Review Article

Neurodegeneration in Alzheimer Disease:
Role of Amyloid Precursor Protein and Presenilin1 Intracellular Signaling

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Alzheimer disease (AD) is a heterogeneous neurodegenerative disorder characterized by (1) progressive loss of synapses and neurons, (2) intracellular neurofibrillary tangles, composed of hyperphosphorylated Tau protein, and (3) amyloid plaques. Genetically, AD is linked to mutations in few proteins amyloid precursor protein (APP) and presenilin 1 and 2 (PS1 and PS2). The molecular mechanisms underlying neurodegeneration in AD as well as the physiological function of APP are not yet known. A recent theory has proposed that APP and PS1 modulate intracellular signals to induce cell-cycle abnormalities responsible for neuronal death and possibly amyloid deposition. This hypothesis is supported by the presence of a complex network of proteins, clearly involved in the regulation of signal transduction mechanisms that interact with both APP and PS1. In this review we discuss the significance of novel finding related to cell-signaling events modulated by APP and PS1 in the development of neurodegeneration.

1. Introduction

Alzheimer disease (AD) is a neurodegenerative disease clinically characterized by progressive dementia, and, neuropathologically, by loss of synapses and neurons, gliosis, and the presence of both amyloid plaques and neurofibrillary tangles. The main amyloid components of plaques are a family of short peptides (Aβ) of 40 or 42 amino acids, in the most common forms, derived from the proteolysis of the type I protein, amyloid β precursor protein (AβPP), upon sequential cleavage by β- and γ-secretases [1]. γ-secretase has been characterized as a multiprotein complex in which presenilins 1 and 2 have a regulatory role [1]. Familial AD forms (FADs) are caused by the overexpression or by mutations in the AβPP gene, or by mutations on the presenilins (presenilins 1 and 2).

The molecular mechanisms underlying the development of AD are not yet known, and also the physiological role of AβPP is still unclear [2]. In particular, it is still debated whether presenilins (PSs) familial mutations cause gain or loss of function in the γ-secretase complex. PS mutations have been presumed to cause FAD by enhancing production of the more toxic Aβ42 over the Aβ40 isoform, thereby conferring a toxic gain of function [3]. However, a number of recent studies have shown that clinically relevant PS mutations impair Aβ40 production without affecting Aβ42 production, leading to the revised view that pathogenic PS mutations consistently shift the cleavage specificity of the mutant protein to favor production of Aβ42 at the cost of Aβ40 [4, 5]. On the other hand, it has been recently suggested that, at least, some FAD-associated PS mutations can cause a nearly complete loss of
the mutant protein’s ability to support γ-secretase activity rather than an absolute or relative overproduction of Aβ42 [6]. Hence, a loss of function can be associated to a shift of the cleavage specificity (Aβ42 at the cost of Aβ40), or to another unknown target substrate of the γ-secretase activity. In this case, the loss of PS function may be a primary event, in the adult mammalian brain, triggering a putative pathogenic cascade which leads to neurodegeneration in AD [7]. Several studies suggest a relevant role for AβPP in maintaining active synapses, and recent evidence has indicated the presence of AβPP in the postsynaptic density, where it may interact with NMDA receptors, thus supporting the observation that NMDA receptors regulated trafficking and processing of AβPP, although via a controversial mechanism of action [8]. Moreover, recent findings have also suggested that AβPP, through an NPTY motif located in its cytodomain, and PSs form functional complexes with different signaling protein, supporting the hypothesis that AβPP and PS1 are at the centre of a complex network of interactions, likely involved in multiple cell-signaling events which are still unknown (Figures 1 and 2) [9, 10]. Even apolipoprotein E (ApoE), which is the most relevant risk factor for developing late-onset AD, rather than being a mere Aβ chaperone, might be involved in complex-signaling pathways through its multiple receptors (LRPs), such as those bearing to the low-density lipoprotein receptor family (LDLR) (for review see [11]). LRPs participate in neuronal functions modulating neurotransmission and thus synaptic stability [12], and several data indicate that LRPs could modulate AβPP processing through the regulation of its endocytic trafficking, implying a possible association between LRPs activity and AD onset (Figure 3) [13]. Taken together, these data suggest a model that links the functions of AβPP, PSs, and LRPs in physiological and pathophysiological conditions as relevant actors in neuronal intracellular signaling.

