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REVIEW

Roles of amyloid precursor protein family members in neuroprotection, stress signaling and aging

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Abstract The roles of amyloid precursor protein (APP) family members in normal brain function are poorly understood. Under physiological conditions the majority of APP appears to be processed along the non-amyloidogenic pathway leading to the formation of the secreted N-terminal APP fragment sAPPα. This cleavage product of APP has been implicated in several physiological processes such as neuroprotection, synaptic plasticity, neurite outgrowth and synaptogenesis. In this review we focus on the role of APP family members in neuroprotection and summarize the cellular and molecular mechanisms which are believed to mediate this effect. We propose that a reduction of APP processing along the non-amyloidogenic pathway during brain aging could result in an enhanced susceptibility of neurons to cellular stress and could contribute to neurodegeneration in Alzheimer's disease.

Keywords Cell death · Apoptosis · Alzheimer's disease · Signal transduction · Autophagy · Stress kinases

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Introduction

Cloning of the gene coding for the amyloid precursor protein (APP) and subsequent identification of mutations in APP and presenilin-1 and presenilin-2 genes in patients with familial Alzheimer's disease (FAD) have provided the basis for a vast number of experimental studies focusing on the complex biochemistry and metabolism of APP, the overwhelming part of which supports the notion that altered APP processing plays a pivotal role in AD, although many questions still need to be answered (Selkoe 2004; Walsh et al. 2007; Kern and Behl 2009). However, most of these studies have focused on a pathophysiological role of Aβ peptides that are generated via the amyloidogenic pathway of APP processing. Despite abundant information on the pathophysiological role of the APP metabolism in AD, the physiological role(s) of APP and its various cleavage products is/are hitherto not well characterized (Anliker and Muller 2006). Presently, it is not clear whether APP (and its homologues APLP1 and APLP2) largely function as surface-bound signaling receptors and/or as adhesion molecules (Herms et al. 2004; Soba et al. 2005) or whether their physiological functions are primarily mediated by soluble ectodomains shedded from the cell surface and secreted into the extracellular space. However, it is evident that under physiological conditions, the majority of APP is processed by α-secretase via the non-amyloidogenic pathway, thus leading to generation of the secreted N-terminal APP processing product, sAPPα (Selkoe 2004; Anliker and Muller 2006; Fahrenholz 2007). There is evidence that sAPPα can function in a multitude of physiological processes including neuroprotection (Mattson et al. 1993; Furukawa et al. 1996; Kögel et al. 2005), modulation of neuronal excitability (Mattson et al. 1993; Mattson and Furukawa 1998), synaptic plasticity (Turner et al. 2003;

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Ring et al. 2007), axonal growth and branching (Moya et al. 1994; Ikin et al. 2007), dendritic outgrowth (Mattson 1997) and synaptogenesis (Mattson and Furukawa 1998; Wang et al. 2011) (see also (Anliker and Muller 2006; Zheng and Koo 2006; Wolfe and Guenette 2007; Wang et al. 2009) for review). Of note, Alzheimer's disease (AD) patients have decreased levels of soluble APPs in their cerebrospinal fluid (Palmert et al. 1990). Thus, loss of the physiological APP function might be crucially implicated in reduced neuronal plasticity, diminished synaptic signaling and enhanced susceptibility of neurons to cellular stress during brain aging, which may contribute to neurodegeneration in both FAD and sporadic AD.

