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The interactions of p53 with tau and Aß represent potential therapeutic targets for Alzheimer's disease

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Abstract

Alzheimer's disease (AD), the most common progressive neurodegenerative disorder, is characterized by severe cognitive decline and personality changes as a result of synaptic and neuronal loss. The defining clinicopathological hallmarks of the disease are deposits of amyloid precursor protein (APP)-derived amyloid-β peptides (Aβ) in the brain parenchyma, and intracellular aggregates of truncated and hyperphosphorylated tau protein in neurofibrillary tangles (NFT). At the cellular and molecular levels, many intertwined pathological mechanisms that relate Aβ and tau pathology with a transcription factor p53 have been revealed. p53 is activated in response to various stressors that threaten genomic stability. Depending on damage severity, it promotes neuronal death or survival, predomimantly via transcription-dependent mechanisms that affect expression of apoptosis-related target genes. Levels of p53 are enhanced in the AD brain and maintain sustained tau hyperphosphorylation, whereas intracellular Aβ directly contributes to p53 pool and promotes downstream p53 effects. The review summarizes the role of p53 in neuronal function, discusses the interactions of p53, tau, and Aβ in the normal brain and during the progression of AD pathology, and considers the impact of the most prominent hereditary risk factors of AD on p53/tau/Aβ interactions. A better understanding of this intricate interplay would provide deeper insight into AD pathology and might offer some novel therapeutic targets for the improvement of treatment options. In this regard, drugs and natural compounds targeting p53 pathway are of growing interest in neuroprotection as they may represent promising therapeutic approaches in the prevention of oxidative stress-dependent pathological processes underlying AD.

Keywords: p53, Aβ, tau, oxidative stress, neuronal apoptosis, Alzheimer's disease

Abbreviations

AD	Alzheimer's disease
AICD	amyloid precursor protein intracellular domain
Aβ	amyloid-β peptides
ApoE	apolipoprotein E
APP	amyloid precursor proteins
BACE1	β-site APP cleaving enzyme 1
BIN1	bridging integrator 1
CBP	CREB-binding protein
ERK1/2	extracellular signal regulated kinase-1/2
GAP-43	growth-associated protein 43
GSK-3β	glycogen synthase kinase-3β
HEK 293	human embryonic kidney 293 cells
HIPK2	homeodomain interacting protein kinase 2
I_2^{PP2A}	inhibitor-2 of protein phosphatase-2A
JNK	c-Jun N-terminal kinase
LDL	low-density lipoprotein
LTP	long-term potentiation
MAP	microtubule-associated protein
MAPKs	mitogen activated protein kinases
Mdm2	murine double minute-2
NFT	neurofibrillary tangles
PHF	paired helical filaments
PKA	protein kinase A
PP2A	protein phosphatase 2A
PS	presenilin

PUMA	p53 up-regulated modulator of apoptosis
ROS	reactive oxygen species
RNS	reactive nitrogen species
TA	transcriptional activation

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1. Introduction to Alzheimer's disease

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder. It leads to personality changes, inappropriate emotional and social behaviours, and progressive decline in cognitive functions of which severe memory loss is the most obvious sign (Sona et al., 2013; Levenson et al., 2014). During AD progression, many of the mechanisms involved in synaptic plasticity become deteriorated, resulting in synaptic dysfunction, synapse loss, and ultimately collapse of neural networks (Spires-Jones and Hyman, 2014; Dennis and Thompson, 2014). Compelling data suggest that failure of synaptic functions is one of the pivotal mechanisms in AD development that directly contributes to cognitive decline seen in AD patients (Sheng et al., 2012; Forner et al., 2017).

In the human brain, extracellular accumulation of amyloid β (Aβ) peptides in senile plaques and intraneuronal deposition of truncated and hyperphosphorylated tau proteins as paired helical filaments (PHF) in neurofibrillary tangles (NFT) are defining clinicopathological hallmarks of AD (Šimić et al., 1998a; Gouras et al., 2010; Armstrong 2013; Martin et al., 2013; Šimić et al., 2016). The incidence of AD increases with age, and as the world's population is getting older, AD represents a growing medical, economic, and social issue (Liu et al., 2013). Despite the considerable progress made in understanding the pathological mechanisms of AD development and progression at the molecular and cellular levels, this knowledge has not yet been successfully translated into the clinics, and currently only symptomatic treatments are available for this devastating disease.

1.1. The amyloid-cascade hypothesis

The most investigated theory of AD pathology, the amyloid-cascade hypothesis, emphasizes the crucial role of increased processing of amyloid precursor protein (APP) (Ehehalt et al., 2003; Armstrong, 2013; Martin et al., 2013). APP is a transmembrane protein that is via the amyloidogenic pathway first cleaved by β-site APP cleaving enzyme 1 (BACE1), the major β-secretase in the brain, and then by the γ-secretase complex to produce a set of hydrophobic Aβ

fragments whose length vary between 37 to 43 amino acids (Chow et al., 2010). Among the generated fragments, Aβ42 is the one that particularly readily self-assembles into a heterogeneous mixture of oligomers and protofibrils that are finally deposited as fibrils in senile plaques (Vetrivel et al., 2005; Blennow et al., 2006; Thinakaran and Koo 2008). As the major depositing species, Aβ42 has long been considered especially neurotoxic. However, numerous Aβ plaques can be found in the brain of individuals without any signs of clinical dementia (Wischik et al., 2014), and clinical trials targeting insoluble deposits of Aβ by active immunization with Aβ42 peptide have been unsuccessful, they affected neither clinical readout nor progression of tau pathology (Holmes et al., 2008; Rosenblum, 2014). There is also a lack of correlation between extracellularly deposited Aβ and severity of cognitive impairment and neuronal loss that ultimately gave rise to an alternative „toxic Aβ oligomer" hypothesis, which suggests that small and soluble Aβ oligomers are in fact the major cause of neuronal toxicity (Wirths et al., 2004; Lublin and Gandy, 2010, Benilova et al., 2012). Accumulation of these diffusible species much better correlates with the disease symptoms and cognitive decline (Aizenstein et al., 2008; Lesné et al., 2008). The small oligomers affect neurotransmission and inhibit synaptic function, induce alterations in hippocampal synaptic plasticity by inhibiting long-term potentiation (LTP) and facilitating long-term depression, and cause learning and memory deficits (Benilova et al., 2012; Spires-Jones and Hyman, 2014). They also may trigger downstream neuronal signalling involved in phospho-tau pathology (Hefti et al., 2013). Recent evidence suggests that harmul effects of soluble Aβ species are exerted by binding to lipid raft proteins including the cellular prion protein and ionotropic and metabotropic glutamate receptors, although this is poorly understood (Rushworth and Hooper, 2011). In addition, Benilova and coworkers (2012) suggested that Aβ peptides exert their effects by non-specific interactions with membrane proteins and targeting membrane lipids, by inducing oxidative damage of plasma membrane components, and by changing membrane dielectric properties and permeability.

Based on observed and proposed effects on synaptic functioning, targeting soluble Aβ oligomers was next suggested as a potential approach in ameliorating AD. Such an approach was

promising but also difficult as soluble oligomers are in equilibrium with the insoluble Aβ deposits (Rosenblum, 2014). In patients with significant amyloid plaque build-up and prominent cognitive impairment, it can be expected that removal of soluble oligomers will continuously promote their release from the plaque sources. With respect to other therapeutic options, extracellular amyloid plaques can be viewed as huge reservoirs of Aβ oligomers with tendency for release in the extracellular environment if plaques themselves are targeted, or if Aβ synthesis from APP is reduced by BACE1 or γ-secretase inhibitors. In fact, it has been suggested that many preclinical and clinical trials targeting Aβ deposits failed due to increase in toxic soluble species (Rosenblum 2014). Therefore, in an effort to target Aβ synthesis, both soluble and insoluble Aβ are probably required for clinical success (Roher et al., 2013; Rosenblum, 2014). The validity of Aβ as the principal causative agent and the main therapeutic target for treatment of cognitive dysfunction in AD has been recently questioned (Wischik et al., 2014). Even if soluble amyloid oligomers are toxic species, how cognitive functions stay intact in healthy individuals with levels of Aβ comparable to those in advanced stages of AD remains entirely elusive.

Animal models are also misleading when considering the therapeutic potential of Aβ approach. Animal models of AD indeed suggest that removal of Aβ and/or prevention of its generation are beneficial therapeutic strategies that improve cognitive deficits (Sheng et al., 2012; Rosenblum 2014). However, no single mouse model mimics all of the aspects of AD in humans (LaFerla and Green, 2012). Although animal models have been invaluable in informing on the cellular and molecular mechanisms of AD progression, there is a significant lack of convergence between the data obtained in preclinical models and in human clinical trials. Several potential explanations could underlie these inconsistencies. First, the most widely used animal models are based on the genetics of hereditary early-onset AD and APP processing, although more than 99% of AD patients have sporadic, late-onset AD. Second, in familial AD various mutations in *APP* and presenilins, the key components of γ-secretase complex which cleave APP, are essential for Aβ accumulation, whereas the etiology of idiopathic AD remains unclear in terms of genetics and

environmental influences. There is also a lack of variability among individuals in animal testing as inbred mouse strains are predominantly used for preclinical testing (LaFerla and Green, 2012). Finally, one of the most prominent differences between AD models and humans is that animal models do not develop the extensive neuronal and synaptic loss seen in AD patients, even at stages when deposition of amyloid plaques is abundant (Boncristiano et al., 2005; Sheng et al., 2012). This indicates that animal models better mimic a prodromal phase of AD (LaFerla and Green, 2012).

1.2. Synaptic loss in AD

Synaptic degeneration is an early event in the pathogenesis of AD (Scheff et al., 2007; Scheff et al., 2014). On the other hand, preservation of synaptic plasticity is essential for cognitive functioning, including learning and consolidation of new memories. A prominent decrease in synaptic density is found in the hippocampus and association cortex in AD, and the severity of cognitive impairment in AD patients strongly correlates with synaptic loss and dysfunction (DeKosky and Scheff, 1990; Sze et al., 1997). In fact, synaptic loss is the best correlate of cognitive impairment in human AD, and better disease predictor than amyloid plaques and tau accumulation (Akram et al., 2008; Overk and Masliah, 2015; de Wilde et al., 2016). In a stereologic analyses aimed to estimate the impact of dendritic spine loss on cognitive impairment, Akram and colleagues (2008) found a strong negative correlation between Braak NFT staging and number of spinophilin-immunoreactive dendritic spines, as a proxy for excitatory synapses, in hippocampus CA1 field and area 9 of the prefrontal cortex, together with negative impact on cognitive functions. The total number of synapses was also found reduced in the outer molecular level of the human dentate gyrus in early AD individuals. A comparable relationship has also been reported between the Mini-Mental State Exam and the total number of synapses (Scheff et al., 2006). In advanced stages of AD, about 40% of synapses are lost in the frontal cortex (Scheff et al., 1990; Brun et al., 1995).

It is likely that the impairment of synaptic functions, as an early event in the course of AD, is reflected by the synaptic loss. Several pathogenic molecular processes may be involved in synaptic

depletion, including perturbations in the synaptic vesicle release machinery and vesicular assembly, intracellular trapping or functional deregulation of glutamate receptors, impairment of mitochondrial function, oxidative stress, axonal transport defects, and deficiency in neurotrophic support (Overk and Masliah, 2014; de Wilde et al., 2016). It has been proposed that early in the progression of the disease these molecular changes are manifested as synaptic dysfunction and are reversible (Shankar et al., 2007; de Wilde et al., 2017). During disease progression, alterations become irreversible, and synaptic dysfunction advances to presynaptic and spine loss, axonal dystrophy and eventually neuronal loss in the cerebral cortex (Šimić et al., 1997; Overk and Masliah, 2014). As mentioned previously, oligomeric Aβ species, irrespective of their origin (synthetic peptides, cultured cells, transgenic animals or AD brain), have prominent toxic effects on synapse structure and function (Shankar et al., 2008; Sheng et al., 2012). Relocalization of hyperphosphorylated tau into dendritic spines may also contribute to synaptic failure (Sheng et al. 2012). Several tau-mediated processes could deteriorate, contributing to functional impairment. Thus, hyperphosphorylated tau may affect axonal transport and modulate the numbers of presynaptic mitochondria and release of synaptic vesicles. It also may disturb glutamate receptors trafficking and targeting at postsynaptic sites in dendritic spines (Hoover et al., 2010). In addition, tau is a substrate for glycogen synthase kinase 3β (GSK-3β) and p38 kinase that both act as important regulators of synaptic function. Besides, tau released in the extracellular space modulates signalling of synaptic receptors. Lastly, tau is important for maintaining the protein composition of the postsynaptic density. It is known that tau targets protein kinase Fyn to the postsynaptic compartment that ultimately affects interaction between NMDA receptors and postsynaptic protein PSD-95. In conclusion, the plethora of tau-mediated functions at synaptic sites suggest that deregulation of tau-driven processes may have a critical role in synaptic degeneration (for review, see Forner et al., 2017).