This review will focus on the involvement of AβPP in cell signaling, exploring the possibility that posttranslational modifications on its C-terminal domain may modulate, together with PSs and LRPs, intracellular pathways involved in cell-cycle progression that in postmitotic neurons may induce neurodegeneration.

2. APP Processing, Interacting Proteins, and Intracellular Signalling

The main amyloid components of senile plaques result from the proteolytic processing of AβPP by β-secretase (BACE1), leading to the formation of C-terminal fragments (CTFs) that are subsequently cleaved by the “γ-secretase-complex” which is responsible for the formation of Aβ (40 or 42 amino acids in length) and the AβPP intracellular domain peptide (AICD) of 58 or 56 amino acids (Figure 1) [1].

These amyloid peptides are considered mainly responsible for the neurodegeneration that occurs in AD. Thus,
the “amyloid hypothesis” sustains that the first step during AD development is the accumulation and the subsequent deposition of Aβ peptides [1, 2, 10, 14–23].

The generation of Aβ40/42 peptides, by the sequential proteolytic activity of β- and γ-secretases, is enhanced by mutations in AβPP and PSs, and it may be prevented by the action of a third protease, the α-secretase, that cleaves AβPP within the Aβ region, thus resulting in the formation of a different subset of CTFs (α-CTFs) that upon γ-cleavage generate shorter and nonamyloidogenic fragments [24].

However, from the point of view of the signaling activity of CTFs, it is still unclear whether α- and β-stubs or the AICD fragments generated by γ-secretase might represent protective or pathologically related molecule [25].

As far as AICD fragments are concern, it was reported that, after binding Fe65 (Figure 1), an adaptor protein mediating assembly of multimolecular complexes through a variety of protein-interaction domains, and the histone acetyltransferase Tip60, AICD translocate into the nucleus where it acts as gene transcription regulators [24, 26–29]. However, this latter event is still debated, because AICD displays a very short half-life and a poorly characterized in vivo transcriptional activity [30].

Recent data have demonstrated that AβPP may signal to the nucleus also using a β-secretase-independent mechanism that involves membrane sequestration and phosphorylation of Tip60 [31].