APP family members and neuroprotection

Several previous studies suggest that neuroprotection may constitute a key physiological function of APP. There is substantial experimental evidence for a neuromodulatory and, especially, a neuroprotective function of APP and sAPPα in neuronal cells and primary neurons in vitro (Araki et al. 1991; Mattson et al. 1993; Schubert and Behl 1993; Bowes et al. 1994; Goodman and Mattson 1994; Roch et al. 1994; Furukawa and Mattson 1998; Guo et al. 1998; Xu et al. 1999; Luo et al. 2001; Kögel et al. 2003, 2005; Esposito et al. 2004; Stein et al. 2004; Han et al. 2005; Gralle et al. 2009), but the exact molecular mechanisms underlying these neuroprotective effects remain to be clearly defined. In light of the high structural similarity between APP and APLPs (as reviewed elsewhere in this journal), APLP1 and APLP2 may possess similar or overlapping physiological functions as APP. It is well established that APP and APLPs can form homo- and heterodimers, arguing for a functional connection between these molecules (Soba et al. 2005; Kaden et al. 2011). APLP1 and APLP2 do not contain an Aβ-domain, but their ectodomains are shedded in an ADAM10-dependent manner similar to that observed for APP (Jacobsen and Iverfeldt 2009; Endres and Fahrenholz 2011; Hogl et al. 2011; Kaden et al. 2011). In line with this hypothesis, neuroprotective IGF-1 signalling induces anti-amyloidogenic processing of APP and ectodomain shedding of APLP1 and APLP2 in human SH-SY5Y neuroblastoma cells (Adlerz et al. 2007). However, the potential neuroprotective function of APLP1 and APLP2 is at the moment rather speculative as it has not been thoroughly investigated so far.

In vivo evidence for a protective role of APP is sparse. However, APP upregulation has been reported following brain injury in mammals and Drosophila (Murakami et al. 1998; Van den Heuvel et al. 1999; Ramirez et al. 2001; Leyssen et al. 2005), and injection of sAPPα or sAPPα domains into the brain of rats with traumatic brain injury had beneficial effects on motor or cognitive outcome (Thornton et al. 2006; Corrigan et al. 2011). In similar fashion, sAPPα was also shown to exert protective effects during ischemic brain injury (Smith-Swintosky et al. 1994), and overexpression of APP in transgenic mice was shown to confer resistance to kainate-induced and chronic forms of excitotoxicity (Mucke et al. 1996; Masliah et al. 1997; Steinbach et al. 1998). As in vitro, however, the relevant cellular and molecular players involved in APP-mediated neuroprotection await identification.

Despite these lines of evidence for a neuroprotective function of APP, the data obtained in APP knockout mouse models are controversial, as enhanced sensitivity of APP-deficient neurons to cell death has not been observed consistently. These discrepancies may in part be explained by the different cell types and mouse models used in the respective studies. In one study, Heber et al. did not observe significant differences in the cell death sensitivity of cortical neurons obtained from APP-deficient animals (Li et al. 1996) in comparison with wt neurons (Heber et al. 2000). Despite the possible functional redundancy of APP family members, Heber et al. also did not detect enhanced vulnerability of cortical neurons derived from APLP2−/− single mutants or APP−/− APLP2−/− and APLP1−/− APLP2−/− double mutants to excitotoxic challenge, as compared to wt neurons. APPΔ mice were generated by a targeted deletion of exon 2 of the *APP gene* still express a shortened APP polypeptide lacking amino acids 20–75, but only at 5% of physiological APP expression levels (Müller et al. 1994; Senechal et al. 2006). Steinbach et al. demonstrated an enhanced susceptibility of APPΔ mice (Müller et al. 1994; Senechal et al. 2006) to kainic acid-induced epilepsy in vivo, but failed to detect an increased sensitivity of cortical and cerebellar neurons obtained from these animals against glutamate- and NMDA-induced toxicity in vitro (Steinbach et al. 1998). However, in other studies, deficiency of APP was associated with reduced survival, increased apoptosis and impaired neurite outgrowth of hippocampal and cortical neurons obtained from APP−/− mice (Zheng et al. 1995), arguing for pro-survival and excitoprotective roles of APP (Perez et al. 1997; Han et al. 2005).