1.3. Genetic background of AD

The majority of AD cases occur later in life, after the age of 65 years. The strongest genetic contributor to the late-onset AD is the presence of ε4 allele of the apolipoprotein E (ApoE) gene. ApoE is a major carrier protein of cholesterol and other lipids that is predominantly secreted by astrocytes in the brain (Kim et al., 2014). The occurrence of AD is increased approximately 12-fold in two ε4 allele carriers in comparison with those without ε4 allele (Liu et al., 2013). For the human ApoE gene there are three alleles (ε2, ε3 and ε4) that vary in only two amino acids (residues 112 and 158). These subtle differences of ApoE isoforms affect their ability to bind lipids, receptors from the low-density lipoprotein (LDL) receptor family, and interfere with Aβ aggregation and clearance (Kim et al., 2009; Liu et al., 2013). Namely, soluble oligomeric forms of Aβ are increased in the presence of Apoε4 (Figure 1; Tai et al., 2014), potentially because ApoE4-containing lipoproteins are less lipidated and form less stable ApoE4/Aβ complexes. This leads to a reduction in ApoE4/Aβ levels and facilitates accumulation of oligomeric Aβ (Tai et al., 2014). ApoE is also involved in the receptor-mediated neuronal uptake of Aβ. Aβ12-28P, a nontoxic peptide antagonist of ApoE/Aβ binding, reduces intraneuronal accumulation of Aβ, inhibits loss of synaptic proteins and prevents synaptic degeneration in neurons co-cultured with astrocytes (Kuszczyk et al., 2013). Furthermore, ApoE and soluble Aβ compete for the uptake pathways in astrocytes. It is shown that ApoE isoforms prevent the uptake and consequent degradation of Aβ by competing for the same clearance pathways in astrocytes (Verghese at al., 2013). Finally, it is assumed that ApoE4 contributes to AD risk by increasing the localization of toxic oligomeric Aβ species to the synapse (Spires-Jones and Hyman, 2014). Thus, it seems that ApoE's influence is not achieved solely via direct binding with Aβ, but also through interactions with other receptors and transporters and cell surfaces (Verghese et al., 2013). In addition to affecting Aβ pathology and downstream synaptic plasticity, ApoE4 also contributes to AD by affecting cholesterol homeostasis, neurovascular functions, and neuroinflammation (Liu et al., 2013). It is also interesting that receptors for ApoE act as signalling molecules able to modulate phosphorylation of various proteins following extracellular ligand binding, which in the end may affect microtubule stability and synapse formation, and

ultimately contribute to AD pathology (Nathan et al., 1995; Hoe et al., 2006; Holtzman et al., 2012). At last, ApoE4 exerts direct transcriptional effects. Its binding sites include ∼1700 promoter regions of genes associated with synaptic function, microtubule disassembly, programmed cell death, aging, insulin regulation and trophic support, all processes that contribute to AD pathogenesis (Theendakara et al., 2016).

Figure 1

1.4. AICD as transcription factor

When cleaving Aβ fragments from APP, γ-secretase simultaneously releases a short cytosolic peptide the APP intracellular domain (AICD) that functions in transcriptional activation. AICD can be generated via both non-amyloidogenic and amyloidogenic pathways, but transcriptionally active AICD is predominantly generated via the amyloidogenic processing pathway (Ceglia et al., 2015).

Several AICD isoforms have been described in cell culture and animal models. It is not known which isoform is the most relevant for AD pathology, but the AICD50 isoform is certainly one of the most studied. It corresponds to residues 50-99 of the C-terminal fragment derived by BACE1 cleavage (Pardossi-Piquard and Checler, 2012) and is generated by the so-called ε-cleavage site of γ-secretase (Müller et al., 2008). Similarly to Aβ, AICD levels are elevated in the brains of AD patients (Ghosal et al., 2009).

AICD is notoriously difficult to study as it is highly unstable and prone to proteolysis. It undergoes rapid catabolic inactivation by the zinc metalloprotease insulysin (insulin-degrading enzyme or IDE), which is the main AICD-degrading enzyme. AICD can also be degraded by the ubiquitin-proteasome system and endosomal/lysosomal activation (Müller et al., 2008). AICD synthesis appears to be tightly regulated by specific adaptor proteins that precisely modulate AICD production. There are more than 20 interacting partners of AICD, but the functional outcome of these protein interactions still need to be determined. The adaptor protein Fe65 is the best characterized interacting partner of AICD: it can modify APP processing and AICD formation (Pardossi-Piquard and Checler, 2012). Most studies suggest that Fe65 binds the C-terminal region of

APP and following γ-secretase cleavage, Fe65 translocates AICD into the nucleus where a ternary complex with Tip60 is formed (AICD-Fe65-Tip60). This complex then drives AICD-mediated transcription (Müller et al., 2008; Pardossi-Piquard and Checler, 2012; Multhaup et al., 2015).

The overall effect of AICD on gene expression is not completely understood. With respect to AD pathology, AICD binds to regulatory *cis*-elements of APP, BACE1, GSK-3β (a pivotal kinase involved in tau phosphorylation), β-degrading enzyme neprilysin and p53 (Multhaup et al., 2015). By affecting expression of these genes AICD modulates various cellular functions including calcium signalling, ATP homeostasis, cytoskeletal dynamics, cellular trafficking, and synaptic plasticity (Pardossi-Piquard and Checler, 2012; Sheng et al., 2012). AICD is also involved in the control of cell death, primarily by promoting p53-dependent death pathways (see paragraph 2.2). AICD also negatively regulates expression of WAVE1. In neuroblastoma N2a cells, depletion of WAVE1 decreases budding of APP-containing vesicles and their trafficking from the Golgi complex to the plasma membrane. This reduces cell-surface levels of APP and ultimately production of Aβ (Ceglia et al., 2015). A decrease in WAVE1 mRNA is also observed in human AD brains, supporting the clinical relevance of WAVE1 downregulation. Ceglia and collaborators proposed that decrease in WAVE1 reflects a negative feedback and homeostatic control for Aβ during disease progression (Ceglia et al., 2015). Recently, AICD was reported to control the expression of phosphatase and tensin homolog (PTEN)-induced kinase 1 (Pink-1), which regulates mitochondrial dynamics and mitophagy. Both of these processes contribute to early-phase AD-linked neurodegeneration (Goiran et al., 2018). In embryonic fibroblasts AICD may be produced inside mitochondria by the activity of mitochondrial γ-secretase. Although the exact role of mitochondrial AICD remains unknown, it is possible that AICD locally contributes to mitochondrial dysfunction (Pavlov et al., 2011). Finally, all of these findings indicate that besides Aβ, other products of APP processing, AICD in particular, may represent potential therapeutic targets for AD (Sheng et al., 2012).

1.5. Tau and its role in neuronal function and AD

Tau, another molecule with an essential role in AD pathology, is the major neuronal microtubule-associated protein (MAP). Mostly due to a substantial number of clinical failures targeting Aβ, the role of tau in AD pathology emerged as a pivotal mechanism of AD neurodegeneration (Wischik et al., 2014; Šimić et al., 2016; Šimić et al., 2017). Besides, the recent view on the neuropathological findings of Braak and collaborators suggests the Aβ pathology appears many years after the onset of tau aggregation pathology (Braak and Braak, 1997; Wischik et al., 2014; Šimić et al., 2017). With advancing age, the human brain is susceptible not only to neuronal tauopathies, but also to tau accumulation in glial cells. Recently, two new neuropathological entities have been introduced. Aging-related tau astrogliopathy (ARTAG) describes the morphological spectrum of tau immunoreactivity detected in glial cells in the aging brain, irrespective of the presence of any other neuropathological disorders or cognitive impairment (Kovacs et al., 2016). In primary age-related tauopathy (PART) NFT are abundantly present in neurons of old-aged individuals, but in the absence or scarcity of Aβ deposits, with cognitive changes that usually range from normal to amnestic (Crary et al., 2014).

The primary function of tau is to promote microtubules assembly and regulate their stability and dynamics, thus affecting cytoskeleton maintenance, axonal transport of organelles, neurite outgrowth, and overall neuronal morphology (Esmaeli-Azad et al., 1994; Choi et al., 2009; Wang and Mandelkow, 2016). Tau is also present at presynaptic and postsynaptic terminals of healthy individuals, and probably participates in maintaining the protein composition of the postsynaptic density (Tai et al., 2012; Spires-Jones and Hyman 2014). Of note, tau has additional roles in the nucleus where it protects DNA integrity and genomic stability (Sultan et al., 2011; Violet et al., 2014; Kaluski et al., 2017).

The biological activity of tau is mainly determined by its degree of phosphorylation, which inversely correlates with ability to bind to microtubules. A certain level of phosphorylation is obligatory and represents an internal mechanism for preserving microtubule network and cellular activity. However, highly phosphorylated tau forms are less capable to bind to microtubules and are

less efficient in stabilizing the cytoskeletal network (Wang et al., 2013). Increased level of hyperphosphorylated soluble tau multimers, specifically in synaptic compartment, correlates with dementia in AD patients (Perez-Nievas et al., 2013). Besides promoting microtubule disruption, hyperphosphorylated tau self-assembles into tangles made of PHF upon detachment, and sequesters normal tau and two other neuronal microtubule-associated proteins, MAP1A/MAP1B and MAP2 (Alonso et al., 2001; Avila et al., 2006; Iqbal et al., 2010). Formation of tau aggregates causes deficits of axonal and dendritic transport, impairing intracellular trafficking of diverse neurotrophins and other functionally important proteins such as brain derived neurotrophic factor (BDNF), metabolic enzymes, heat shock proteins, chaperones and proteins involved in synaptic homeostasis (e.g. synapsin and clathrin) (Stokin and Goldstein, 2006; Wang et al., 2013; Roy, 2014). Ultimately, impairment of axoplasmic flow slowly progresses to retrograde degeneration (Šimić et al., 1998a; Alonso et al., 2001; Ballatore et al., 2007). Proteasome activity is also significantly inhibited by extensive tau phosphorylation and probably contributes to tau aggregation and the observed 4- to 5-fold increase in total tau levels in the frontal and temporal cortex of AD patients (Khatoon et al., 1994; Avila, 2006; Poppek et al., 2006; Chesser et al., 2013).

Tau binding to microtubules is also determined by the presence of particular tau isoform (Kremer et al., 2011). Tau is encoded by a single gene, but due to alternative splicing 6 major isoforms exist in the adult human brain that differ by the presence of two, one or zero inserts of 29 residues (2N, 1N, 0N) at the N-terminus, and either three or four semiconserved repeats of 31-32 amino acids (3R, 4R) in the C-terminal microtubule-binding domain (Buée et al., 2000; Simic et al., 2009; Wang et al., 2013). Expression of these isoforms is developmentally regulated and each exhibit distinct affinities for microtubules. Furthermore, tau undergoes additional post-translational modifications (such as glycosylation, truncation, nitration, acetylation, sumoylation and ubiquitination) that all may affect tau phosphorylation, formation and deposition of aggregates, as well as intracellular signalling cascades and neuronal viability (Wang and Liu, 2008; Wang et al., 2013).

1.5.1. Tau hyperphosphorylation in AD

Enhanced tau phosphorylation results from the activity of many proline-directed and non-proline-directed serine/threonine (Ser/Thr) kinases, and tyrosine (Tyr) kinases (Martin et al., 2013; Wang et al., 2013). Ser/Thr kinases GSK-3β, cyclin-dependent kinase 5 (cdk5) and casein kinase 1/2 (isoforms 1α/1δ/1ε/2) phosphorylate tau at most of the sites known to be phosphorylated in AD. These kinases are granted by some researchers to be the crucial factors in the progression of the disease, and promising therapeutic targets in rescuing neuronal cells against tau-induced toxicity (Martin et al., 2013; Wang et al., 2013). The other relevant Ser/Thr kinases involved in tau phosphorylation are mitogen activated protein kinases (MAPKs) that include extracellular signal regulated kinase-1/2 (ERK1/2), c-Jun N-terminal kinase (JNK) and p38, calcium and calmodulin-dependent protein kinase II, tau-tubulin kinase 1/2, and cyclic AMP-dependent protein kinase (PKA), PKB/Akt, and PKC (Morishima-Kawashima et al., 1995; Avila, 2006; Martin et al., 2013; Beharry et al., 2014; Lee and Kim, 2017). In general, it is considered that proline-directed kinases (that act on Ser/Thr followed by proline) are more important than non-proline-directed kinases as they phosphorylate tau at numerous sites. However, because non-proline-directed kinases (such as PKA and calcium/calmodulin kinase II) act at only a limited number of sites, their importance may be underestimated as primed phosphorylation of tau by these kinases facilitates the subsequent phosphorylation of tau by proline-directed kinases, including GSK-3β and cdk5 (Iqbal et al., 2009; Simic et al., 2009). Multiple phosphorylation sites of tau are mainly clustered in the flanking regions of the microtubule-binding domain (Wang et al., 2013; Wang and Mandelkow, 2016). Apart from tau phosphorylation, aberrant phosphorylation in general is an important step in the pathogenesis and progression of AD. The pattern of phosphorylation of numerous proteins is altered in different brain regions, synergistically promoting transition from a presymptomatic to a symptomatic state of AD. Many of aberrantly phosphorylated proteins are involved in cytoskeletal maintenance and synaptic function (Perluigi et al., 2016).