More recently, Stante et al. have suggested that the presence of Fe65 into the nucleus may have a protective role, and that its translocation depends on AβPP. They propose that DNA repair defects could significantly contribute to the neurodysfunction and neurodegeneration observed in AD, and that an involvement of the Fe65-APP complex in the response of the cells to DNA damage and in the DNA repair machinery could represent a possible mechanism contributing to neuronal degeneration observed in AD pathology [32].
Indeed, new data suggest that, during embryonic development, AICD release, triggered by extracellular signals activating the β-secretase-dependent cleavage, may be involved in the control of neurogenesis [33]. Conversely, Vogt and Coll showed that the overexpression of AICD in mice caused abnormal neuronal networks and increased seizure susceptibility [34]. Other studies demonstrated that AICD may induce the expression of neprilysin, an enzyme known for its specific Aβ-degrading activity, through a direct modulation of its promoter [35]. At the same time, it is noteworthy that the C-terminal portion of AβPP and in particular the last 20 amino acids in the cytoplasmic tail which contains the well-known YENPTY (Figure 1) motif present in several receptor tyrosine kinase (TK) is a docking site for different intracellular proteins involved in signal transduction. Traditionally, this sequence was described as internalization motif, while now it has been recognized to play a central role also in the regulation of multiple interactions with intracellular proteins [9, 36]. In particular, in receptor TK, tyrosine residue can be phosphorylated to generate the NPXpY motif, which represents a docking site for several intracellular adaptor proteins through the phosphorytrosine-binding domain (PTB). Similarly, the adaptor proteins Shc and Grb2 can bind AβPP (or its CTFs) in the presence of phosphorylated tyrosine in this motif (Figure 1). However, AβPP (or its CTFs) and the AβPP-related proteins, APLP1 and APLP2, can also interact with several other signalling proteins, including XI1 [37], Fe65 [37, 38], mDab [39], c-Abl [40], JIP-1 [41], and Numb [36, 41], (Figure 1) independently of the phosphorylation of the tyrosine residue within the YENPTY motif. From a functional point of view, the interaction between the neuron-specific adaptor protein Fe65 and AβPP via the second PTB domain of Fe65 [37, 38] was shown to modulate AβPP processing, favoring the generation of Aβ and AβPP trafficking, in several cell lines [26, 42]. Another adaptor that binds to AβPP is mDAB. It is a protein related to the reelin pathway and interacting with YENPTY motif through a PTB domain. mDAB is active during embryogenesis, where it regulates the position of neurons in the brain laminar structure [43], and mDAB binding increases the amounts of mature AβPP and Aβ formation [44]. On the contrary, XI1 stabilizes AβPP conformation in membrane, inhibiting Aβ secretion in cultured cells [45], likely impairing AβPP trafficking to sites containing active γ-secretase complexes [46]. JIP’s are member of JNK-scaffolding family proteins kinases, implicated in different signal pathway, including neuronal apoptosis. JNK-interacting proteins JIP1b and JIP2 bind to the cytoplasmic tail of AβPP. The expression of JIP1b stabilizes immature AβPP and decreases the AβPP ectodomain, Aβ40/42 and CTFs abundance [47].

All these observations suggest that some of these protein-protein interactions may play a role in the modulation of the amyloidogenic pathway and thus might have a role in neurodegeneration.

The role of Aβ peptides as unique cause of neuronal toxicity and AD is highly debated, and recent data have challenged the “amyloid only” hypothesis, questioning the role of APP and PSs as mere amyloid producers. The central role of APP and PSs in the genesis of AD is unquestionable; however, phenotypical heterogeneity among patients, and even among familial patients with the same genetic mutation, is commonly observed, implying that other genes might have a role in regulating the onset and severity of the neurodegeneration in FAD and, likely, in sporadic AD. For these reasons, considering that APP and PSs are key players in a complex network of interactions with many different intracellular adaptors, it is tempting to hypothesize that, in parallel to amyloid formation, APP and PSs may induce neurodegeneration through specific alterations in neuronal signaling pathways [48].

In this context, it was reported that other two adaptor proteins, which have been involved in the regulation of the amyloidogenic pathway, ShcA and growth factor receptor-bound protein 2 (Grb2) are able to interact with the cytodomain of AβPP in the presence of specific tyrosine 682 phosphorylation in the YENPTY motif of AβPP cytodomain [36, 49]. ShcA (or ShcC) adaptors connect growth factor receptors to specific signaling pathways (typically Ras/ERK1/2 pathway but also PI3K/Akt signalling) and are involved in cell proliferation differentiation and apoptosis and neuronal development [50, 51]. Also the role of Grb2 in Ras-signaling pathway is well known as well as its involvement in the activation of the mitogen-activated protein kinase (MAPK) pathways cascade (Figures 1 and 2) [50, 52–54]. It is worth noting that ERK1/2 activity is increased in AD brains [55–57] and that activated MAPKs have been involved in the abnormal hyperphosphorylation of Tau in AD [58].