Mechanisms of APP-dependent neuroprotection: ion homeostasis and survival signaling

sAPPα-mediated neuroprotection may be associated with rapid effects on ion channel function and with delayed transcription-dependent processes (Mattson et al. 1997). sAPPα was proposed to activate potassium channels and suppresses NMDA currents to limit Ca^{2+} overloading and excitotoxic damage in neurons (Furukawa et al. 1996; Furukawa and Mattson 1998; LaFerla 2002). Of note, sAPP

production itself is activity dependent (Nitsch et al. 1993; Fahrenholz 2007), for review, indicating that sAPPα production could be upregulated by neurons under conditions of excitotoxicity. Thus, sAPPα may protect neurons from overexcitation and may act as an intrinsic feed-back mechanism.

In addition to stabilization of calcium homeostasis, sAPPα seems to have pleiotropic effects on several survival signaling pathways, most prominently on the PI3K/Akt pathway (Cheng et al. 2002; Wehner et al. 2004; Eckert et al. 2011; Jimenez et al. 2011), the NF-κB pathway (Guo et al. 1998; Cheng et al. 2002) and the ERK pathway (Greenberg et al. 1995; Cheng et al. 2002; Venezia et al. 2006; Nizzari et al. 2007) (Fig. 1). Anti-apoptotic signaling by APP may also involve the p38 mitogen-activated protein kinase/MEF2 pathway (Burton et al. 2002). The cellular receptor of sAPPα coupling sAPPα to these downstream signaling pathways is hitherto unknown. However, one putative cell surface receptor of secreted APP is membrane-bound holo-APP itself. It is clearly established that holo-APP can homodimerize (and heterodimerize with APLP1 and APLP2) (Soba et al. 2005; Kaden et al.). Interestingly, enforced dimerization of APP, e.g., by the N-terminally binding antibody 22C11, can trigger activation of the JNK stress signaling pathway (possibly via binding of the APP intracellular domain to the scaffolding protein c-Jun N-terminal kinase (JNK) interacting protein-1b (JIP1b) and recruitment of JNK upstream kinases) and induce a caspase-dependent, apoptotic cell death (Mbebi et al. 2002; Bouron et al. 2004). In a recent study, sAPPα was shown to bind to holo-APP at the cell surface, thereby disrupting APP homodimers (Gralle et al. 2009), and this disruption of APP dimers by sAPPα was necessary for the anti-apoptotic effect of sAPPα in neuroblastoma cells.

In addition to JIP1b, the APP intracellular domain (AICD) couples APP to diverse other intracellular signaling pathways. The Src homology 2 (SH2) domain of Abl or the PTB domain of Shc may interact with APP when the tyrosine in the YENPTI sequence is phosphorylated, suggesting a role for APP in tyrosine kinase-mediated signal transduction. Shc and GRb2 may then couple the AICD to intracellular survival pathways (ERK, PI3K/Akt) (Venezia et al. 2006). Therefore, it is currently unclear wether in addition to the possible sAPPα-mediated abrogation of pro-apoptotic signaling via APP, holo-APP may also be directly involved in survival signaling.

Besides holo-APP, several other surface proteins are candidates for the elusive APP receptor. The candidate receptors where direct protein binding of APP or APP fragments has been demonstrated in vitro are the death receptor DR6 (coupling the N-terminal APP fragment N-APP to apoptosis) (Nikolaev et al. 2009), p75 and Integrin-β1 (Young-Pearse et al. 2008; Kim and Tsai 2009; Nikolaev et al. 2009) (Fombonne et al. 2009). Despite a lack of evidence for direct protein binding, sAPPα-mediated neuroprotection may also require expression of the insulin receptor (IR) (Jimenez et al. 2011).