Among the mentioned kinases, GSK-3β regulates multiple cellular processes besides phosphorylation, and has attracted much interest as a player in the pathogenesis of sporadic and familiar forms of AD. By GSK-3, tau is phosphorylated at 42 residues (Martin et al., 2013). GSK-3β is able to promote formation of tangle-like filaments in cell-free systems, stimulate phosphorylation of tau in neuronal cell cultures and induce tau hyperphosphorylation and cognitive decline in animal models (Hooper et al., 2008; Lei et al., 2011; Jazvinšćak Jembrek et al., 2013). Presenilin 1, as a part of γ-secretase complex that operates the second cut of APP to produce Aβ, participates in the regulation of GSK-3β-mediated tau phosphorylation by bringing tau and GSK-3β in close proximity. AD-related mutations in presenilin 1 show increased ability to bind GSK-3β and stimulate tau-directed kinase activity (Takashima et al., 1996). In addition to tau phosphorylation, GSK-3β may promote apoptosis in diverse neurodegenerative paradigms, including AD. The intracellular distribution of GSK-3β is dynamically affected by proapoptotic stimuli, enabling the initiation of death-related signalling cascades. For example, in intact human SH-SY5Y cells (a neuroblastoma cell line) GSK-3β was found predominantly in the cytosol, but upon various apoptotic interventions it accumulated in the nucleus, which facilitated interactions with nuclear substrates (Bijur and Jope, 2001).

On the longest human tau isoform (2N4R) that contains 441 residues, 80 Ser or Thr phosphorylation sites have been identified, and most of them are on Ser-Pro and Thr-Pro motives. With five additional Tyr residues, approximately 20% of all tau amino acids can be phosphorylated (Johnson and Stoothoff, 2004; Wang et al., 2013). Of these 85 residues, 28 are specifically phosphorylated in AD, 16 are found to be phosphorylated in both AD and healthy brains, 31 represent sites of phosphorylation in healthy brain, whereas the last 10 phosphorylation sites are not fully characterized yet (Martin et al., 2013). However, it is suspected that phosphorylation of only about 15 residues is of physiological or pathological relevance *in vivo* (Johnson and Stoothoff, 2004; Hanger et al., 2009; Kremer et al., 2011).

Tau NFT pathology in AD develops in a defined temporal and spatial order (Braak and Braak, 1991; Lace et al., 2009; Wang and Mandelkow, 2016; Rüb et al., 2016). In contrast to Aβ plaque deposition whose distribution pattern and overall quantity have limited importance for staging AD pathology, the topographic progression of tau pathology is the basis of the Braak and Braak staging system of AD, and correlates well with cognitive decline in AD patients (Braak et al., 2006; Nelson et al., 2010). However, in the hippocampus of AD brain, the neuronal loss is generally more prominent than NFT formation (Šimić et al., 1998b). The somatodendritic accumulation of conformationally altered, but nonfibrillar tau, is the first sign of the disease. Further pathological changes are detected by antibodies raised against the early forms of hyperphosphorylated tau, such as CP-13 antibody, and later by antibodies indicative of advanced stages of tau hyperphosphorylation, such as AT8 and PHF-1, when NFT can be found in neuronal bodies and neuritic processes (McKee et al., 2008; Götz et al., 2010).

It is well established that hyperphosphorylation attenuates tau's role in microtubule stabilization, but its causative role in tau aggregation is poorly understood. Previous studies suggested that hyperphosphorylation promotes PHF formation (Alonso et al., 2001), but more recent findings indicate that hyperphosphorylation alone is not crucial for fibril formation, although increase in phosphorylation facilitates formation of oligomers, but not fibrils (Tepper et al., 2014). The latter is also questionable as both tau-tau and tau-tubulin interactions through the repeat domain may be interrupted by phosphorylation (Wischik et al., 1996; Lai et al., 2016).

Besides affecting aggregation and clearance of Aβ, ApoE isoforms may affect tau and microtubules by modulating signal transduction pathways that regulate activity of tau kinases. In one study, treatment of primary neurons with each of the three ApoE isoforms inhibited phosphorylation of GSK-3β, reduced accumulation of phosphorylated tau and increased unphosphorylated tau, and affected the pattern of tau distribution in neuronal cells. These effects were mediated by extracellular interactions with ApoE receptors (from the LDL-receptor family), and were least pronounced for ApoE4, in accordance with the fact that the more severe phospho-

tau pathology and prominent axonopathy in the AD brain are attributed to the ApoE4 isoform (Hoe et al., 2006). In addition, ApoE might bind tau in an isoform-specific manner, and it is likely that ApoE binding blocks tau phosphorylation. As ApoE4 binds tau less avidly than other isoforms, it is proposed that through this mechanism ApoE4 may increase the likelihood of GSK3-mediated tau hyperphosphorylation (Small and Duff 2008). Also, it has been shown that truncated forms of ApoE (which can be found in the AD brain and cultured neurons), induce formation of NFT-like inclusions that consist of truncated ApoE, phosphorylated tau and phosphorylated neurofilaments of high molecular weight. If compared to ApoE3, ApoE4 is more vulnerable to truncation and generates more intracellular inclusions (Huang et al., 2001).

In addition to increased phosphorylation, decrease in the activity of different phosphatases similarly can result in tau hyperphosphorylation. Activity and/or expression of protein phosphatases-1, -2A, -2B and -5 (PP1, PP2A, PP2B, PP5), and phosphatase and tensin homolog deleted on chromosome 10 (PTEN), are altered in AD brains (Voronkov et al., 2011; Martin et al., 2013). Phosphoprotein phosphatases PP1, PP2A, PP2B and PP5 may dephosphorylate tau at different sites. Among them, PP2A is considered as the most important in dephosphorylating tau, and its activity is downregulated in AD brains (Zhou et al., 2008; Voronkov et al., 2011; Wang et al., 2013). The activity of PP2A is decreased as activation of GSK-3β results in enhanced accumulation of inhibitor-2 of protein phosphatase-2A (I_2^{PP2A}) (Liu et al., 2008). I_2^{PP2A} increase is associated with PP2A inhibition and concurrent tau hyperphosphorylation. Accordingly, downregulation of I_2^{PP2A} restores PP2A activity and reduces tau phosphorylation and accumulation, inhibits GSK-3β via PKA activation, ameliorates amyloidogenesis, and improves cognitive functions and dendritic plasticity in the human tau transgenic mice (Zhang et al., 2014b). Similarly, it is found that GSK-3β activation inhibits PP2A, whereas PP2A inhibition activates GSK-3β, indicating a plausible synergistic action of kinases and phosphatases in AD (Wang et al., 2013).

1.5.2. Interplay between Aβ and tau hyperphosphorylation in AD

A connection between soluble Aβ and tau protein phosphorylation is well documented in AD pathology. Accumulating evidence indicates that soluble Aβ induces tau phosphorylation (Jin et al., 2011; Bloom, 2014; Stancu et al., 2014; Nery et al., 2014), and GSK-3β is recognized as an important link between Aβ and tau pathologies (Figure 2; Huang and Jiang, 2009; Jazvinšćak Jembrek et al., 2013). Accumulation of Aβ oligomers inhibits phosphatidylinositol-3-kinase (PI-3K) and downstream Akt survival signalling pathways, consistent with the activation of GSK-3β and phosphorylation of tau (Takashima et al., 1996; Magrané et al., 2005). Natural Aβ dimers obtained from AD brain and applied at subnanomolar concentrations are able to induce tau hyperphosphorylation at AD-specific residues, disrupt the microtubule organization and provoke neuritic dystrophy (Jin et al., 2011). Treatment of cultured hippocampal rat neurons with soluble Aβ oligomers results in tau mislocalization to dendritic spines in a phosphorylation-dependent manner, together with the development of synaptic dysfunction (Miller et al., 2014). In another similar study, localized early changes following Aβ treatment were investigated. They observed missorting of endogenous tau in the somatodendritic compartment, and in regions with missorted tau found local elevation of Ca^{2+}, enhancement of tau phosphorylation at sites specific for AD-Tau, changes in kinase activities, reduced mitochondrial density, and loss of spines and microtubules. Similar changes are also induced by other types of cell stressors (e.g. exposure to H_2O_2 or glutamate), suggesting a common signalling pathway that results in tau pathology (Zempel et al., 2010).

Figure 2

Lloret and co-authors (2011) demonstrated that Aβ upregulates the expression of a regulator of calcineurin 1 (RCAN1), whereas enhanced levels of RCAN1 contribute to the enhancement of tau phosphorylation by two different molecular mechanisms. First, RCAN1 inhibits calcineurin activity, a serine-threonine phosphatase that dephosphorylates tau, and second, RCAN1 upregulates GSK-3β activity. Accordingly, RCAN1 overexpression has been linked to AD neuropathology (Harris et al., 2007; Wong et al., 2015). Primary neurons from $RCAN1^{-/-}$ mice exhibit an increased resistance to cell death under oxidative challenges that can be reverted by RCAN1 overexpression (Porta et al., 2007). Of two RCAN1 isoforms, RCAN1.1 and RCAN1.4, prevention of RCAN1.1 accumulation is

considered as potential approach in AD treatment as RCAN1.4 is present only in negligible amounts (Wu et al., 2014). Aβ42 oligomers may also induce endoplasmic reticulum stress, and Ca^{2+} released from endoplasmic reticulum stores is involved in GSK-3β activation and tau phosphorylation (Resende et al., 2008). Aβ oligomers may further modulate activity of GSK-3β via Wnt signalling. Namely, neurotoxic Aβ species bind to the cysteine-rich domain of Wnt receptor Frizzled at, or near, the Wnt-binding site and inhibit the canonical Wnt signalling pathway. This may modulate tau phosphorylation as canonical Wnt signalling inhibits kinase activity of GSK-3β (Magdesian et al., 2008). Aβ-facilitated increase in tau phosphorylation is likewise demonstrated in animal models. Injection of Aβ42 in the hindbrain ventricle of zebrafish embryos reduced cognitive abilities and promoted tau phosphorylation at GSK-3β specific sites at larval stage. These specific behavioural and molecular effects were reversed by lithium chloride, a GSK-3β inhibitor (Nery et al., 2014). In a double-transgenic mouse model expressing low levels of Arctic mutant Aβ that mimics the near physiological levels of soluble Aβ found early in AD, soluble Aβ forms facilitate cognitive impairment and profoundly influence the progression of tau pathology (Chabrier et al., 2012). Studies performed on triple transgenic (3×Tg-AD) mice also confirmed that pathological tau forms are found together with the accumulation of Aβ oligomers (McKee et al., 2008). Accordingly, treatment with γ-secretase modulators that reverses Aβ-induced tau pathology also reduces phospho-tau levels in animal models of AD (McKee et al. ,2008; Lanzillotta et al., 2011). In addition, Aβ oligomers induce caspase-3 activation that leads to Akt1 cleavage and inactivation, and downstream removal of tonic GSK-3 inhibition that contributes to Aβ42 oligomers-induced inhibition of LTP (Jo et al., 2011). Namely, in physiological conditions, protein kinase Akt phosphorylates GSK-3β at Ser9 and induces its inhibition (Lei et al., 2011). Both caspase-3 and GSK-3 inhibitors were effective in the prevention of Aβ-induced LTP inhibition, once again highlighting the potential of targeting GSK-3 in preventing cognitive impairment in AD.

1.5.3. Tau truncation in AD

Normal tau is natively unfolded protein and has little tendency for aggregation. Under physiological conditions, the tau molecule tends to change its global conformation to form a shape comparable to a paperclip, in which the N-terminal long arm, C-terminal short arm and the repeat domains all approach each other (for review, see Wang and Mandelkow, 2016). Besides phosphorylation, tau cleavage is another important modification characteristic of tau pathology in AD (Johnson et al., 1997). The tau cleavage generates fragments that are specifically C-terminally truncated at Glu391 and restricted to the repeat microtubule-binding domain of the full-length protein (Novak et al., 1993; Kolarova et al., 2012). After producing the MN423 anti-tau monoclonal antibody against tau proteins cleaved at Glu391, Novak and colleagues showed that MN423 stains all hallmarks of tau neurofibrillary pathology in AD (Novak et al., 1991; Novak et al., 1993). The finding that this antibody does not react with full-length tau suggests that tau is endogenously truncated in AD brains (Wischik et al., 1997, 2014, 2017; Lai et al., 2016). According to this view, truncation of tau prevents the formation of a paperclip and is a pivotal event that promotes oligomerization and aggregation of tau proteins (Kovacech and Novak, 2010; Jadhav et al., 2015; Zhou et al., 2018). Cycles of proteolytic removal of N- and C-termini (short and long tau arms) followed by stepwise addition of further tau seem to be independent of any amyloid pathology (Wischik et al., 2014). Truncated tau is capable of seeding tau aggregation in PHF at the expense of normal tau (Wang et al. 2009; Harrington et al., 2015).

As they are proteolytically stable, tau oligomers are probably transported unchanged to axon terminals where they can damage synapses and impair their function. More importantly, these truncated fragments are able to spread between interconnected neurons and initiate the pathological neurofibrillary cascade in previously healthy neurons (Šimić et al., 2016). Tau pathology spreads progressively throughout the brain by cell-to-cell transfer, within neuronal circuits that are synaptically connected (Liu et al., 2012c). Propagation of tau misfolding is mediated by prion-like mechanisms in which extracellularly released fibrillar tau aggregates escape a donor cell, which may also happen after degeneration of cellular compartments, and following entry into

neighbouring recipient cells, directly get in contact with the natively folded tau protein. This induces conformational change and seeds fibrillization of native tau, triggering aggregation (Kfoury et al., 2012: Brettschneider et al., 2015). Although the mechanisms underlying the process of propagation are not completely understood, it is known that blocking endocytosis inhibits transmission of tau pathology. Upon clathrin-mediated endocytotic internalization, tau aggregates permeabilize the endosomal membrane that allows leakage of tau aggregates into the cytoplasm and promotes initiation of new pathological cycle (Michel et al., 2014; Calafate et al., 2016). Likewise, low-molecular weight tau aggregates and fibrils can be internalized through bulk endocytosis. Uptake occurs in the somatodendritic compartment and is followed by anterograde transport to axon terminals, as well as in axonal terminals where it is followed by retrograde transport to the cell body (Wu et al., 2013).

