase; AICD, APP intracellular domain; APH1, anterior pharynx-defective 1; APP, amyloid precursor protein; ATP, adenosine triphosphate; Aβ, amyloid beta; BACE1, β-secretase 1; BACE2, β secretase 2; CCCP, Carbonyl cyanide m-chlorophenyl hydrazine; COX, cytochrome oxidase or complex IV; CTF, C-terminal fragment; CTF83, C-terminal fragment 83; CTF99, C-terminal fragment 99; cybrid, cytoplasmic hybrid; DRP1, dynamin related protein 1; EGF, epidermal growth factor; ER, endoplasmic reticulum; GSH, glutathione; IDE, insulin degrading enzyme; IL6, interleukin 6; MnSOD/SOD2, manganese superoxide dismutase; mtDNA, mitochondrial DNA; PEN2, Presenilin enhancer 2; PET, positron emission tomography; PFKFB3, 6-phosphofructo-2-kinase-fructose-2,6-biphosphatase 3; PGC1α, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGC1β, Peroxisome proliferator-activated receptor gamma coactivator 1-beta; PKC, protein kinase C; PPARγ, Peroxisome proliferator-activated receptor gamma; PP1α, protein phosphatase 1 α; PS1, Presenilin 1; PS2, Presenilin 2; ROS, reactive oxygen species; sAPPα, soluble APP α; sAPPβ, soluble APP β; TACE, tumor necrosis factor-alpha converting enzyme; TIM23, translocase of the inner mitochondrial membrane 23; TNFα, tumor necrosis factor α; TOMM40, translocase of the outer mitochondrial membrane 40.

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Webster et al., 1998). Here, we review evidence for the relationship between mitochondria, bioenergetics, and APP processing.

2. Amyloid precursor protein

In humans the *APP* gene is located on chromosome 21. Alternative splicing generates 8–11 APP protein isoforms of varying amino acid length (305, 639, 677, 695, 696, 714,733, 746, 751,752, 770) (Matsui et al., 2007; Sandbrink et al., 1996). It is important to note APP splicing may vary between species (i.e. rodent versus human), and there may be additional unidentified splice variants. Of the currently known isoforms, APP 751 and 770 are expressed in glial cells, while APP 695 is the predominate form expressed in neurons (Matsui et al., 2007). APP is a type I transmembrane protein which is trafficked through both secretory and endocytic pathways.

Cellular localization of APP is dynamic. In the secretory pathway APP moves from the endoplasmic reticulum (ER) to the plasma membrane (Haass et al., 2012). During this process APP is post-translationally modified (phosphorylation, tyrosine sulphation, and N- or O- linked glycosylation) (Bhattacharyya et al., 2013; Lee et al., 2003; Pahlsson et al., 1992). APP cleaved at the plasma membrane is internalized (this requires a YENPTY motif), where it is endocytosed by either endosomes or lysosomes (Lai et al., 1995). Data from overexpression studies suggest the majority of APP is trafficked to the trans-Golgi network, while only 10% arrives at the plasma membrane (Haass et al., 2012). As mentioned above, the YENPTY domain is required for APP endocytosis. Mutations in this domain inhibit amyloidogenic APP processing (La Rosa et al., 2015; Perez et al., 1999). This domain contains a cytosolic adaptor in which proteins that contain a phosphotyrosine binding domain bind to APP. These adaptor proteins include but are not limited to Fe65, Dab1, Mint 1, Mint 2, Mint 3, and JNK (Haass et al., 2012; Thinakaran and Koo, 2008).

2.1. APP processing pathways

APP processing is dependent on secretase enzymes, which yield products that are secreted into the extracellular space or which remain within or associated with the cell. APP processing is generally divided into two pathways, non-amyloidogenic and amyloidogenic. The non-amyloidogenic pathway begins with α-secretase-mediated cleavage of APP at amino acid 687 (in the APP 770 isoform) which releases the ectodomain, soluble APP α (sAPPα), into the extracellular space. As a result, a C-terminal fragment of APP that is 83 amino acids in length (CTF83) remains embedded in the plasma membrane. Cleavage of CTF83 by γ-secretase releases a small p3 fragment into the extracellular space and the APP intracellular domain (AICD) into the cytoplasm (Fig. 1). Conversely, amyloidogenic processing begins with β-secretase-mediated APP cleavage at amino acid 671 (in the APP 770 isoform). As a result, a smaller ectodomain, soluble APP β (sAPPβ), is released into the extracellular space. A larger APP C-terminal fragment that is 99 amino acids in length (CTF99) remains embedded in the plasma membrane. Finally, cleavage of CTF99 by γ-secretase releases Aβ into the extracellular space and the AICD into the cytoplasm (Fig. 1). Numerous in depth reviews of APP processing pathways are available (Haass et al., 2012; Zhang et al., 2011).