Although the molecular mechanisms underlying the activation of anti-apoptotic signaling pathways (PI3K/Akt, ERK and NF-κB) by sAPPα are currently not well understood, activation of these pathways by APP/sAPPα may ultimately lead to the activation of genes involved in stress responses and neuronal survival. However, so far, only a few studies have addressed this particular subject (Stein et al. 2004; Kögel et al. 2005). Neuroprotective genes that have been shown to be activated by APP/sAPPα on the transcriptional level include antioxidative defense genes MnSOD, peroxiredoxin-2 and catalase, the anti-amyloidogenic gene transthyretin, as well as insulin-like growth factor 2 (IGF2) and insulin-like growth factor–binding protein 2 (IGF-BP2) (Stein et al. 2004; Kögel et al. 2005). Alternatively, or in addition to the above-mentioned avenues of neuroprotection, these beneficial effects may be

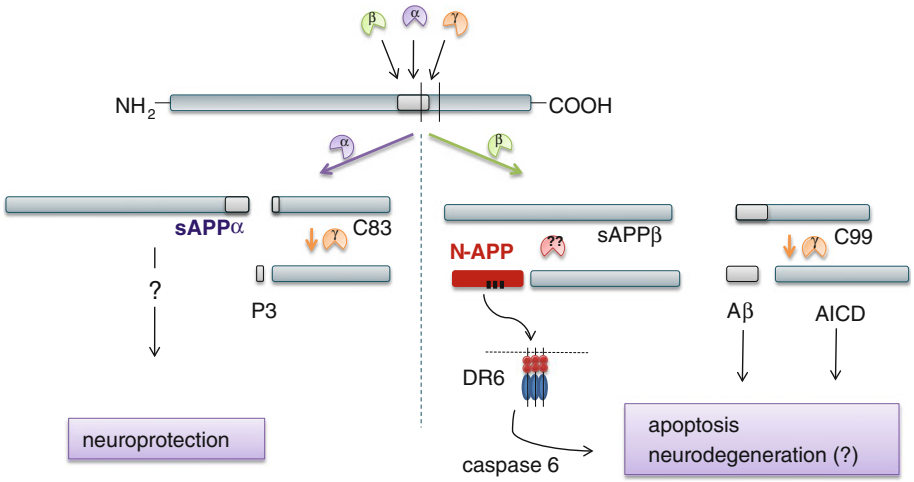

Fig. 1 Proteolytic processing of APP via the non-amyloidogenic (*left*) and the amyloidogenic (*right*) pathways, and major, APP-derived proteolytic fragments. Amongst the various APP cleavage products, sAPPα has consistently been implicated in mediating APP-dependent neuroprotection, whereas Aβ, AICD and N-APP are believed to be involved in mediating neurotoxic effects of APP. Please refer to the text of the article for a more detailed discussion

complemented by APP's role in enhancing neuronal cell adhesion (Bowes et al. 1994; Roch et al. 1994).

Cytoprotection by APP and APLPs via regulation of stress signalling pathways

The c-Jun N-terminal kinase (JNK)-signalling pathway is a central stress signalling pathway implicated in neuronal plasticity, neuroregeneration and neurodegeneration, and increasing evidence points to a pivotal role of the JNK signalling pathway in brain aging and many types of neurodegeneration (Bozyczko-Coyne et al. 2002). JNKs are activated by a wide variety of stress stimuli and have been identified as critical upstream regulators of the mitochondrial pathway of apoptosis (Putcha et al. 2003). Interestingly, we have previously demonstrated APP-dependent transcriptional repression of c-Jun and reduced basal c-Jun N-terminal kinase (JNK) activity in PC12 cells (Kögel et al. 2005). Stress-induced activation of the JNK signalling pathway and subsequent apoptosis were likewise reduced by autocrine sAPPα signaling in cells overexpressing APP and after addition of exogenous sAPPα (Kögel et al. 2005; Copanaki et al. 2010; Eckert et al. 2011). Conversely, overexpression of the Swedish mutant of APP did not inhibit stress-triggered JNK activation and cell death (Kögel et al. 2005). The protective effect of APP/sAPPα could be mimicked by an MLK inhibitor that inhibits upstream JNK-activating kinases of the mixed lineage kinase (MLK) family (Kögel et al. 2005) or by direct inhibitors of the JNK pathway (Eckert et al. 2011). Collectively, these data suggest an important physiological role of APP and α-secretase activity in the control of JNK/c-Jun signalling, target gene expression and cell death activation in response to cytotoxic stress (Fig. 1).