A critical requirement that initiates tau aggregation is binding to a solid-phase substrate that exposes a high-affinity tau-tau binding domain and permits binding (Lai et al., 2016). Once triggered, the aggregation process is self-propagating thereafter. Wischik and colleagues (2017) argued that products of failed clearance may become a seeding mechanism of tau aggregation. They suggested that critical binding substrate could be generated by aberrant processing of neuronal proteins, particularly of membrane proteins from mitochondria. Once the repeat-domain fragment is exposed in appropriate conformation, the dynamics of microtubule assembly and disassembly could be governed by differential binding affinities. Namely, tau-tubulin binding interactions have lower binding affinity than pathological tau-tau interactions, irrespective of its phosphorylation status (Lai et al., 2016). This means that redistribution of tau into insoluble/aggregated neurofibrillary pool is a biophysical consequence of intrinsic kinetic properties that promote high affinity tau-tau binding interactions (Šimić et al., 2016). According to proposed scenario, disturbed APP turnover and abnormal Aβ production would simply contribute to the progressive decline of the endosomal–lysosomal processing and incomplete mitochondrial clearance (Wischik et al., 2017).

Although many tau fragments are found in AD, proteases implicated in their generation are poorly identified. Caspases, calpains, mammalian asparagine endopeptidase, thrombin and cathepsin represent potential contributors to tau processing (Zhang et al. 2014). Several caspases, including caspase-3 can cleave tau at Asp421 (Jarero-Basulto et al., 2013). Interestingly, in peptides containing the proposed caspase-3 cleavage region, phosphorylation of neighbouring Ser422 brings resistance to truncation (Sandhu et al., 2017). Thus, although it is generally considered that phosphorylation favours tau aggregation, it is possible that phosphorylation at some specific sites may be protective. Besides caspase-3, caspase-6 also cleaves tau at Asp421. Active caspase-6 and tau cleaved by caspase-6 are abundantly present in neuritic plaques, neuropil threads, or NFT in all stages of AD. The level of caspase-6-cleaved tau is similar in very severe to mild cases. This indicates that caspase-6 activity is not the result of advanced neurodegeneration but is present very early in the course of AD (Albrecht et al., 2007). Truncation at Asp402 and N-terminal cut at Asp13 are also attributed to caspase-6 activity (Jarero-Basulto et al., 2013). Finally, expression of human truncated tau protein in transgenic rats induces characteristic hallmarks of tau pathology (tau hyperphosphorylation, axonal damage and NFT formation), together with neurobehavioral alterations (Hrnkova et al., 2007). Similarly, anti-tau antibodies that block development of tau seeding activity, improved cognitive deficits *in vivo* (Yanamandra et al., 2013). Thus, when considering novel therapeutic strategies in AD, all these findings suggest that targeting tau truncation, clearance, and aggregation could be more promising approach than inhibition of its phosphorylation.

1.5.4. Tau acetylation in AD

Besides tau phosphorylation and truncation, other post-translational modifications of tau may contribute to AD pathology. In this context tau acetylation may serve important role in tau aggregation in AD. *In vitro* and in cellular models, tau can be acetylated by acetyltransferases p300 and CREB-binding protein (CBP), and deacetylated by histone deacetylase 6 (HDAC6) and sirtuin 1

(Kontaxi et al., 2017). Remarkably, in the absence of CBP or p300, an intrinsic tau acetyltransferase activity can mediate tau self-acetylation via acetyl-CoA reactive cysteine residues. Tau 4R isoforms display higher levels of autoacetylation in comparison to 3R isoforms (Kontaxi et al., 2017). As acetylation sites are mainly clustered within the lysine-rich microtubule-binding domain and acetylated tau is unable to bind to microtubules, it is possible that tau autoacetylation represents an autoregulatory mechanism for prevention of tau-microtubule interactions (Kontaxi et al., 2017; Trzeciakiewicz et al., 2017). Interestingly, intrinsic tau acetylation is coupled to autoproteolytic tau cleavage within the R2 and R4 repeats generating distinct N- and C-terminal tau fragments that are widely detected in human AD brain and CSF (Cohen et al., 2016).

Of all putative acetylation sites, Lys174, Lys274, Lys280 and Lys281 have received most attention as critical residues associated with the formation of pathogenic tau (Kontaxi et al., 2017). Acetylation at Lys174 occurs very early in the disease progression, before detectable NFT deposition. The acetyl-mimic tau mutant K174Q impairs tau clearance, promotes monomeric tau accumulation, enhances formation of dimeric tau and induces profound cognitive and behavioural deficits *in vivo* (Min et al., 2015). Related to epidemiological studies that suggest a reduced risk for AD in patients taking non-steroidal anti-inflammatory drugs (NSAIDs) (Wang et al., 2015), Min and colleagues further found that salicylate-mediated reduction of Lys174 acetylation via p300 inhibition actually could be a key underlying mechanism of its beneficial health effects (Min et al., 2015). Acetylation at Lys280 is consistently detected in tau transgenic mouse models and brain tissue from patients with tauopathies. It is found specifically in the disease-affected tissue, suggesting a causative role in pathological tau transformation (Cohen et al., 2011). Tau acetylated at Lys280 is detected at all stages of AD pathology, although more prominently in subjects with moderate to severe tau pathology. Such temporal distribution suggests that phosphorylation preceded acetylation at Lys280, and is later followed by truncation and neuronal death (Irwin et al., 2012). Acetylation of Lys280/Lys281 in the binding domain also impairs tau–microtubule interactions and enhances the seed-dependent aggregation of full-length tau, conferring to loss of

tau function and gain of toxic function. As both Lys280 acetylation and its deletion (e.g. in Pick´s disease) can result in tauopathy, it is considered that deletion or acetylation of this lysine residue neutralizes the net positive charge within the microtubule-binding region and abrogates interactions between tau and microtubules (Trzeciakiewicz et al., 2017). Moreover, tau acetylation at Lys280/Lys281 led to tau dephosphorylation at residues Ser202/Thr205 via PP2A phosphatase activity indicating acetylation-dephosphorylation cross-talk (Trzeciakiewicz et al., 2017). Similarly, an acetylation–phosphorylation switch at Lys321/Ser324 has been revealed. Acetylation of Lys321 (within a KCGS motif of repeat region) was found essential for prevention of tau aggregation *in vitro.* This means that acetylation at this residue provides efficient molecular strategy to prevent phosphorylation at Ser-324 that otherwise would impair tau function (Carlomagno et al., 2017). In accordance, KXGS motifs in AD patients are hypoacetylated, suggesting that deacetylation of KXGS motifs increases susceptibility for the development of tau pathology (Cook et al., 2014).

Studies performed on transgenic mice with lysine-to-glutamine mutations at residues 274 and 281 of human tau protein have shown that abnormal acetylation at these sites disrupts synaptic plasticity and exacerbates memory impairment by reducing levels of KIdney/BRAin (KIBRA) protein which plays an important role in learning and memory and is enriched at postsynaptic sites. Accordingly, in AD patients with dementia, increased levels of tau acetylation were linked to KIBRA deficiency, thus suggesting a novel mechanism of tau-mediated synaptic dysfunction and cognitive impairment (Tracy et al., 2016).

Finally, acetylation and ubiquitination target the same lysine residues in the microtubule-binding domain, indicating competition between these post-translational modifications (Morris et al., 2015). Hence, it is suggested that tau acetylation, at the expense of polyubiquitinylation, reduces turnover of normal and hyperphosphorylated tau. Ultimately, impaired clearance increases the pool of available tau, directly contributing to tau aggregation (Kontaxi et al., 2017). All these findings strongly suggest that targeting tau acetylation could have profound implications for therapeutic strategies and biomarker development in the future.

1.6. Oxidative stress in AD

The pathogenesis of AD is also tightly linked to increased oxidative stress, particularly in the period directly preceding the onset of the first symptoms of the disease (Multhaup et al., 2002; Bonda et al., 2010; Jazvinšćak Jembrek et al., 2015). Oxidative stress is induced by elevated generation of reactive oxygen species (ROS). In the brain, it is characterized by the accumulation of damaged macromolecules (proteins, lipids, nucleic acids and carbohydrates), mitochondrial dysfunction, ATP depletion, impaired proteolysis and autophagy, axonal degeneration, and pronounced microglial activation and inflammation. All these events ultimately contribute to widespread neuronal death (Lucassen et al., 1998; Bonda et al., 2010; Galindo et al., 2010; Axelsen et al., 2011). The effects of oxidative stress are catalysed by transition metals (such as zinc and copper). Increased accumulation of these metals in AD may affect APP metabolism resulting in neurotoxic processes (Multhaup et al., 2002). A number of studies in cell lines, animal models, and human volunteers indicate that oxidative stress, mitochondrial function, endoplasmic reticulum stress response and immune function are affected by ApoE genotype as well (Jofre-Monseny et al., 2008; Dose et al., 2016).

The crosstalk between proteinopathy, oxidative stress, and mitochondrial dysfunction represents a contributing factor in the pathogenesis of AD. Oligomers and aggregated proteins may cause mitochondrial damage and impair bioenergetic homeostasis, fusion/fission processes, and mitophagy. Damaged mitochondria in turn facilitate ROS generation and initiate cell death cascades (Prentice et al., 2015). The interaction between oxidative stress and Aβ may occur at multiple levels. Several ROS-responsive transcription factors may induce expression of APP, BACE1, and γ-secretase and increase production and accumulation of Aβ (Picone et al., 2015; Ganguly et al., 2017). In turn, it is well established that Aβ induces ROS generation and downstream mitochondrial failure (Hu and Li, 2016). Furthermore, Aβ can bind transition metals that initiate redox-cycling reactions, or may promote ROS production via NADPH oxidase-dependent mechanisms following

microglial activation (Ganguly et al., 2017). In addition, Aβ progressively accumulates within the mitochondrial matrix, which might contribute to Aβ-mediated mitochondrial dysfunction. The interactions between Aβ and Aβ-binding alcohol dehydrogenase (ABAD) induce ROS generation in close correlation with synaptic dysfunction and learning and memory deficits (Chen and Yan, 2007). Aβ also inhibits degradation of mitochondrial presequence peptides. Deregulation of preprotein maturation modulates protein turnover resulting in disturbed mitochondrial proteome, which might have detrimental consequences on mitochondrial function (Mossmann et al., 2017). Regarding tau, prolonged oxidative stress enhances tau phosphorylation through increased activity of JNK and p38 and suppression of PP2A activity (Su et al., 2010). Hence, it is considered that oxidative stress disturbs signalling pathways leading to tau hyperphosphorylation. Exposure to Aβ also induces p38 activation and leads to tau hyperphosphorylation, whereas Aβ-induced effects could be prevented if neurons are co-incubated with trolox, a potent antioxidant. These findings are confirmed *in vivo*, in APP/PS1 double transgenic mice that express a high level of phospho-p38 in the hippocampus (Giraldo et al., 2014).

2. Role of p53 in neuronal biology

The transcription factor p53 plays a major role in DNA damage response, maintaining of the genome integrity and tumour suppression (Liu et al., 2015). As p53-controlled genes regulate a heterogeneous repertoire of biological processes, the impairment of p53 expression and activity results in wide spectrum of disorders, including cancer, neurodegeneration, and metabolic diseases (Stanga et al., 2010). p53, together with its relatives p63 and p73, regulates cell cycle, apoptosis, developmental differentiation and senescence (Eizenberg et al., 1996; Moll and Slade, 2004; Bourdon, 2007; Wei et al., 2012; Wang et al., 2014). Proteins p63 and p73 can be involved in the same regulatory networks as p53, or transmit signals to the p53 pathways, thus actively participating in final cellular responses (Levrero et al., 2000; Collavin et al., 2010; Wei et al., 2012). However, as p53, p63 and p73 transgenic knockout mice develop distinct phenotypes, each gene

controls unique biological functions in addition to evolution of mutual roles and responsibilities (Murray-Zmijewski et al., 2006; Bourdon, 2007).

Regarding the p53-guided cellular response to various genotoxic challenges, one of which is oxidative stress, the appropriate response to oxidative injury relies on p53 ability to sense the intensity of the damage. In general, p53 ensures antioxidative activities in mild oxidative injury to promote cell survival, but if the overall cellular health is seriously compromised (when the antioxidative capacity is greatly surpassed), p53 exhibits prooxidative activity that ends in cell death (Liu and Xu, 2011). To accomplish its roles, p53 binds to target DNA sequences and promotes or represses expression of genes that mediate p53-dependent functions (Figure 3). In non-neuronal cells, p53 also changes its intracellular location and, by direct protein-protein interactions with the Bcl-2 family members, triggers apoptotic cascade (Mihara et al., 2003; Schuler and Green, 2005; Speidel 2010). In postnatal cortical neuron, it seems that the apoptotic action of p53 does not implicate this transcription-independent mechanism at mitochondrial/cytoplasmic site. Instead, it requires transcriptional activation of p53-upregulated modulator of apoptosis (PUMA), a member of the BH3-only proteins from the Bcl-2 family. PUMA induces neuronal death through Bax-mediated permeabilization of the outer mitochondrial membrane that causes cytochrome c release and caspase activation (Uo et al., 2007; Chatoo et al., 2011; Wang et al., 2014). However, mitochondrial translocation of p53 has been reported in neuronal death, although it was related to apoptosis-independent events (Zhao et al., 2013). In addition, it was found that caspase inhibitors do not always prevent neuronal death, indicating that apoptotic processes downstream of Bax also can be caspase-independent (for review, see Miller et al., 2000).