The α-secretase is a membrane bound zinc metalloproteinase consisting of the A Disintegrin And Metalloprotease (ADAM) family members ADAM9, ADAM10, ADAM19, and Tumor Necrosis Factor Converting Enzyme (TACE)/ADAM17 (Asai et al., 2003; Buxbaum et al., 1998; Lammich et al., 1999). ADAM10 appears to be the dominant α-secretase in neurons (Kuhn et al., 2010). Other substrates for α-secretase include NOTCH receptors, tumor necrosis factor α (TNFα), epidermal growth factor (EGF) receptor ligands, cadherins, and interleukin 6 (IL6) receptor (Haass et al., 2012). Cleavage of APP by α-secretase is dependent on both the α helical conformation of the cleavage site and the distance between the bond undergoing hydrolysis and the plasma membrane (Sisodia, 1992). Details about α-secretase function, structure, and regulation have been reviewed elsewhere (Allinson et al., 2003; Lichtenthaler, 2011)

The β-secretase 1 (BACE1) is required for APP cleavage and is rate limiting for the generation of Aβ from APP. Knockout of BACE1, but not BACE2, completely blocks the generation of Aβ (Cai et al., 2001; Haass et al., 2012). Beyond APP BACE1 also cleaves myelin, voltage dependent sodium channels, platelet selecting glycoprotein ligand 1, type II α 2,6 sialytransferase, and interleukin like receptor type II (Haass et al., 2012). BACE1 is largely membrane bound with highest activity in an acidic pH environment (Haass et al., 1993a; Haass et al., 1993b; Selkoe et al., 1996). BACE1 structure, function, and cell trafficking are reviewed in depth elsewhere (Cole and Vassar, 2007).

The γ-secretase, an aspartyl protease, is comprised of four subunits. These include Presenilin 1 (PS1), Presenilin 2 (PS2), nicastrin, anterior pharynx defective (APH-1), and PS enhancer (PEN2) (Francis et al., 2002). PS1 and PS2 form the catalytic domain of γ-secretase while APH-1 may act as a stabilizer, PEN2 acts as a regulator/enhancer of activity, and nicastrin serves as a substrate receptor (Bolduc et al., 2016; Dries and Yu, 2008; Holmes et al., 2014). The cleavage event catalyzed by γ-secretase does not occur at a single site as there are three cleavage sites on APP separated by three amino acids; ε, γ, and ζ. γ-secretase assembly, trafficking, and substrates have been reviewed elsewhere (De Strooper et al., 2012; Dries and Yu, 2008; Haapasalo and Kovacs, 2011).

The location of APP processing is still unclear. Data support APP processing at the plasma membrane, ER, trans-Golgi network, endosome vesicles, mitochondria, and lipid rafts (Choy et al., 2012; Devi and Ohno, 2012; Di Paolo and Kim, 2011; Haass et al., 2012; Hartmann et al., 1997; Hicks et al., 2012; Placido et al., 2014). Further uncertainty exists in the field regarding the existence of intracellular Aβ (Wirths et al., 2012), as some have argued this could represent an artifact of overexpressing a mutant human transgene in mice (Oakley et al., 2006; Youmans et al., 2012). It is important to note, though, that studies depicting intracellular Aβ have also been performed in post-mortem human brains (Aho et al., 2010; Glabe, 2001; Gyure et al., 2001; Hashimoto et al., 2010; Takahashi et al., 2002).

The hypothesis that amyloidogenic APP processing occurs within endosomes is supported by discrete yet convincing studies (Koo and Squazzo, 1994). For example, endosomes contain the optimum pH for BACE1 activity, APP and BACE1 interact within the endosomal pathway, and APP CTFs are processed in endosomes. Furthermore, inhibition of endosomal signaling prevents amyloidogenic APP processing (Haass et al., 1993b; Haass et al., 2012; Selkoe et al., 1996). APP trafficking/recruitment to endosomes of the trans-Golgi network are both sites at which Aβ has been shown to be generated (Choy et al., 2012; Edgar et al., 2015; Morel et al., 2013).

Lipid rafts bring APP and BACE1 together, providing an interaction interface for amyloidogenic APP processing. Lowering cholesterol levels in N2a neuroblastoma cells reduces Aβ production. It is hypothesized that APP within lipid rafts undergoes amyloidogenic processing, while APP not found within lipid rafts is subjected to non-amyloidogenic processing (Ehehalt et al., 2003). γ-secretase may also exist within lipid rafts (Urano et al., 2005). Overall, cholesterol and lipid metabolism may play a pivotal role in determining where and how APP is processed (Di Paolo and Kim, 2011; Hicks et al., 2012).

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