What may be the mechanisms underlying sAPPα-mediated suppression of the JNK pathway? Given the model proposed by Gralle and colleagues (Gralle et al. 2009) sAPPα may theoretically interfere with APP dimerization, thereby blocking downstream activation of JNKs under stress conditions. JIP1b is a member of the JIP family that possess a PTB domain and interacts with the YENPTY motif of the AICD whereas JIP2 binds more weakly to the AICD (Matsuda et al. 2001; Scheinfeld et al. 2002; Inomata et al. 2003). JIP-1b interaction enhances JNK-mediated threonine-668 phosphorylation of APP, indicating that JIP-1b may function as a scaffold between APP and JNK (Taru et al. 2002; Inomata et al. 2003). Upstream kinases MLKs (MLK3) and ASK1 may be recruited to the scaffold, both of which can be inhibited via phosphorylation by Akt.

There is also evidence for suppression of other stress kinases by sAPPα. Han and colleagues could demonstrate modulation of the cdk5 pathway by APP and APLP1 (Han et al. 2005). In fact, overexpression of APP or APLP1 suppressed basal and stress-induced CDK5 activation, and in the case of APP, sAPPα was shown to be the responsible fragment for inhibiting CDK5 activation. Furthermore, neuronal sensitivity to excitotoxic damage in neurons derived from APP-deficient mice was increased and was shown to be mediated through a mechanism involving CDK5 overactivation through a calcium/calpain/p25 pathway. Recently, it was also demonstrated that sAPPα can inhibit the GSK3β stress signaling pathway (Jimenez et al. 2011). The authors proposed a model in which sAPPα acts through IGF-1 and/or insulin receptors to induce the PI3K/Akt pathway and to phosphorylate and inhibit the activity of GSK-3β (Jimenez et al. 2011). Since there is also a potential cross talk between Akt and the JNK pathways, as Akt is known to directly inhibit the JNK upstream kinase MLK3 (Barthwal et al. 2003), pleiotropic effects of sAPPα on the complex interplay between pro-apoptotic and survival pathways (as summarized in Fig. 2) are very likely, with the final outcome in regard to cell survival and cell death depending on the cellular context.

Possible physiological functions of APP in promoting apoptosis

In a recent seminal study, a drastically different, opposing role of APP has been proposed. Nikolaev et al. demonstrated that APPsβ can be further processed by a yet unknown protease to yield an amino-terminal fragment of sAPPβ (N-APP) implicated in axonal pruning and induction of neuron death via binding to the death receptor DR6 and caspase induction during development (Kim and Tsai 2009; Nikolaev et al. 2009). The significance of the newly identified N-APP fragment (Nikolaev et al. 2009) has so far only been studied in development, and its potential relevance to the adult nervous system, in particular with regard to brain aging and neurodegeneration, needs to be elucidated. It is conceivable that the age-associated changes in the metabolism of APP might lead to the loss of sAPPα function on the one hand and also to a concurrent shift to formation of sAPPβ and N-APP with potentially detrimental consequences.