Figure 3

p53 is an intrinsically unstable protein and is present only in minute concentrations. Intracellular stability and activity of p53 are regulated by various mechanisms, including post-translational modifications, protein-protein interactions and conformational state (Brooks and Gu 2003; Jenkins et al. 2009; Stanga et al., 2010; Karve and Cheema 2011). Under normal physiological conditions, p53 is maintained at a low basal level by its negative regulators, mainly murine double

minute-2 (Mdm2), as well as COP1 and Pirh2. These E3 ubiquitin ligases directly interact with p53 and promote its proteasomal degradation, which consequently inhibits p53-mediated functions (Wang et al., 2011). Mdm2 is the principal antagonist of p53 action (Figure 4). Inhibition is supported by a cytoplasmic protein Mdm4, a member of the Mdm2 family that besides binding to p53 also binds to Mdm2. The resulting heterodimer then represses p53 activity by promoting Mdm2-mediated degradation (Mancini et al., 2016). In addition, Mdm2 binds to the transactivation domain of p53 and inhibits transcription, and also exports p53 from the nucleus (Ashcroft and Vousden 1999). Furthermore, Mdm4 is involved in post-translational modifications of p53 by promoting phosphorylation of p53 at Ser46 by homeodomain interacting protein kinase 2 (HIPK2). This step participates in mitochondrial, as well as transcriptional activity of p53 towards repression of anti-apoptotic and activation of pro-apoptotic targets (Mancini et al., 2016). Besides phosphorylation, in response to DNA damage, a plethora of other covalent posttranslational modifications (including acetylation, methylation, sumoylation among others) is introduced by a variety of specific enzymes that disrupts interactions of p53 with Mdm2, leading to its stabilization and transcriptional activation (Hooper et al., 2007; Puca et al., 2009b). An important modifying role of posttranslational modifications is also demonstrated by mathematical simulations. Such an approach predicts that acetylated p53 will gradually increase and activate the pro-apoptotic protein Bax under severe DNA damage, whereas levels of phosphorylated p53 will be important for cell repair during slight DNA damage (Fan et al., 2014).

Figure 4

Oligomerization is also a contributing factor in p53 activation. Assembly of tetramers (dimers of dimers) is required for rapid induction of apoptotic cell death, whereas dimeric p53 species exhibit growth arrest functions. Monomeric variants are inactive, supporting cell growth. In tetramer conformation p53 exhibits the highest affinity to its DNA-binding elements and efficiently triggers apoptotic transcriptional program (Chène, 2001). Thus, in resting cells the most abundant oligomeric species are p53 dimers that neither promotes cell death nor cell growth, but shift toward tetrameric forms is expected under cellular stress (Fischer et al., 2016). By promoting

formation of monomeric or tetrameric structures, multiple p53-binding partners can modify p53 oligomerization and affect cellular response to stress (van Dieck et al., 2009).

Furthermore, p53 is redox-regulated and its redox state is another important mechanism in the control of its function (Bykov et al., 2009). It is shown that oxidative environment disrupts conformation of wild-type p53 and inhibits its binding to DNA (Hainaut and Milner, 1993; Phatak and Muller, 2015). Reducing conditions are important for p53 to bind a zinc ion in the core domain and to fold in the appropriate conformation for DNA binding. Thus, p53 may undergo subtle variations in the levels of activity depending on the intracellular redox status and zinc bioavailability (Pavletich et al., 1993; Bykov et al., 2009).

Genes from the p53 gene family produce multiple protein isoforms that share structural and amino acid sequence homology in their transactivation, DNA-binding and oligomerization domains (reviewed in Slade et al., 2010 and Wei et al., 2012). All family members possess two promoters, P1 and P2. There are also two distinct transcriptional activation (TA) domains, of which TA1 is critically involved in response to acute DNA damage (Raj and Attardi, 2017). In general, transcription from the P1 promoter generates full-length isoforms that contain TA domains, whereas the alternative P2 promoter gives rise to N-terminally truncated isoforms (ΔN) without TA domains (Slade et al., 2010; Wei et al., 2012). By the combination of alternative promoter usage, alternative initiation of translation from two distinct sites within P1 promotor, and alternative splicing, the p53 gene in particular gives rise to four major isoforms: full-length p53 and three truncated versions Δ40p53, Δ133p53, and Δ160p53, which lack the first 39, 132, and 159 amino acids, respectively, at the N-terminus (Bourdon et al., 2005, Bourdon 2007; Marcel et al., 2010; Khouri and Bourdon, 2011; Wei et al., 2012). Δ40p53 isoforms lack the first transactivation domain (TA1) but retain the second (TA2), whereas Δ133p53 and Δ160p53 miss both TA domains and are devoid of the part of the DNA-binding region (Murray-Zmijewski et al., 2006; Pehar et al., 2014). By alternative splicing of p53 pre-mRNA (that mostly occurs at the 3'), additional α, β and γ isoforms of full-length p53 and all truncated versions are created (Khoury and Bourdon, 2011; Pehar et al., 2014). Only full-length

p53 assembles into a transcription-competent tetrameric complex that binds to p53-responsive elements in DNA, or translocates to mitochondria upon stress induction (Bourdon, 2007; Graupner et al., 2009). All β and γ isoforms lack oligomerization domain resulting in decreased transcriptional activity (Wei et al., 2012). The exact functional role of truncated p53 isoforms is not fully clarified, particularly in the central nervous system (CNS). However, p53 regulates the transcription of Δ133p53 isoforms. DNA damage causes p53 to bind directly to internal promoter inducing the expression of Δ133p53, whereas Δ133p53 regulates p53-induced apoptosis (Aoubala et al., 2011). The p63 and p73 isoforms with entire TA domain (TAp63 and TAp73) may mimic the function of p53 and promote transcription of p53 target genes (Moll and Slade, 2004), while ΔN truncated isoforms compromise p53 function acting as a direct antagonist to p53. Certain p63/p73 isoforms bind directly to internal promoter of p53 and regulate Δ133p53 expression (Marcel et al., 2012). Besides, same authors report that Δ133p53 regulates the anti-proliferative effects of p63/p73 complex. It was also found that p53β and ∆40p53α form complex with full-length p53 (Courtois et al., 2002; Bourdon et al., 2005), and that all p53 isoforms form complexes with TAp73 while Δ133p53 isoforms inhibit TAp73 apoptotic activity (Zorić et al., 2013). In general, the formation of protein heterocomplexes between family members has been found previously (reviewed in Moll and Slade, 2004). Formation of stable heterocomplexes is a mechanism for dominat negative inhibitory effect of N-terminally truncated isoforms on the tumor suppressor activities of wtp53, Tap63 and Tap73 leading to loss of transactivation and proapoptotic abilities (Zaika et al., 2002).

All members of the p53 gene family are involved in normal development (Bourdon 2007). Ferreira and Kosik (1996) studied the role of p53 in CNS development. They showed that p53 is expressed in neuroblasts and is downregulated when migrating neurons reach their place. The suppression of p53 expression accelerates neuronal differentiation, together with induction of MAP1B and dephosphorylation of tau. Hence, it is possible that expression of p53 in neuroblasts prevents neuronal terminal differentiation. Mice functionally deficient for all p53 isoforms are viable and mostly normal in their development, but die of cancer by 6 months of age.

The p73 isoforms play important roles in neuronal survival during development of the nervous system (Pozniak et al., 2000). In particular, ΔNp73 is the predominant form of p73 in the developing brain and cultured neonatal sympathetic neurons, and is required to counteract p53-mediated apoptotic neuronal death, which normally occurs during development. Apoptosis induced by the withdrawal of the nerve growth factor leads to p53 increase and pronounced decrease of ΔNp73 in primary neuronal cultures. Neurons can be rescued from death induced by nerve growth factor withdrawal or p53 overexpression if ΔNp73 levels are increased by viral transfection (Pozniak et al., 2000). Isoforms ΔNp73 may repress the PUMA/Bax system and inhibit both TAp73- and p53-induced apoptosis (Melino et al., 2004). The p73 isoforms promote survival in peripheral nervous system as well as in CNS neurons, and likely play a role not only during development, but also in the long-term maintenance of at least some populations of adult neurons. In $p73^{-/-}$ animals, the number of cortical neurons is normal at birth, but due to enhanced apoptosis decreases postnatally. This process continues into adulthood when the number of cortical cells is reduced by half in comparison with wild-type littermates. Similarly, overexpression of ΔNp73 isoforms rescues cortical neurons from apoptotic stimuli (Pozniak et al., 2002). Mice lacking all p73 isoforms are born without deformities but exhibit profound defects in neurogenesis, such as hippocampal dysgenesis, hydrocephalus, and abnormalities in pheromone sensory pathways (Yang et al., 2000). They also exhibit reproductive and behavioural deficits, and generally die within the first 2 months. However, to distinguish the functions of specific isoform, mice selectively deficient for TAp73 or ΔNp73 were generated. $TAp73^{-/-}$ mice suffered from infertility, aging and hippocampal dysgenesis, and showed genomic instability and enhanced aneuploidy (Tomasini et al., 2008). ΔNp73-deficient mice were viable, fertile, and displayed signs of neurodegeneration confirming neuroprotective role of ΔNp73 (Wilhelm et al., 2010). p63-null mice are born with truncated limbs and lack many epithelial structures indicating that p63 is necessary for limb development and epidermal morphogenesis (Murray-Zmijewski et al., 2006; Collavin et al., 2010; Khoury and Bourdon, 2011).

In CNS, p53 often correlates with progressive impairment of neuronal functioning and ultimately neuronal death in *in vitro* and *in vivo* studies. Similarly, the absence of p53 expression offers protection against various acute toxic insults (Morrison and Kinoshita, 2000; Morrison et al., 2003). Thus, it is found that overexpression of p53 induces widespread apoptotic death of cultured rat hippocampal pyramidal neurons (Jordán et al., 1997). The p53 also contributed to excitotoxic neuronal death via apoptotic and autophagic mechanisms in rat striatum (Wang et al., 2009). It has been shown that neuronal degeneration after kainate-induced excitiotoxic injury negatively correlates with p53 expression. In wild-type mice expressing two p53 alleles ($p53^{+/+}$) kainate injection resulted in extensive degeneration of pyramidal cells in the hipoccampus, whereas neurons of p53 knock-out mice ($p53^{-/-}$) were resistant. Interestingly, the pattern and severity of hippocampal damage was similar in p53 defficient mice and heterozygous mice harbouring one p53 allele, demonstrating that the expression of only one p53 gene is sufficient to initiate death cascade (Morrison et al., 1996). Excitotoxic processes, as well as both apoptotic and necrotic neuronal cell death, in association with increased levels of p53 mRNA and the protein itself, are found after epileptic seizures, cerebral ischemia and trauma (Plesnila et al., 2007; Engel et al., 2010; Engel et al., 2011; Rachmany et al., 2013). In delayed neurodegeneration following traumatic brain injury in mice, p53 rapidly accumulates in the damaged brain tissue and translocates to the nucleus, simultaneously with the inhibition of NF-κB transcriptional activity (Plesnila et al., 2007). In another study, mitochondrial translocation of p53 and association with cyclophilin D (CypD) was required for the mitochondrial pore opening that precedes oxidative stress-induced neuronal death (Vaseva et al., 2012). p53 also translocated to mitochondria and associated with CypD in SH-SY5Y cells exposed to oxygen glucose deprivation/reoxygenation that ends in apoptosis-independent cell death (Zhao et al., 2013).

In addition to its well-recognized neurotoxic potential, p53 may exhibit beneficial effects. By studying a *Drosophila* model of tau-mediated neurodegeneration (in flies that carry human tau with the R406W mutation), it was discovered that p53 actually may exert a neuroprotective role as it

regulates expression of genes involved in synaptic function (Figure 3). It is suggested that in response to DNA damage p53 protects postmitotic neurons from degeneration and preserves their function by counteracting synaptic injury and maintaining synaptic function (Merlo et al., 2014). Hence, synaptic function might be another promising target in p53-dependent neuroprotection from neurodegeneration. p53 also integrates various extracellular signals, such as neurotrophins and axon guidance cues, and regulates neurite outgrowth and axonal regeneration (Di Giovanni et al., 2006; Tedeschi and Di Giovanni, 2009; Di Giovanni and Rathore, 2012). Accordingly, inhibition of p53 function by inhibitors or siRNAs resulted in collapse of axonal growth cone, whereas overexpressed p53 promoted larger growth cones. Similarly, deletion of nuclear export signal of p53 prevented its axonal distribution, together with growth cone collapse (Qin et al., 2009). Acetylation of lysine residues of p53 was found essential for axonal outgrowth and regeneration after neuronal damage in mice. Namely, p53 forms a transcriptional complex with its acetyltransferases CBP and p300, which results in transactivation of the axonal growth-associated protein 43 (GAP-43), a typical marker of outgrowth and regeneration that also participates in the formation of new interneuronal connections (Tedeschi et al., 2009). Buizza et al. (2013) suggested that the role of p53 in neurodegeneration should be re-examined as it is possible that the impairment of p53 action, rather than excessive activation, is critical in determining impairment of synaptic and neuronal functioning in neurodegenerative diseases.