The pathogenic correlation between Shc/Grb2 binding to AβPP during AD development is supported by the observation that the complexes AβPP (or CTFs)/ShcA or Grb2 are significantly increased in AD brain as compared to controls [55]. The increased phosphorylation/activation of ERK1/2, often described in AD brain, is also observed in thrombin-activated astrocytes [55], suggesting that, in this model, ERK1/2 may be activated by AβPP through ShcA. These data give prominence to the biological importance of AβPP phosphorylation for its functions and the regulation of intracellular adaptor binding as events responsible for the induction of glial-associated mitogenic pathway. Furthermore, ERK1/2, activated by Aβ in vitro, plays a role in AβPP processing and phosphorylates Tau in a PHF-Tau similar manner [59]. However, it is conceivable that a different signaling Aβ-independent might as well activate tau phosphorylation by ERK1/2 via the intracellular signaling regulated by the AβPP/CTFs-Shc-Grb2 pathway (Figure 1).

AβPP cytodomain also interacts with other proteins directly linked to signal transduction mechanisms. In particular, AβPP binds to the heterotrimeric GTP-binding protein Go [60–63] that comprises up to 1% of all membrane-associated proteins in the developing nervous system [55]. There is evidence that AβPP cytodomain binds proteins involved in cell-cycle regulation such as AβPP-binding protein 1 (APP-BP1) [64] and p-21-activated kinase 3 (PAK3) [65] which is a serine/threonine kinase involved in DNA synthesis and neuronal apoptosis. These data are consistent with a model in which AβPP is a component of a Go multiprotein complex, including PAK3, to transduce
extracellular signals to the cytoplasm. In this model, the FAD APP-mediated pathway, leading to tentative neuronal cell-cycle activation (see below), consists of the APP-Golgi-PAK3 formation, followed by the activation of the AβPP-BP1 through JNK [25].

Considering all these aspects, it is possible to hypothesize that posttranslational modifications of AβPP, or in its CTFs, such as a selective phosphorylation, might couple them, to different cellular pathways. These observation supports the hypothesis that AβPP may act as a receptor/transducer molecule in multiple cell-signaling events, the comprehension of which may have implications either for the normal biological function of AβPP, for its processing and for its pathological role in the genesis of AD [66–68].

3. Presenilins Modulation of Intracellular Signaling

Presenilins 1 and 2 are multitransmembrane proteins that, associated to nicastrin, APH-1 and PEN-2, form high-molecular γ-secretase complex, involved in Aβ production via intramembrane cleavage of AβPP (Figures 1 and 2) [69–71]. These proteins are highly expressed in brain but have been detected also in several different tissues. Amount of PSs are localized in the nuclear membrane, kinetochores, and centrosomes [72, 73]. At present more than 182 different mutations (and some deletions) in PS1 have been associated with inherited early onset AD (Alzheimer disease and Frontotemporal Dementia Mutation Database 2006) [56, 74, 75] while only 13 mutations have been found in PS2 that are definitively linked to FAD [15, 16, 76].

Besides their involvement in Aβ formation, PSs regulate the cleavage of other signaling receptors and transducers such as Notch-1, ErbB4, DC44, and LDL-receptor-related proteins and cadherins [1, 69, 77–79]. PSs also affect different other signaling molecules, such as wingless-type MMTV integration site family (Wnt) signal transduction pathway, which is evolutionary conserved and controls many events during the embryogenesis [80]. At cellular level, this pathway regulates morpholohgy, proliferation, and motility of the cell. Wnt pathway plays a central role during tumorigenesis, and the inappropriate activation of this pathway has been observed in several human cancers [81]. It has been shown that Wnt-ligand-mediated signaling leads to the accumulation of cytosolic β-catenin. Cytosolic β-catenin will then translocate into the nucleus to bind to members of the T-cell factor (Tcf)/lymphoid-enhancing factor (Lef) family of DNA-binding proteins leading to the transcription of Wnt target genes. In the absence of Wnt ligand, axin recruits CK1 causing the initiation of the β-catenin phosphorylation cascade by glycogen synthase kinase-3 β (GSK-3β). Phosphorylated β-catenin is recognized by β-transducin repeat-containing protein (β-TrCP) and degraded by the proteosome, reducing the level of cytosolic β-catenin. It was reported that β-catenin interacts with PSs, and that PS1 promotes β-catenin degradation regulating phosphorylation by cyclin-dependent kinase 5 (CDK5) and GSK-3β [82–84]. Importantly, GSK-3β was implicated in various neurological disorders, including AD [85]. Gosal and Coll showed that AICD-overexpressing transgenic mice may have an abnormal activation of GSK-3β. These mice exhibit AD-like characteristics, including hyperphosphorylation and aggregation of tau, neurodegeneration, and working memory deficits that are prevented by treatment with lithium [86].