Another fragment of APP which has been implicated in promoting apoptosis is the (released) APP intracellular domain (AICD) generated via regulated intracellular proteolysis (RIP) by γ-secretase at the γ- and/or ε-cleavage site (Kinoshita et al. 2002; Müller et al. 2008). In a manner analogous to the Notch signalling pathway, AICD binds to several cofactors involved in the regulation of transcription, in particular Fe65, Tip60 and CP2 (Müller et al. 2008). Upon interaction with its cofactors, AICD is stabilized, thus enabling its translocation to the nucleus where it

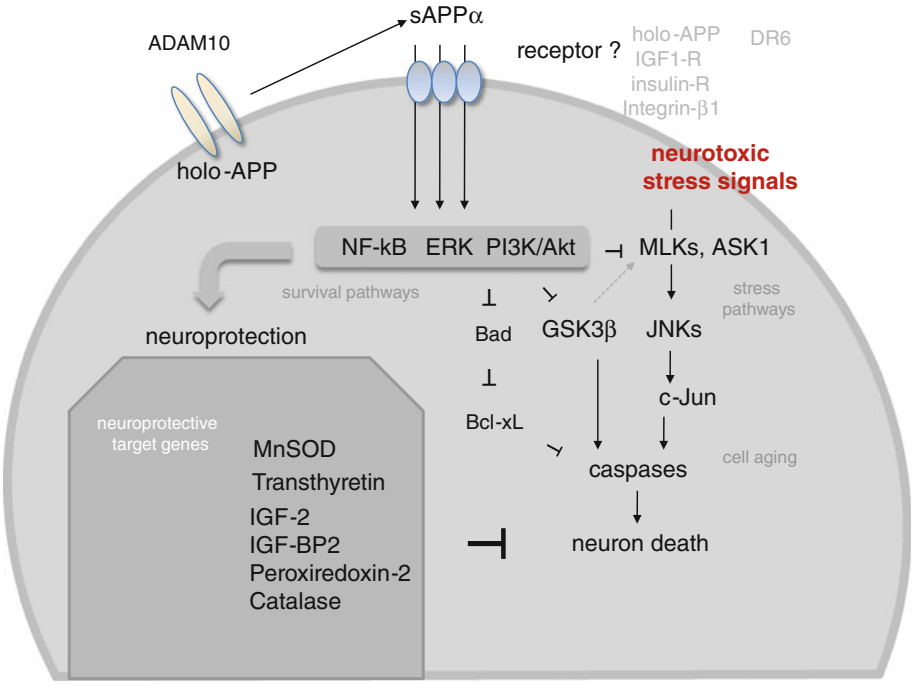

Fig. 2 Model of APP-dependent neuroprotection, possible neuroprotective cofactors and major intracellular pathways that have been associated with this physiological function of APP. APP is cleaved by α-secretase along the secretory pathway to generate sAPPα which can act in paracrine and autocrine fashion. By binding to a hitherto unidentified cellular receptor, sAPPα can trigger several neuroprotective signaling pathways (NF-κB, PI3K/Akt, ERK), enhance the expression of downstream target genes (MnSOD, transthyretin) and antagonize stress-induced pro-death pathways (JNK/c-Jun, GSK3β). Please refer to the text of the article for a more detailed discussion

is implicated in the regulation of several putative target genes (Müller et al. 2008). Similar to the formation of N-APP from its precursor sAPPβ, it has been proposed that AICD is preferentially generated via the amyloidogenic pathway of APP processing (Goodger et al. 2009; Belyaev et al. 2010). The molecular mechanisms underlying AICD-induced apoptosis are not clearly understood, but may include transcriptional activation of the stress kinase GSK3β and contribution to activation of the p53-mediated apoptotic pathway (Kinoshita et al. 2002; Kim et al. 2003; Ozaki et al. 2006; Nakayama et al. 2008). Recently, we have also demonstrated that AICD can suppress the expression of the anti-apoptotic Alzheimer's disease susceptibility gene ApoJ/Clusterin (Müller et al. 2008) and potentiate ER stress-mediated apoptosis (Kögel et al. 2011).

