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Review

Expression and function of APP and its metabolites outside the central nervous system

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ABSTRACT

Amyloid precursor protein (APP) derived amyloid beta (Aβ) peptides have been extensively investigated in Alzheimer's disease pathology of the brain. However, the function of full length APP in the central nervous system remains unclear. Even less is known about the function of this ubiquitously expressed protein and its metabolites outside of the central nervous system. This review summarizes key aspects of the current understanding of the expression and function of APP and its proteolytic fragments in specific non-neuronal tissues.

1. Introduction

Much of the study of amyloid precursor protein (APP) has focused on changes in the central nervous system during Alzheimer's disease (AD) pathology. As previously reviewed (Zhang et al., 2012; Zheng and Koo, 2011), in the central nervous system (CNS) full length APP has been suggested to function as a cell surface receptor contributing to cell adhesion and cell–cell interactions via its extracellular domain possibly through trans-dimerization. The C-terminus of APP contains a YENPTY sequence between residues 682 and 687 that is a consensus sequence for a phosphotyrosine binding domain interaction. The N-terminal fragment, sAPP-α, is neuro-protective, promotes neurite outgrowth and synaptogenesis, facilitates learning and memory, acts as a growth factor and regulates cell adhesion. On the other hand, the N-terminal sAPP-β fragment can stimulate axonal pruning and neuronal cell death. APP cleavage to generate the amyloid beta (Aβ) peptide can lead to peptide-mediated neurotoxicity, neurofibrillary tangle formation and synaptic loss. The APP intracellular domain (AICD) fragment that is often generated during proteolytic processing is capable of behaving as a transcription factor, controlling cell death and neprilysin-mediated Aβ degradation, altering calcium and ATP homeostasis, and regulating intracellular trafficking and cytoskeletal dynamics. However, considerably less work has been published describing the function and expression of full-length APP or its cleavage products outside the central nervous system in spite of the well-recognized ubiquitous expression pattern.

2. APP expression, processing, and structure

Amyloid precursor protein (APP) is a type I integral membrane protein with a large extracellular N-terminal domain, a hydrophobic transmembrane domain, and a short C-terminus intracellular domain (Dyrks et al., 1988; Kang et al., 1987). There are three major isoforms of the protein derived from alternative splicing, APP751, APP770, APP695, with APP695 demonstrating highest levels of expression in brain (Ponte et al., 1988; Tanaka et al., 1988, 1989). APP processing has recently been extensively described elsewhere (Zhang et al., 2012; Zheng and Koo, 2011) and will, therefore, not be heavily detailed here. Briefly, APP undergoes post-translational processing via two pathways, the non-amyloidogenic and the amyloidogenic. In the non-amyloidogenic pathway, APP is sequentially cleaved first by

Abbreviations: AChRs, acetylcholine receptors; ADAM, a disintegrin and metalloprotease domain; AD, Alzheimer's disease; APP, amyloid precursor protein; Aβ, amyloid beta; APH1, Anterior pharynx-defective 1; AICD, APP intracellular domain; BACE1, β-secretase; CNS, central nervous system; FAD, familial Alzheimer's disease; IBM, inclusion-body myositis; IL-6, interleukin-6; MIP-1α, macrophage inflammatory protein-1α; MCP-1, monocyte chemotactic protein-1; NMJs, neuromuscular junctions; PEN2, Presenilin enhancer 2; PKC, protein kinase C; TNFα, tumor necrosis factor α.

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α-secretase (ADAMs) to generate an N-terminal sAPP-α fragment. The remaining C83 C-terminal fragment is further cleaved by γ-secretase (Presenilin1 or Presenilin2, Presenilin enhancer 2 (PEN2), Anterior pharynx-defective 1 (APH1) and Nicastrin) to release a P3 peptide and its C-terminal intracellular counterpart, the APP intracellular domain (AICD). In the amyloidogenic processing pathway, APP is again sequentially cleaved but first by the β-secretase (BACE1) to now yield the N-terminal sAPP-β fragment. The remaining C99C-terminal fragment undergoes and γ cleavages by γ-secretase to release the amyloid beta (Aβ) 1-40/42 peptides and an AICD. A characteristic accumulation of Aβ peptides in the brains of AD patients has helped to draw research focus to these particular peptide metabolites of APP. Finally, APP can also be processed by caspase 3 to release cytotoxic C31 and Jcasp fragments. Amyloid precursor protein and mRNA have been shown to be expressed in the brain, thymus, heart, muscle, lung, kidney, adipose tissue, liver, spleen, skin, and intestine (Akaaboune et al., 2000; Galloway et al., 2007; Herzog et al., 2004; Joachim et al., 1989; Lee et al., 2008; Sandbrink et al., 1994; Selkoe et al., 1988; Yamada et al., 1989). Therefore, even though the function and processing of APP in neurons may appear particularly relevant to the study of AD, the wide-spread expression of the protein suggests it has a broader role in both normal and disease physiology.

3. APP function and Aβ pathology in skin

APP expression in the mammalian epidermis is predominantly in basal keratinocytes, but can also be found in the melanotyes and in melanoma cells (Herzog et al., 2004; Hoffmann et al., 2000). APP is also expressed in vitro in the immortalized human keratinocyte cell line, HaCaT, as well as in proliferating primary keratinocytes (Herzog et al., 2004). Aβ deposits have been reported beneath the epidermal/dermal junction as well as near small blood vessels and glandular structures in human tissue (Joachim et al., 1989).