In cultured cells expressing PSs FAD mutants, the intracellular trafficking of β-catenin is altered, while in cells from PS-null animals cytosolic β-catenin levels and β-catenin-mediated Lef/Tcf signaling are increased [83], thus resulting in the activation of the downstream target cyclin D1 and accelerated entry into the S phase of the cell cycle [87].

Another relevant role for PSs is Notch processing. Notch signaling is involved in cell fate regulation, cell differentiation, proliferation, and apoptosis as well as neurodegeneration [88, 89]. Notch is a membrane receptor whose C-terminal domain (NICD), upon interaction with appropriate ligands, translocates into the nucleus where it activates the CSL family of transcription factors. NICD formation depends on γ-secretase complex as the AICD fragment of AβPP [78].

PSs play a role in apoptosis, since FAD mutants cause cell death or induce secondary events that may lead to apoptosis [90]. Animals, in which PS1 and PS2 genes are deleted, show deficit in learning, memory, synaptic function and neuronal death [91]. The processes beneath these effects are unknown, but the findings that PS1 interacts with anti-apoptotic member of Bcl-2 family might indicate a possible mechanism [92, 93].

PS1 is also essential for efficient N-cadherin trafficking from ER to plasma membrane. Cadherins, including E-cadherin and neuronal cadherin (N-cadherin), are a family of type I transmembrane proteins that mediate Ca2+-dependent cell-cell adhesion, and recognition [94, 95]. PS1-mediated delivery of N-cadherin to the plasma membrane is important to exert its physiological function, including the control of the state of cell-cell contact [96].

PS1 is involved in the intramembrane cleavage of CD44, a cell surface adhesion molecule for the extracellular matrix components which is implicated in a wide variety of physiological and pathological processes including the regulation of tumor cell growth and metastasis [70].

Recently, also the low-density receptor-related protein (LRP) has been shown to be cleaved by a γ-secretase-like activity [97]. It is important to note that LRP receptors are activated by apolipoprotein E, a well-known risk factor for the developing of late onset AD in carriers of the ε4 alleles [98, 99]. It is, however, still unknown if the processing by γ-secretase and the apolipoprotein E-mediated signaling on neuronal LRPs might modulate a single pathway, and which is the physiological significance for these processes.

PS1 also modulates basal level of ERK1/2 activity through a ras-Raf-MEK-dependent pathway activated by a direct binding with the SH2 domain of Grb2 (Figure 2) [100–102]. ERK family is one of the most ubiquitous cellular signaling mechanisms, whose activation links extracellular stimuli to cell proliferation, survival, and differentiation, but also cell death and apoptosis [103–105]. In this respect, it is worth of
note to observe, as mentioned above, that ERK1/2 pathway is also modulated by AβPP (Figures 1 and 2).

Taken together, these data suggest that PS1 and/or AβPP are able to modulate different intracellular signalling pathway through a plethora of intracellular mediators; when the signaling activated by PS1 and AβPP become dysfunctional in neurons, in particular the activation of the cell cycle-machinery induced by ERK1/2, the neurodegenerative process may be activated (Figure 2).

4. AβPP, Presenilins, and Cell Cycle

The hypothesis that cell-cycle abnormalities and aberrant neuron cell-cycle reentering may cause neuronal death in AD is supported by different experimental findings including AD patients brain analysis and data obtained by in vitro experiments.