APP biochemistry and cellular aging

Since aging is the most reliable risk factor for sporadic late-onset AD, the impact of the cell aging on the onset and progression of AD pathobiochemistry is of central importance and has been largely neglected in recent decades. Here, possible changes in the expression, maturation and cleavage of endogenous APP are of particular interest, especially when taking into account that sporadic AD develops over decades. Employing a primary human cell model of aging, we found that during cell aging, there is a drastic change in APP maturation: the biochemical processing of endogenous APP is downregulated during the aging of replicative senescent IMR-90 cells (Kern et al. 2006). In fact, the generation of intracellular APP cleavage products C99, C83, and AICD gradually declines with increasing cellular life span and is accompanied by a reduced secretion of sAPPα (Kern et al. 2006). Further, the maturation of APP was reduced in postmitotic senescent cells, which we found to be directly mediated by age-associated increased cellular cholesterol levels. Of the APP-processing secretases, protein levels of constituents of the γ-secretase complex, presenilin-1 (PS1) and nicastrin, were progressively reduced during aging, resulting in a progressive decrease in γ-secretase enzymatic activity. ADAM10 (a disintegrin and metalloprotease 10 and α-secretase) and BACE (β-site APP-cleaving enzyme) protein levels exhibited no age-associated regulation, but, interestingly, BACE enzymatic activity was increased in aged cells. PS1 and BACE are located in detergent-resistant membranes (DRMs), well-structured membrane microdomains, exhibiting high levels of cholesterol and caveolin-1. Of note, there is a redistribution of the age-associated increased amount of cholesterol in the membrane, and obviously, the general lipid raft structure is changed in old cells. Although total levels of both structural components of DRMs were upregulated in aged cells, their particular DRM association was decreased. This age-dependent membrane modification was associated with an altered distribution of PS1 and BACE between DRM and non-DRM fractions, very likely affecting their APP processing potential. Taken together, we have found a significant modulation of endogenous APP processing and maturation in human fibroblasts caused by age-associated alterations in cellular biochemistry (Kern et al. 2006).

Outlook on the investigation of APP's physiological role

Because 1) significant changes in the APP processing of aged postmitotic cells exist when compared to young cells and 2) also in primary neuronal cultures of aged animals there are dramatic changes observed (Hajieva et al. 2009), additional alterations may impact on APP biochemistry and function. Interestingly, we recently found a modified protein quality control (PQC) in aged IMR-90 cells. These results were consistent with those obtained in primary aged neurons as well as in the brain of aged mice. We found that the important members of the PQC machinery, BAG1 and BAG3, regulate proteasomal and macroautophagic pathways, respectively, for the degradation of polyubiquitinated proteins. Further, we could demonstrate a molecular switch from BAG1 to BAG3 expression in aged cells and an increase in macroautophagy for turnover of polyubiquitinated proteins (Gamerdinger et al. 2009). Interestingly, the BAG3/BAG1 ratio was also elevated in neurons during aging of the rodent brain, where, consistent with a higher macroautophagy activity, we found increased levels of the autophagosomal marker LC3-II as well as higher cathepsin activity. We conclude that the BAG3-mediated recruitment of the macroautophagy pathway is an important adaptation of the protein quality control system to maintain protein homeostasis in the presence of an enhanced pro-oxidant and aggregation-prone milieu characteristic of aging (Gamerdinger et al. 2009). Such an adaptation can represent a protective mechanism of aged cells against enhanced intracellular protein stress (Behl 2011). Interestingly, the disturbance of the lysosomal function has been associated with AD pathogenesis (Cataldo et al. 2000; Boland et al. 2008) (reviewed in Pimplikar et al. 2011). Since intact lysosomal function is essential for protein degradation via autophagy and the endosomal recycling of APP can either lead to its degradation via the autophagosomal/lysosomal pathway (Ehehalt et al. 2003; Grbovic et al. 2003) or alternatively to reentry of APP in the secretory pathway and retargeting to the surface (Thinakaran and Koo 2008), the complex interplay between lysosomal function/autophagy and APP biochemistry demands further investigation. Moreover, the potential impact of sAPPα on the intracellular protective adaptation to proteotoxic stress is an interesting target mechanism that needs to be addressed in the future.

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