2.1. p53 in the pathogenesis of AD

Elevated p53 immunoreactivity has been observed in sporadic and familial AD, particularly in cortical neurons of the frontal and temporal lobes, and cortical and white matter glial cells distributed in brain regions undergoing degeneration (de la Monte et al., 1997; Kitamura et al., 1997; Alves da Costa et al., 2006; Hooper et al., 2007; Chang et al., 2012). Increased p53 expression was also found in transgenic mice carrying mutant familial AD genes. In some degenerating neurons of these mice, as well as in human AD, p53 expression increases in parallel with intracellular

accumulation of Aβ (Ohyagi et al., 2005). Increased levels of p73 are also found in hippocampal pyramidal neurons of AD patients, in neuritic processes, NFT-like structures, and within the nucleus (Wilson et al., 2004). TAp73 binds to a series of the p53 responsive elements and activates transcription of same p53 target genes (Slade and Horvat, 2011). p73 also drives the expression of microRNA (miR)-34a that in turn regulates expression of several synaptic proteins in cortical neurons, including synaptotagmin I and syntaxin 1A. A significant increase of both miR-34 and TAp73 is observed in the AD hippocampus, together with the reduction of the synaptic proteins (Agostini et al., 2011). p53 is also important regulator of expression of miRNAs, and several miRNAs, particularly from the miR-34 family, have been identified as direct transcriptional targets of p53. More importantly, tau mRNA is validated as miR-34 target (Dickson et al., 2013; Rokavec et al., 2014).

Astrocytes are essential for proper neuronal functioning in CNS. Recently, it was proposed that dysfunction in neuron-astrocyte crosstalk might contribute to the development of neurodegenerative diseases, including AD. Effects of astrocytes on neurons can be either toxic or protective. Various pro-inflammatory cytokines secreted by a senescence-associated secretory phenotype (SASP) exert neurotoxic effects, whereas neuroprotective outcome is mediated via secretion of neurotrophic growth factors. Two p53 isoforms, Δ133p53 and p53β, are expressed in astrocytes. They determine beneficial or detrimental effects of astrocytes on neurons. In cultured senescent astrocytes, expression of Δ133p53 isoform decreases, whereas expression of p53β that exerts neurotoxicity, increases. Similarly, astrocytes from AD patients show increased levels of senescence, together with decreased expression of Δ133p53 and increased expression of p53β. This further implies that p53 isoforms and regulatory mechanisms involved in the switch of expression phenotype are potential targets for therapeutic interventions in neurodegenerative diseases (Turnquist et al., 2016). Furthermore, it is known that nitric oxid (NO) activates p53 (Yakovlev et al., 2010). NO production is likely upregulated in AD brain as reactive astrocytes expressing neuronal

NO synthase are found around Aβ plaques, which also may play an important role in the pathogenesis of AD (Šimić et al., 2000).

2.2. p53 and oxidative stress

Regarding the role of p53 in neuronal oxidative stress status, the basal oxidative and nitrosative stress levels are reduced in the brain of p53-null mice compared to wild-type, as reflected by reduced DNA damage, decreased accumulation of lipid peroxidation adducts and protein carbonyls, attenuated protein nitrosylation, and enhanced activation of cellular antioxidative factors such as thioredoxin-1. This suggests that directing therapeutic strategies toward inhibition of pro-oxidant p53 activities and p53-mediated protein oxidation and lipid peroxidation might have beneficial effects on neurodegenerative processes in AD (Chatoo et al., 2011; Barone et al., 2012; Barone et al., 2015). The threshold of oxidative stress necessary for activation of p53-mediated pro-oxidant effects is lower in neurons than in other tissues, and in physiological conditions p53 behaves mostly as pro-oxidant, mainly through direct repression of antioxidant genes. These findings might indicate that pro-oxidant activity of p53 is not necessarily dangerous for neurons, but perhaps serves still unknown role in synaptic communication or neuronal plasticity (Chatoo et al., 2011). However, under pathological conditions, p53 drives neurons into more severe pro-oxidant state characterized by the p53-mediated activation of pro-oxidant genes and additional repression of antioxidant genes (Chatoo et al., 2011).

Oxidative stress is tightly linked to mitochondrial dysfunction. p53 contributes to many mitochondria-related processes, including initiation of apoptotic and necrotic death pathways, autophagy/mitophagy, mitochondrial biogenesis, cellular metabolism and regulation of redox homeostasis, depending on its subcellular localization, expression levels, interactions with binding partners, and cellular conditions (Wang et al., 2014). p53 ensures quality of mitochondrial function at several levels. First, p53 is important for mitophagy, a specific form of autophagy devoted to elimination of damaged and unfunctional mitochondria that produce excess ROS (Hoshino et al.,

2013). Second, p53 preserves optimal mitochondrial functioning by contributing to the generation of new mitochondria. In that respect, p53 acts as a guardian of the mitochondrial genome as well. It protects the mitochondrial genome by directly interacting with repair proteins (Park et al., 2016). Third, p53 may promote the assembly of the ATP synthase complex. Related to bioenergetics functions, p53 also affects cellular metabolism by regulating intracellular glucose levels, glycolytic ATP generation and the oxidative phosphorylation machinery. For instance, p53 transcriptionally stimulates the expression of apoptosis-inducing factor (AIF) that promotes biogenesis and function of mitochondrial complex I. As electron-chain transfer in the process of ATP synthesis generates ROS, in physiological conditions p53 simultaneously maintains high glutathione levels to preserve redox balance (for review, see Liang et al., 2013; Wang et al., 2014). Finally, appropriate mitochondrial size and shape are also essential for normal mitochondrial functioning, particularly in neuronal cells where mitochondrial transport at long distance is obligatory to fulfil high energy demands. By modulating expression of fission/fusion proteins, p53 ultimately participates in the regulation of mitochondrial dynamics and energetic homeostasis (Wang et al., 2014).

Apart from physiological functions, in oxidative stress p53 may influence mitochondria through nuclear, cytosolic and intra-mitochondrial sites. As mentioned previously, in p53-mediated apoptosis, nuclear p53 is activated by increased generation of free radicals and modulates expression of its targets (Culmsee and Mattson, 2005). p53 is also involved in the regulation of specific necrotic death that results from acute energetic failure and opening of the mitochondrial permeability transition pore (mPTP), a multimeric protein complex whose formation induces collapse of the mitochondrial membrane potential ($\Delta\Psi_m$) and damage of mitochondrial membrane integrity. These events exacerbate ROS generation, oxidative stress and calcium release from mitochondrial stores, further contributing to the impairment of mitochondrial function, translocation of death proteins from mitochondria, and propagation of death cascade (Rao et al., 2014; Prentice et al. 2015). It has been confirmed that mPTP-mediated alterations in mitochondrial structure and function have profound impact on neuronal injury in AD (Rao et al., 2014). In

ischaemia induced oxidative stress, p53 accumulates in the mitochondrial matrix and initiates mPTP opening by directly interacting with cyclophilin D (CypD), a mPTP regulator (Vaseva et al., 2012). Of note, the interaction of Aβ with CypD promotes mPTP formation and is linked to cellular and synaptic perturbations (Rao et al., 2014). Many proteins involved in autophagy are also regulated by p53. In non-neuronal cells, the overall impact depends on subcellular localization of p53 protein. Via transcription-dependent mechanism nuclear p53 activates autophagy under stress conditions, whereas intracellular (cytoplasmic) p53 seems to attenuate autophagy (Maiuri et al., 2010).

Preservation of cellular redox homeostasis and ROS-mediated cell signalling is also directly regulated via modulated expression of pro- and antioxidant proteins in a p53-dependent manner. p53 modulates both the generation and elimination of ROS (Wang et al., 2014). One of the p53-regulated ROS scavenger is manganese superoxide dismutase that protects mitochondria against superoxide radicals (Holley et al., 2010). Furthermore, a p53-inducible gene named TIGAR (TP53-induced glycolysis and apoptosis regulator) reduces fructose-2,6-bisphosphate levels, resulting in glycolysis inhibition and overall ROS decrease. TIGAR functions correlate with protection from ROS-induced apoptosis, whereas knockdown of endogenous TIGAR expression sensitized cells to p53-induced death (Bensaad et al., 2006: Zhou et al., 2016). In regard to AD, TIGAR expression is progressively reduced as severity of dementia increases, suggesting that optimal TIGAR levels offers protection against oxidative damage (Katsel et al., 2013).

2.3. Cooperation of Aβ and p53 in AD progression

As mentioned before, Aβ is derived from APP via two sequential cleavages. The second cut is made by γ-secretase, a high-molecular weight complex of four distinct proteins, presenilin 1 (PS-1) or presenilin 2 (PS-2), nicastrin, anterior pharynx defective-1 (Aph-1), and presenilin enhancer-2 (Pen-2). Presenilins cleave BACE1-derived βAPP and produce neurotoxic Aβ fragments. Not surprisingly, presenilin mutations are important contributors to familial AD (de Strooper 2007; Bialopiotrowicz et al., 2012). Of note, in human embryonic kidney (HEK) 293 cells and

telencephalon specific murine neuronal model, overexpression of both wild-type and mutated PS-2 increases p53 immunoreactivity and transcriptional activation, and enhances susceptibility to cell death by triggering apoptosis via the p53-dependent mechanisms (Alves da Costa et al., 2002). Accordingly, various approaches that reduce presenilin activity, such as presenilin loss or inactivation, γ-secretase inhibitors, and βAPP depletion, decrease amount and overall activity of p53, and reduce p53 mRNA expression (Alves da Costa et al., 2006). In addition, it is discovered that the AICD, a γ-secretase-derived intracellular C-terminal fragment of βAPP, directly interacts with p53, triggers increase in p53 activity and mRNA level, and enhances p53-dependent cell death by stimulating pro-apoptotic caspase-3 activity (Alves da Costa et al., 2006; Ozaki et al., 2006). Further studies revealed that all members of the γ-secretase complex control p53-mediated cell death, whereas p53 may regulate directly or indirectly the expression and transcription of PS-1, PS-2 and Pen-2, indicating that disturbed crosstalk between p53 and γ-secretase proteins might be involved in the pathogenesis of AD (Checler et al., 2010). Various APP missense mutations are also associated with hereditary AD. The wild-type APP (in contrast to AD-mutated forms) protects neuroblastoma cells against UV irradiation-induced apoptosis or p53 overexpression by inhibiting DNA-binding activity of p53 and p53-mediated gene transactivation (Xu et al., 1999). Hence, it is possible that disruption of this neuroprotective APP function could contribute to neuronal degeneration, probably by enhancing susceptibility to secondary insults due to impaired p53 signalling.

An increased amount of unfolded p53 has been found in peripheral cells of AD patients. A cytofluorimetric method used for the detection of conformationally altered p53 protein in blood cells also enables the discrimination of AD patients from healthy control and patients suffering from other forms of dementia (Lanni et al., 2008; Lannie et al., 2010b). In addition, the method was valuable to predict progression to AD in patients with mild cognitive impairment, two years before clinical diagnosis of AD. Although p53 was able to identify only a subset of converting patients, high expression of unfolded p53 could be considered as a strong risk factor for AD development (Lanni

et al., 2010b). As conformational alteration of p53, both in control subjects and AD patients, is age-dependent, an approach that utilizes p53 conformation is sensitive enough only in younger patients. The sensitivity to discriminate subjects with AD from non-demented individuals before the age of 70 was 90%, with the specificity of 77% (Lanni et al., 2008). If combined to APOε4 genotyping, the method yields diagnostic power comparable to that obtained by monitoring biomarkers from the cerebrospinal fluid (Lanni et al., 2010b).

Similar to blood cells, increased amount of unfolded p53 was found in fibroblasts from AD patients (Uberti et al., 2006). In general, conformational changes of any protein can result from gene mutations and/or post-translational modifications, and those found in AD seems to be independent of p53 gene mutations (Uberti et al., 2006). In comparison with non-AD cells, p53 expression was higher in AD fibroblasts in basal conditions, but its DNA-binding ability and transcriptional activation were impaired following exposure to oxidative insult (Uberti et al., 2002, 2006). SH-SY5Y cells stably overexpressing APP751wt (SY5Y-APP cells) also showed unfolded p53 conformation. This structural reorganization is likely a consequence of tyrosine nitration and results in compromised neuronal functioning. These cells had increased levels of APP and APP metabolites, increased Aβ peptide immunoreactivity, enhanced levels of oxidative stress markers, and were more resistant to toxic oxidative insult. Namely, while mock cells responded by activation of p53 signalling and transactivation of pro-apoptotic gene, SY5Y-APP cells lacked pro-apoptotic properties of p53 as the result of high expression of unfolded isoform. Although these results seem to be in contrast with the pro-apoptotic role of p53 during oxidative injury, in a wider context, the authors suggested that this "no-death" effect accumulates deficient neurons in the brain that may impair neuronal functioning and development of the disease (Buizza et al., 2013). In another study, HEK 293 cells stably transfected with APP expressed conformationally altered and transcriptionally inactive p53 form, and, compared to untransfected cells, were less sensitive to doxorubicin, a cytotoxic agent that induces DNA damage and p53-dependent apoptosis (Otsuka et al., 2004). Treatment of APP-expressing HEK293 cells with inhibitors of β- and γ-secretases prevented

generation of unfolded p53 form and restored vulnerability to doxorubicin. Furthermore, in untransfected HEK cells, conformational changes of p53 and reduced sensitivity to doxorubicin were induced by exposure to nanomolar concentrations of Aβ and antagonized by vitamin E, emphasizing important roles of both Aβ and prooxidant environment in p53 protein folding and consequent decline of its biological activity (Uberti et al., 2007). Interestingly, nanomolar concentrations of Aβ peptide (Aβ40 was used in the study), that are not toxic *per se*, may induce switch to unfolded p53 conformation in fibroblasts of non-AD subjects. This means that the tertiary structure of p53 and the initiation of p53-mediated apoptotic signalling is influenced by very low concentrations of soluble Aβ (Figure 5; Lanni et al., 2007). In yet another study dealing with conformational state of p53, oxidative stress was analysed in immortalized lymphocytes derived from early onset AD and subjects with AD-related mutations. In comparison with control group, the signs of oxidative stress were evident only in subjects with AD-related mutations, but conformationally altered p53 protein was found in both early onset AD and AD-related mutation lymphocytes. Enhancement of tyrosine nitration was found in unfolded p53 form compared to wild-type p53 in both cases. The authors concluded that ROS/RNS accumulation contributes to alteration of p53 conformation and that altered p53 might be considered as an early marker of impaired redox homeostasis in these patients (Buizza et al., 2012).