Chromosome missegregation and trisomy 21 mosaicism have been associated with mutations in AβPP and PSs [72]. Aberrant expression of cell-cycle proteins and tetraploidy in neurons from AD patients have been described [106]. In AD brains, the activation of several cell-cycle components has been detected, including cdc2, cdk4, p16, Ki-67, cyclin B1 and cyclin D, p25 (the regulatory subunit of cdk5) [107, 108], as well as the increased expression activity of genes encoding for cell-cycle proteins [109]. It was observed that hippocampal pyramidal and basal forebrain neurons, in AD brain show markers of DNA replication [110], and it was speculated that the state of tetraploidy is lethal to neurons [110].

Increasing observations suggest that aberrant activation of cell cycle may affect the formation of neurofibrillary tangles with hyperphosphorylation of Tau protein in AD brain. It is well known that p25/cdk5 complex hyperphosphorylates Tau and reduces its ability to associate with brain. It is well known that p25/cdk5 complex hyperphosphorylates Tau protein in AD and cell cycle components have been associated with mutations in AβPP and PSs [72].

5. AβPP, Presenilins, and LRPs

Low-density lipoprotein receptors (LDLRs) are type I integral membrane proteins currently composed of 10 members. LDLR possesses a wide array of ligands with different functions from cellular cholesterol uptake in the liver to cell specification and neuronal positioning during embryogenesis. ApoE, complexed in HDL and VLDL, is the major ligand for these receptors, and, being the ε4 allele of APOE gene, the most relevant risk for the development of late-onset AD, several studies support a role for these receptors in the pathogenesis of AD [116]. Although the molecular mechanisms underlying the association between ApoE alleles and AD development have not yet been completely elucidated, ApoE, along with its receptor-LDLR and LDL-receptors related protein (LRP), was reported to modulate Aβ production and clearance. Lack of LDLRs increased amyloid deposition and impaired cognitive behavior in AD transgenic mice [117]. ApoE colocalizes in amyloid deposits in brain parenchyma [118], and its lipidation state affects the ability to bind Aβ [119].

Beside its role as Aβ chaperone, ApoE might modulate specific internalization and signaling events via binding to its receptors. Some of them possess shared adaptors with AβPP; in particular Fe65 and JIP1 bind to LRP8, LRP1, and megalin. Indeed γ-secretase cleavage regulates the intramembrane proteolysis of LRP8, LRP1, and of SOR-1/LRP11. It is tempting to speculate that LRPs could affect AβPP processing and signaling (and vice versa) through γ-secretase and ApoE-mediated stimuli.

LRPs possess at least one NPxY motif in their cytoplasmic tail (except SOR-1/LRP11), and this motif, present in AβPP as well, is critically required for receptor interaction with adaptors proteins and for internalization. It has been recently demonstrated that several LRPs family members modulate AβPP processing by affecting different aspects of AβPP trafficking [120]. For example, LRP8 is a member of the LDLR family that is highly expressed in the brain [121]. It has been recently proposed that the physiological role of LRP8 might include the regulation of signal transduction pathways rather than endocytosis of lipoproteins and other ligands [116]. It is known that LRP8 interacts with AβPP, enhancing the level of AβPP at the cell surface, and reducing its internalization [122, 123]. Overexpression of LRP8 induces an increase in AβPP association with lipid rafts and decreases AβPP-CTFs levels [116].

ApoE was reported to induce Dab1 phosphorylation and ERK1/2 activation and JNK inhibition via LRPs. This pathway depends on the presence of Ca ++ influx through the NMDA receptor, but it is independent of Dab1 [124].

Overall these data indicate a likely involvement of LRP8 as modulator of AβPP processing, by affecting its endocytic trafficking and the proportion of AβPP present in lipid
rafts. These events may have consequence on the γ-secretase-mediated cleavage of AβPP and on its neurodegeneration-related signaling activity.