Aspects of APP function in the epidermis have already been reviewed (Herzog et al., 2004) and all of these will, therefore, not be extensively repeated. However, several key points will be re-emphasized. It appears that APP promotes cell adhesion to several components of the extracellular matrix based upon its in vitro interactions with perlecan, laminin, collagen type IV, and entactin. Studies using wild type and $APP^{-/-}$ mice demonstrate that APP may also function as a membrane receptor and regulate behavior of the axonal transport protein, kinesin-I, which mediates movement of membrane-bound compartments such as melanosomes along microtubules. Interestingly, APP also appears to regulate copper homeostasis as suggested by its in vitro ability to reduce Cu(II) to Cu(I) leading to oxidative stress and apoptosis in the basal epidermis in human keratinocytes.

In addition to these functions attributed to full length protein, the APP fragment, sAPPα, promotes human keratinocyte proliferation and migration and regulates melanocyte function in vitro. This is consistent with the fact that $APP^{-/-}$ keratinocytes have reduced proliferative and cell substrate adhesion potential. These findings suggest that sAPPα belongs to a family of structurally similar cysteine-rich growth factors for epidermal keratinocytes involved in growth, differentiation and wound repair.

APP or its metabolites may also play some role in epidermal pathology. For instance, APP levels are upregulated in keratinocytes in psoriasis, a very common chronic inflammatory human skin disease in which keratinocyte proliferation and differentiation are perturbed leading to alteration in epidermal thickness and composition (Romanowska et al., 2009). Processing of APP to Aβ in vitro in human psoriasis patient keratinocytes increases transcription of kynureninase, which can induce an inflammatory skin reaction (Romanowska et al., 2009). Increased APP expression also correlates with advanced melanoma progression in human tissues and downregulation by RNA interference in vitro in human melanoma cell lines results in terminal and irreversible differentiation (Botelho et al., 2010).

APP processing and Aβ release have also been shown to be regulated by protein kinase C (PKC) activity in cultured skin fibroblasts from familial Alzheimer's disease (FAD) patients, in which phorbol ester stimulation of PKC-α activity increases sAPP-α and decreases Aβ secretion (Gasparini et al., 1998). Aβ secretion is basally elevated in cultured skin fibroblasts from FAD patients, suggesting that FAD has a deficit in PKC activity. FAD cultured fibroblasts also have increased total membrane bound calcium with attenuated calcium uptake as well as increased lactate production and altered glucose utilization compared to non-AD controls. This suggests that APP may be involved in regulating a disease phenotype in FAD epidermis (Gasparini et al., 1998).

Collectively, these findings from the skin indicate that APP and its metabolites have a role in regulating epidermal cell phenotypes with a significant ability to modulate proliferative and migratory behavior. Disease-associated changes in expression or processing of APP correlate with perturbations of these behaviors in a variety of diseases.

4. APP function and Aβ pathology in adipose tissue

APP and its Aβ fragments are also expressed in human adipose tissue adipocytes and macrophages (Lee et al., 2008). Obesity upregulates APP levels in vivo in human adipose tissue, which correlates with insulin resistance, hyperinsulinemia, and an increase in the expression profile of the proinflammatory genes, monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), and interleukin-6 (IL-6), in human adipocytes in vitro (Lee et al., 2008). Elevated human adipocyte APP gene expression in vivo also correlates with increased plasma Aβ40 levels (Lee et al., 2009). Tumor necrosis factor α (TNFα) stimulation increases APP protein levels in vitro in 3T3-L1 adipocytes in a dose-dependent manner (Sommer et al., 2009). This correlates with an observed increase in levels of adipose tissue TNFα and APP in a murine model of diet-induced obesity although agonist antibody stimulation of APP does not alter in vitro murine adipocyte viability, proinflammatory TNFα secretion, or differentiation state (Puig et al., 2012). These data from both rodent and human studies indicate that APP expression in adipose tissue appears to be correlatively up-regulated during pro-inflammatory conditions, such as obesity, and is positively regulated by direct proinflammatory stimulation of adipocytes. However, the function of APP or its metabolites basally or during proinflammatory upregulation in adipose tissue remains unclear.

5. APP function and Aβ pathology in intestine

APP is expressed in the intestine and is localized to enterocytes, neurons, and smooth muscle of the muscularis externa in mice (Puig et al., 2011). APP and Aβ levels are increased in absorptive columnar epithelial cells in mice fed a high fat diet that is enriched in saturated fat and cholesterol. However, Aβ levels are attenuated by fasting for 65 h suggesting that APP or its metabolites may regulate chylomicron biosynthesis (Galloway et al., 2007). Aβ immunoreactivity colocalizes with apo B in small intestine enterocytes along the lengths of the villi and Aβ levels are attenuated in mice fed a diet free of saturated fat but supplemented with cholesterol, again supporting the idea that Aβ is involved in chylomicron biosynthesis (Galloway et al., 2009; Pallebage-Gamarallage et al., 2009). Enterocyte Aβ immunostaining localizes to perinuclear regions suggesting a location within the golgi apparatus or rough endoplasmic reticulum (Galloway et al., 2007). Comparing wild type and $APP^{-/-}$ mice demonstrates that APP expression also regulates the behavior of enteric neurons, macrophages and epithelial cells to modulate motility and absorption as well as barrier integrity (Puig et al., 2011). $APP^{-/-}$ mice also have an attenuated intestinal inflammatory profile suggesting that APP may regulate host–microbe interaction or susceptibility to gastrointestinal inflammatory disease (Puig et al., 2011). There may also be some contribution of APP or its metabolites to traditionally non-intestine related disease.