Figure 5

Not surprisingly, conformation-induced loss of p53 DNA-binding activity in SY5Y-APP cells also compromised expression of GAP-43, the p53 target gene (Buizza et al., 2013). In comparison with AD cases that display low tangle density, expression of GAP-43 mRNA is severely reduced in AD brains with high NFT formation. As the number of NFT correlates with the decrease in cerebral glucose metabolism and synaptophysin expression, these findings further imply that high NFT accumulation, together with reduced axonal outgrowth and synaptic loss might be related to disturbed p53 functioning (Coleman et al., 1992).

How soluble Aβ promotes generation of unfolded and dysfunctional p53 form? In studies aimed at resolving the molecular mechanisms underlying the impairment of p53 activity, kinase

HIPK2 emerged as an important player. HIPK2 is an evolutionary conserved Ser/Thr kinase that activates p53 in response to genotoxic stimuli, and also acts as a corepressor for homeodomain transcription factors (Mancini et al., 2016). HIPK2 interacts and phosphorylates p53 at Ser46 that ensures conformational stability of p53 and promotes its apoptotic action (Hofmann et al., 2002; Kuwano et al., 2016). HIPK2 also interacts with histones acetyltransferase CBP. HIPK2-related phosphorylation at Ser46 promotes CBP-mediated acetylation of p53 at Lys382. This acetylation step is necessary for full activation of p53 transcriptional activity and results in enhanced expression of pro-apoptotic p53 target genes (Hofmann et al., 2002; Puca et al., 2009b; Stanga et al., 2010). HIPK2 knockdown results in p53 protein misfolding and impairment of its DNA binding and transcriptional activity which can be restored by zinc supplementation (Puca et al., 2009a). In HEK293 cells stably expressing wild-type APP, endogenous products of APP metabolism downregulate HIPK2 expression, likely through activation of HIPK2 proteasomal degradation. Furthermore, in non-transfected HEK293 cells exposed to low amounts of soluble Aβ, HIPK2 DNA-binding to its target promoters was compromised (Lanni et al., 2010a). Among hampered HIPK2 targets, promoter of metalloprotein metallothionein 2A (MT2A) was considered interesting as metallothioneins may modulate p53 transcription due to zinc-chelating activity (Méplan et al., 2000). Indeed, in HEK-APP cells, HIPK2 reduction was associated with MT2A mRNA upregulation, whereas zinc supplementation restored Aβ-induced inhibition of pro-apoptotic transcriptional activity of p53 in response to doxorubicin (Lanni et al., 2010a). Furthermore, MT2A expression was found upregulated in fibroblasts from AD patients and zinc supplementation strongly reduced unfolded conformation of p53 in these cells (Lanni et al., 2010a). In addition, zinc treatment also restored DNA binding activity of HIPK2 (Lanni et al., 2010a). Altogether, this strongly suggests that Aβ-induced HIPK2 degradation is responsible for compromised p53 folding and decreased vulnerability to noxious stimulus, presumably via MT2A-dependent mechanism. Aβ/HIPK2/MT2A/p53 pathway is activated before initiation of the amyloidogenic cascade, and as a result of this activation, affected cells are unable to properly activate apoptotic signaling. Thus,

compromised p53 function following exposure to a noxious stimulus may contribute to the prolonged survival of injured dysfunctional cells (Lanni et al., 2010a). As will be explained later, postponed death is a characteristic of dying neurons in AD.

However, toxic exposure to micromolar concentrations of oligomeric Aβ42 may lead to neuronal death within 24 hours, via p53-dependent and p53-independent upregulation of PUMA (Akhter et al., 2014). The authors proposed that in rat cortical neurons Aβ triggers p53 activation that induces PUMA. Aβ also inhibits phosphatidylinositol-3-kinase (PI-3K/Akt) pathway that further leads to activation of Forkhead transcription factor FoxO3a. FoxO3a then translocates to the nucleus and directly induces expression of PUMA. In cooperation with Bim, another BH3-only protein, PUMA finally carries out the death cascade in response to Aβ42. Therefore, it seems that both p53 and FoxO3a participate in the regulation of PUMA expression following Aβ exposure (Figure 5; Akhter et al., 2014).

In the presence of stress stimuli, p53 phosphorylation at Ser15 leads to its stabilization by preventing interaction with Mdm2. This phosphorylation step is mediated by kinases ERK1/2 and p38 (She et al., 2000). Human post-mortem tissue from AD patients has elevated levels of phosphorylated p38 (pp38) immunoreactivity, particularly in the hippocampal formation. Enhanced pp38 was mainly found in neurons bearing early neurofibrillary pathology, but not in typical fibrillary tangles and senile plaques, and most pp38-labeled neurons contained only a small amount of phospho-tau (Sun et al., 2003). As p53 is a substrate of pp38 (She et al., 2000), it is possible that enhanced phosphorylation of p38 may result in changed pattern of p53 phosphorylation and affect its functioning. In addition to p53, p38 also phosphorylates tau and GSK-3β, and contributes to neuroinflammation, indicating that targeting p38 pathway might be a separate, but p53-associated approach with promising potential in the prevention and/or treatment of AD-related pathological processes (Munoz and Ammit, 2010; Lee and Kim, 2017). Furthermore, ceramide signalling via JNK, ERK and p38 MAPK cascades ultimately induces neuronal death through caspase-3 activation and upregulation of death-related genes, including p53 (Willaime et al., 2001; Stoica et al., 2005).

Ceramides are the major molecules of sphingolipid metabolism and important lipid second messengers implicated in AD susceptibility and progression. They are increased in AD brains and they affect both Aβ generation and tau deposits (Fillipov et al., 2012; Mielke et al., 2012; Jazvinšćak Jembrek et al., 2015).

2.4. Effects of p53 on tau pathology and GSK-3β activity

As evidenced in HEK293A cells, p53 may induce tau phosphorylation at the Ser199/Ser202/Thr205 epitopes. The effects of p53 on tau phosphorylation are probably indirect as tau and p53 are predominantly expressed in different cellular compartments. Accordingly, increase in tau phosphorylation is attributed to the transcription of p53 target genes or kinase(s) downstream in p53 signalling (Ferreira and Kosik, 1996; Hooper et al., 2007). Similarly, another member of p53 family, TAp73α, also promotes phosphorylation of human 2N4R tau in HEK293A cells via its transcriptional activity (Hooper et al., 2006). However, p73 is essential for preventing neurodegeneration (Killick et al., 2011). Haploinsufficiency for p73 leads to behavioural and anatomical changes characteristic for age-related neurodegeneration, and induces accumulation of phospho-tau-positive filaments, probably by inducing JNK activation, whereas p73 reduction in mice with amyloid pathology speeds up formation of NFT and neuronal death (Wetzel et al., 2008). It was proposed that ΔNp73 protects neurons against tau hyperphosphorylation and Aβ-induced neurofibrillary degeneration, and preserves cognitive functioning (Mattson and Ashery, 2009; Benosman et al., 2011). The predicted mechanisms by which ΔNp73 protects neurons includes antagonizing pro-apoptotic p53 function, and suppression of intracellular JNK signalling (Lee et al., 2004; Wetzel et al., 2008; Mattson and Ashery, 2009). Yet, it should be mentioned that another study failed to support p73 as a contributor to AD pathogenesis in the same animal model (Vardarajan et al., 2013).

An open question related to neuronal death in AD is that despite the high levels of p53 and enriched environment in proapoptotic stimuli (such as Aβ and oxidative stress), most of the

neurons do not commit apoptotic suicide, but instead go through a prolonged neurodegenerative process that continues over years (Wang and Liu, 2008). As a potential explanation for apoptotic resistance, it was found that PP2A inhibitor I_2^{PP2A} regulates p53 and Akt activities. A coordinated upregulation of all three proteins has been observed in a transgenic mouse model of AD (tg2576 mice) and AD patients. Liu and co-workers (2012a) have shown that overexpressed I_2^{PP2A} induces activation of Akt, but upregulated Akt in turn counteracts cell apoptosis induced by I_2^{PP2A}-dependent upregulation of p53. Thus, although the potential for promoting apoptotic events exists due to elevated I_2^{PP2A} and upregulation of p53, simultaneous activation of Akt aborts initiation of apoptotic pathways (Liu et al., 2012a).

It is likewise possible that tau phosphorylation itself renders neuronal cells more resistant to apoptotic death and prone to prolonged neurodegeneration. One of the proposed mechanisms of neuroprotective effect of tau phosphorylation is related to prevention of oxidative damage. It is assumed that NFTs function as a primary line of antioxidant defence by protecting cellular components from ROS attack (Smith et al., 2002; Wang and Liu, 2008). Yet another mechanism of hyperphosphorylated tau-related resistance to apoptosis was demonstrated in neuroblastoma N2a cells with GSK-3 overexpression, and was related to decreased phosphorylation of β-catenin (Li et al., 2007). β-Catenin is a phosphoprotein involved in Wnt signalling and is phosphorylated by GSK-3β (Wu and Pan, 2010; Vallée and Lecarpentier, 2016). Unphosphorylated β-catenin is more stable and can be translocated into nuclei where it supports neuronal survival. Thus, the anti-apoptotic function of tau hyperphosphorylation was assigned to the competitive inhibition of β-catenin phosphorylation by GSK-3β and consequential facilitation of β-catenin pro-survival function (Li et al., 2007). In N2a cells and in tau transgenic mouse model (*Mapt*$^{tm1(EGFP)Klt}$ Tg(MAPT)8cPdav/J, htau), overexpression of tau without exogenous activation of kinases also conferred increased resistance to chemically-induced apoptosis (Wang et al., 2010). In that study, overexpression of tau resulted in lower constitutive expression of p53 and its decreased phosphorylation, reduced cytochrome c release and inhibition of caspase-9 and caspase-3, as well as reduced phosphorylation and

increased expression and nuclear translocation of β-catenin. Thus, the anti-apoptotic effect of tau overexpression *per se* was explained by a mechanism that involves both β-catenin and p53 pathways. It is proposed that tau spontaneously induces activation of endogenous kinase(s), likely Cdk-5 and GSK-3β, that antagonize phosphorylation of p53 at Ser33 (phosphorylation at Ser33 increases p53 stability and apoptotic outcome) and therefore prevent the downstream activation of p53-driven pro-apoptotic elements (Wang et al., 2010). Besides enhanced activation of p53, DNA damage induces large and prolonged increase in the activity of GSK-3β. For example, camptothecin and etoposide treatment of human neuroblastoma SH-SY5Y cells provoked increase in p53 levels together with prominent increase of GSK-3β activity (Watcharasit et al., 2002). These authors found that GSK-3β activation was achieved by a phosphorylation-independent mechanism (without changes in GSK-3β phosphorylation) that involves direct binding of p53 to GSK-3β (Watcharasit et al., 2002). However, not only was nuclear GSK-3β activated by association with p53, but activated GSK-3β contributed substantially to the transcriptional and mitochondrial activities induced by p53. The regulatory role of GSK-3β on the transcriptional action of p53 in the nucleus was demonstrated by large reductions of p53-induced increases in the levels of p53 target genes Mdm2, p21, and Bax after lithium-induced GSK-3β inhibition (Watcharasit et al., 2003). Regarding the influence on the mitochondrial p53 apoptotic signalling, GSK-3β inhibition prevented cytochrome *c* release and activation of caspase-3. It is interesting that p53 regulates its own interactions with GSK-3β. Two domains of p53 have been identified that regulate binding to GSK-3β. Taken together, these findings confirm that these two proteins cooperate as partners in regulating cellular response to DNA damage. Upon DNA damage, p53 has higher expression and regulates the actions of GSK-3β whereas GSK3β, in turn, stimulates the activity of p53 (Figure 6; Watcharasit et al., 2003). GSK-3 also controls p53 abundance and activity via Mdm2 phosphorylation. Namely, phosphorylation of Mdm2 by GSK-3 is required for proteosomal degradation of p53, and inhibition of GSK-3 prevents Mdm2-dependent p53 degradation (Kulikov et al., 2005). A stochastic simulation model also indicated that when cells are stressed, the Mdm2/p53 complex is disrupted, and GSK-3β/p53

complex is formed (Proctor and Gray, 2010). The model further anticipates that increased transcriptional activity of p53 and increased kinase activity of GSK-3β lead to increased Aβ production and tau phosphorylation. Accordingly, under normal conditions Aβ is cleared from cells, tau is dephosphorylated, and DNA damage repaired. If deficiency in DNA repair is present and DNA damage persists, the aggregates are much more likely to accumulate that in turn results in increased ROS production and further DNA damage, stimulating further activation of p53 and GSK-3β and even more aggregation (Proctor and Grey, 2010).