Upon binding, LRP8 transduces reelin signaling during neuronal development [125], and recent evidence has indicated that it interacts with the NR2A and NR2B subunits of NMDA receptor [126], being involved in neuronal functions such as maturation of NMDA receptor composition in the hippocampus, and the regulation of long-term potentiation [127]. Importantly, it has been determined that LRP8 ligand reelin is found in neuritic plaques of transgenic mice overexpressing AβPP [128], suggesting a possible association with AD. Subsequently, a novel interaction between reelin and AβPP was discovered, leading to increase in the cell surface levels of AβPP and affecting AβPP processing and Aβ production [8]. It was shown that reelin signaling in excitatory synapses can restore normal synaptic plasticity, which is impaired by oligomeric Aβ peptides at concentrations within the range detectable in the brains of AD patients. At high concentrations of Aβ peptides, reelin can no longer overcome the Aβ-induced functional suppression, and this condition coincides with a complete blockade of the reelin-dependent phosphorylation of NR2 subunits in NMDA receptors. This reversal requires the LRP receptor-dependent activation of tyrosine kinases of the Src family. It was proposed a model in which Aβ, reelin, and LRP receptors modulate neurotransmission and thus synaptic stability as opposing regulators of synaptic gain [12]. A schematic representation of potential roles of LRP in normal brain function and in neurodegenerative processes is depicted in Figure 3.

6. Small Nuclear RNA in AD

Recent discoveries in molecular genetics of mammalian genome have shed light on a widespread transcription of noncoding regions, devoted to the regulation of the protein-coding genome expression. The mechanisms of action of these transcripts are various and different in nature, although all of them are devoted to the regulation of fundamental genetic pathways involved in the determination of the cell phenotype [129–132].

Alternative splicing is a central component of human brain complexity whose regulatory mechanisms are still largely unclear. The recent discovery of factors that control alternative splicing might contribute to clarify the molecular basis of physiological and pathological processes [133]. In two recent works, we described the discovery of two novel RNA polymerase III-dependent, noncoding RNAs (ncRNA) transcripts, named 17A and 38A. In particular, it was shown that the expression of 17A induces an alternative splicing of GABA-B2 receptor leading to the formation of a non-functional protein. The ncRNA 17A is normally expressed in the human brain but is highly upregulated in the brain of AD patients. The stable expression of 17A in SH-SY5Y neuroblastoma cells enhances the secretion of Aβ and the Aβ x-42/Aβ x-40 peptide ratio. Indeed the synthesis of 17A is upregulated in response to inflammatory stimuli, suggesting that it may be induced by AD-related inflammation and that it could contribute to neurodegeneration in AD [134].

In the other study, we found that IL1-α-dependent up-regulation of another ncRNA, named 38A, named 38A, drives the synthesis of an alternatively spliced form of the potassium channel-interacting protein (KCNI4). The alternative KCNI4 isoform cannot interact with the γ-secretase complex, resulting in modification of γ-secretase activity, AβPP processing, and increased secretion of β-amyloid enriched in the more toxic Aβ x-42 species.

This alternative splicing shift is observed at high frequency in tissue from AD patients, suggesting that RNA polymerase III transcribed ncRNA may be upstream determinants of alternative splicing of significantly proteins involved in the brain homeostasis and that their inflammation-dependent overexpression may induce alterations in the Aβ production contributing to the neurodegeneration during AD development [135].

In this context, a more detailed investigation of ncRNA functional mechanisms might allow to identify new molecular connections with neurodegenerative diseases like those identified in AD.

7. Environmental Factors and AD Pathoetiology

In recent years, several data have showed evidence that environmental and/or nutritional factors may play a causal, disruptive, and/or protective role in the development of AD although the initiating molecular events are not entirely known. While a direct causal role for aluminum or other transition metals (copper, zinc, and iron) in AD has not yet been definitively demonstrated, epidemiological evidence suggests that elevated levels of these metals in the brain may be linked to the development or progression of the neurodegenerative processes during AD [136].

Aluminum role in AD has been investigated for decades. Recent studies have identified aluminum in early neurofibrillary tangle (NFT) of hippocampal CA1 neurons from brains of aged patients [137]. However, aluminum contribution to AD remains controversial, lacking physiological mechanistic role.

Iron deposition in the brain is another important proposed mechanisms in the pathophysiology AD. Excessive iron can contribute to the formation of free radicals, leading to lipid peroxidation and neurotoxicity, which can result in cell membrane damage and cell death [138]. Recently, it has been shown that iron concentration in AD patients brain was significantly higher than those of nondemented controls. In particular iron deposition in parietal cortex and hippocampus at the early stage of AD were positively correlated with the severity of patients cognitive impairment [139].

Also zinc was reported to accelerate the aggregation of the Aβ peptides and to play a role in the control of inflammatory responses. Inflammation clearly occurs in pathologically vulnerable regions of the AD brain with increased expression of acute phase proteins and proinflammatory cytokines which are hardly evident in normal brain and that could participate in the induction of neuronal death. In particular,
cytokine expression may be regulated by zinc availability, so influencing inflammatory network phenotypic expression [140].

New lines of study show that lead exposures in early life has been implicated in subsequent progression of amyloidogenesis in rodents during old age. This exposure resulted in an increase in proteins associated with AD pathology: AβPP and Aβ peptide [141].

Recent work has shown that in vitro metal ligands such as clioquinol (CQ) increase the intracellular level of copper. The increase in intracellular copper was correlated with a dramatic and rapid decrease in levels of extracellular Aβ including Aβ1–40 and 1–42 [142]. It has been previously reported that CQ/copper complexes trigger the activation of PI3K and its downstream modulator Akt and the inhibition of glycogen synthase kinase 3 that in turn potentiated ERK1/2 phosphorylation [143, 144].

It is not clear if and how environmental factors take part to pathway discussed in this review, in which both AβPP and PS1 participate in the same signaling pathway leading, through Grb2 binding, to ERK1/2 activation and neurodegeneration. However, we may speculate that ERK1/2 activation by copper may contribute to the signal transduction system activated by AβPP, and PSs.

8. Concluding Remarks

The toxicity of Aβ peptides, eventually triggered or modulated by environmental or genetic factors, is a central dogma in AD genesis, which has been recently challenged by new achievements [48]. In particular, AβPP and PS1 participate in a plethora of protein–protein interactions and signaling pathways, suggesting that beside their implication for amyloid formation might also modulate specific cell signaling events involved in neuronal homeostasis that in a pathological context may lead to neurodegeneration.

In this scenario, it is under investigation the possible contribution of other receptors, such as LRP5, which interact with AβPP, could modulate its processing, are often target of γ-secretase cleavage, and share with AβPP relevant adaptors such as Fe65 and JIP1. It is tempting to hypothesize that the role of ApoE isoform 4 in AD, rather than being linked only to Aβ formation and clearing, might be also due to a specific receptor-mediated function which hampers AβPP physiological signaling and homeostatic control. In this vision, a unique pathway in which ApoE isoform 4, LRP5, AβPP, and PSs share common signal transduction events may represent the keystone that may explain Aβ formation and neurodegeneration.

We would like to underline that, among these events, AβPP and PSs may affect ERK1/2 signaling through ShcA/Grb2 transduction system, with a net relevance for cell-cycle regulation that in postmitotic neurons may lead to cell death. Also some LRP5s, as possible modulators of AβPP processing by affecting its endocytic trafficking and the proportion of AβPP present in lipid rafts, as well as the activity of the γ-secretase complex, could modulate ERK1/2 signaling via ShcA/Grb2 or through parallel pathways.

A parallel and complementary issue is given by the brain complexity and by the largely unexplored world of noncoding genome. The tip of the iceberg hides potentially relevant genomic control systems that may explain the widespread phenotypic variability, even among familial patients, observed in AD.

A more deep understanding of these complexes mechanism is necessary, in order to open new prospects for therapeutic applications in neurodegenerative disorders.

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