Figure 6

Elevated p53 also may contribute to tau pathology by transcriptional control of specific genes. One of these genes is the bridging integrator 1 (*BIN1*) gene, the second most important risk locus for late onset AD (Harold et al., 2009; Lambert et al., 2009; Seshadri et al., 2010). Bin1 participates in various AD-related cellular processes such as calcium homeostasis, clathrin-mediated endocytosis and endocytic recycling, inflammation and apoptosis, but primarily affects AD by modulating tau pathology (Wigge et al., 1997; Tan et al., 2013; Holler et al., 2014). In AD, the level of Bin1 protein inversely correlates with the levels of total tau, phosphorylated tau, the amount of NFT pathology and tau pathology propagation, atrophy of hippocampus, and glucose metabolism, but not with Aβ deposition (Holler et al., 2014; Wang et al., 2016). In more advanced Braak and Braak stages (BBIV-V), a significant increase in the percentage of CA1 pyramidal neurons with BIN1 cytoplasmic immunoreactivity was found together with negative correlation between BIN1 immunoreactivity in neuropil areas and NFT burden (Adams et al., 2016). The decreased expression of Bin1 protein is not related exclusively to AD, but also to the development of tau-mediated neurodegeneration in other models of tauopathies (De Jesús-Cortés et al., 2012). At the transcriptional level, the total Bin1 mRNA is upregulated in the AD brain. In particular, expression of smaller isoforms is elevated but the amount of the largest neuron-specific isoform 1 is significantly reduced (Holler et al., 2014). The decreased levels of Bin1 promote propagation of tau pathology within synaptically connected neuronal circuits by overactivating GTPase Rab5, and by increasing endocytotic flux and endosomal trafficking (Calafate et al., 2016). Most importantly, in human post-

mortem frontal cortex it was demonstrated that p53 binds the promoter and the first intron of the human *BIN1* gene supporting the notion that p53 may play a critical role in AD by regulating genes involved in tau pathology and progression (Merlo et al., 2014).

Recently, it was reported that AD patients have reduced levels of SIRT6, a histone deacetylase that promotes DNA repair (Jung et al., 2016; Kaluski et al., 2017). p53 directly binds the SIRT6 promoter and regulates SIRT6 expression (Zhang et al., 2014a). In primary mouse cortical neurons and HT22 mouse hippocampal cells which possess functional cholinergic markers and are used to improve our understanding of mechanisms involved in cognitive decline (Liu et al., 2009), Aβ decreased expression of SIRT6, whereas p53 upregulation by Nutlin-3, a selective small molecule Mdm2 antagonist, prevented SIRT6 decrease and Aβ-induced DNA damage (Jung et al., 2016). Likewise, in the mouse brain, decrease in SIRT6 expression increased DNA damage and toxic tau phosphorylation, promoted neuronal death and induced behavioural defects. SIRT6 also regulates tau stability by affecting its proteosomal degradation, and by increasing activity of GSK-3α/β that promotes tau phosphorylation. Taken together, it seems that SIRT6 is important for maintaining genomic stability of the brain and that its depletion results in toxic tau stability and phosphorylation (Kaluski et al., 2017). Hence, p53-regulated SIRT6 could represent a novel tau target for therapeutic intervention in AD and age-related neurodegeneration.

2.5. Role of AICD in p53 expression

As previously mentioned, p53 expression is partly regulated by transcriptionally active APP-derived AICD fragments and AICD overexpression may facilitate neurodegeneration (Passer et al., 2000; Alves da Costa et al., 2006; Chow et al., 2010; Dislich and Lichtenthaler, 2012; Pardossi-Piquard and Checler, 2012). AICD overexpression increases both transactivation of p53 promoter and p53 activity. This further induces an increase in caspase-3 activity that could be abolished by the p53 inhibitor pifithrin-α. In fact, cotransfection with AICD, Fe65, and Tip60 has been associated with a drastic increase in total and pifithrin-α-sensitive caspase-3 activity (Alves da Costa et al.,

2006). AICD transfection also increases the number of apoptotic cells, with an additional increase in the presence of Fe65 and Tip60. Alves da Costa and coworkers (2006) also found that in sporadic AD the level of insulin-degradying enzyme (IDE) that catabolizes AICD was significantly reduced. As IDE levels were not decreased in patients with familial AD, they proposed that reduced degradation of AICD contributes to enhanced p53 expression in idiopathic AD. Similar to AICD, overexpressed Aβ42 also may directly bind to and activate the p53 promoter leading to p53-dependent apoptosis of neuronal cells. Of note, nuclear accumulation of Aβ42 with sequential enhancement of p53 mRNA and activation of p53 cascade can be induced by exposure to the oxidizing agent hydrogen peroxide (Ohyagi et al., 2005).

To accomplish its role, AICD binds to internal ribosome entry site (IRES) structures on the translating p53 mRNA. In particular, it has been shown that AICD regulates translation of Δ40p53 (p44), a short isoform of the p53, through a mechanism that requires direct binding to the second IRES of the p53 mRNA (Li et al., 2015). With respect to AD, the levels of Δ40p53 increase during aging (Pehar et al., 2014). Overexpression of Δ40p53 resemble to an accelerated form of aging characterized by premature cognitive decline, synaptic defects, exacerbated tau phosphorylation and reduced lifespan. This shortened isoform binds to promoters of various tau kinases (including GSK-3β) and activates their transcription, which ultimately enhances tau phosphorylation. Based on these findings, it is suggested that a misbalance in the p53/p44 ratio might promote altered tau metabolism and cognitive decline that characterizes aging (Pehar et al., 2010; Pehar et al., 2014).

The AICD phosphorylation at Thr668, specifically observed in the brain, is essential for its nuclear translocation and transcriptional function (Chang et al., 2006). The phosphorylation is mediated by several kinases, including GSK-3β, and facilitates BACE1 cleavage of APP (Lee et al., 2003). In differentiated PC12 cells and rat primary cortical neurons AICD fragments exert neurotoxic effects by a mechanism that involves increase in the expression of GSK-3β and downstream upregulation of tau phosphorylation, together with the activation of apoptotic cascade (Chang et al., 2006). AICD-overexpressing transgenic mice also show abnormal activation of

GSK-3β and characteristic AD-like pathology, including hyperphosphorylation and age-dependent aggregation of tau, neurodegeneration, and working memory impairment (Ghosal et al., 2009), although this was not confirmed in a similar study on AICD transgenic mice crossed with hTau mice (Giliberto et al., 2010).

Expression of APP770 and Swedish mutant form of APP also increases AICD levels in the nucleus and upregulates GSK-3β at transcriptional and translational levels (Kim et al., 2003). On the contrary, decrease in APP processing via inhibition of the β-secretase cleavage site reduces active form of GSK-3β and p53 levels in a triple transgenic mouse model of AD (Rabinovich-Nikitin and Solomon, 2014). Finally, as increase in AICD generation leads to an increase in both p53 expression and tau hyperphosphorylation (Figure 6), inhibition of the amyloidogenic pathway that ultimately reduces AICD and p53 levels may represent another potential treatment strategy for AD.

2.6. Natural compounds targeting p53 pathway: a promising approach for AD therapy?

As the world's population is getting older, AD is recognized as one of the major health care issues. Tremendous efforts are put forward to improve current therapeutic options that rely principally on acetylcholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonist memantine (Neugroschl and Sano, 2010; Götz et al., 2012). Unfortunately, these drugs only alleviate symptoms of the disease, and do not prevent or slow down its progression. As mentioned previously, for many years, the main target of novel pharmacotherapies was based on the amyloidogenic hypothesis, with two major approaches being reduction of Aβ generation and clearance of existing Aβ plaques (Folch et al., 2016), but the outcome was overall disappointing. Considering the therapeutic potential of γ-secretase inhibitors for alleviating AD, it is shown that they could affect p53 and lead to tumorigenicity. For example, genetic suppression of Notch signalling (Notch gene is p53 target) in primary human keratinocytes was sufficient to induce formation of squamous cell carcinoma (Lefort et al., 2007). With respect to pharmacological manipulation of tau pathology, various approaches are under investigation, including agents that

act as microtubule stabilizers, inhibitors of tau kinases, inhibitors of tau acetylation, and antibody-based immunotherapies (Mondragón-Rodríguez et al., 2012; Panza et al., 2016). Other therapeutic strategies target enhancement of mitochondrial function, serotonin receptors, nerve growth factors, as well as other approaches (Neugroschl and Sano, 2010).

The potential of targeting p53 for the prevention or cure of AD is only partially explored. As p53 is critically involved in neuronal death in several experimental settings and is related to pathological processes in neurodegenerative diseases, it has been suggested that p53 inhibitors might represent a promising approach for several neurodegenerative conditions (Culmsee and Mattson, 2005; Chang et al., 2012). Molecules that prevent activation of p53-dependent apoptotic cascade potentially may prolong neuronal survival and protect neurons against apoptotic stimuli. There is ample evidence that p53 depletion prevents neuronal death. Thus, pifithrin-α, a synthetic inhibitor of transcription-dependent p53 activity, was effective against neuronal death induced by DNA-damaging agents, Aβ and glutamate. The neuroprotection was due to decreased p53 DNA-binding activity, reduced expression of Bax and inhibition of caspase activation, and prevention of mitochondrial dysfunction. Similarly, neurons from mice given pifithrin-α were more resistant to focal ischemic injury and excitotoxic damage suggesting that agents that inhibit p53 may attenuate the severity of neuronal injury in neurodegenerative conditions (Culmsee et al., 2001). Addition of pifithrin-α or expression of a dominant-negative p53 also reduced kainate-triggered excitotoxic death, together with the prevention of mitochondrial changes and dendrite degeneration (Neema et al., 2005). Similarly, neurodegeneration after traumatic brain injury was significantly reduced by pifithrin-α. Inhibition of p53 activity was accompanied with the simultaneous increase in NF-κB transcriptional activity and enhanced expression of NF-κB downstream targets within a therapeutic window relevant for clinical applications (Plesnila et al., 2007).

Natural compounds targeting p53 pathway are also of great interest in neuroprotection as they may represent promising therapeutic strategy against AD (Nakanishi et al., 2015). Some studies have suggested that dietary phytochemicals, such as flavonoids, may be neuroprotective

(Vauzour et al., 2008; Nehlig 2013; Davinelli et al., 2016). Although direct evidence is lacking and further research is required, results of some studies indicate that targeting p53 pathways by natural compounds might be promising approach in neuroprotection. Thus, in PC12 cells injured by oxygen–glucose deprivation, protosappanin B, a bioactive dibenzoxocin derivative isolated from *Caesalpinia sappan* L., exerted the neuroprotective effects. Protosappanin B prevented apoptosis-related events, stimulated the expression of GAP-43, and promoted degradation of p53 protein via activation of a Mdm2-dependent ubiquitination process (Zeng et al., 2015). Another interesting compound is osmotin, a plant protein extracted from *Nicotiana tabacum*. Its intraperitoneal application alleviated Aβ42-induced tau hyperphosphorylation by regulating the aberrant phosphorylation of PI-3K, Akt and GSK-3β, ultimately preventing Aβ42-promoted and p53-mediated activation of apoptotic pathways, neurodegeneration, synaptic dysfunction and memory impairment in wild type C57BL/6J mice (Ali et al., 2015).

In recent years, ginseng (an herb commonly used in traditional Chinese medicine) has attracted much attention for its potential in improving cognitive functions (Shi et al., 2010; Liu et al., 2012b; Qiu et al., 2014). Ginsenoside Rh2 (G-Rh2), a saponin isolated from the root of ginseng, was able to attenuate Aβ-induced cytotoxicity in rat brain astrocytes (Shieh et al., 2008). When G-Rh2 was injected into tg2576 AD model mice, it reversed behavioural defects, improved learning and memory performance, and reduced formation of senile plaques at 14 months of age (Qiu et al., 2014). Furthermore, in primary hippocampal neurons, G-Rh2 increased soluble APPα (sAPPα) levels, inhibited APP endocytosis and reduced secretion of Aβ40 and Aβ42 by reducing cholesterol and lipid raft concentrations (Qiu et al., 2014). Likewise, ginsenoside Rg1 (G-Rg1) improved spatial learning and memory capacity in rat model of AD. G-Rg1 also reduced BACE1 level and apoptosis (Zhang et al., 2012). However, evidence of the neuroprotective mechanism that relate ginsenosides and p53 in AD is still lacking. Caution is required as G-Rh2 induces the activation of caspase-8 in human cancer cells in p53-dependent manner (Guo et al., 2014). Of note, caspase-8, the initiator

caspase of the death receptor-mediated apoptotic pathway, leads to the activation of caspase-3 within neurons of the AD brain (Rohn et al., 2001; Bredesen 2009).

Thymoquinone is yet another natural compound with promising potential in AD treatment. It can be found in black seed (*Nigella sativa* seed), and similarly to ginsenosides, acts as chemopreventive agent via induction of p53 and p53-downstream targets (Gali-Muhtasib et al., 2004). Thymoquinone reduced oxidative stress and mitochondrial dysfunction in differentiated PC12 cells exposed to Aβ25-35 (Khan et al., 2012), and in cultured hippocampal and neocortical rat neurons exposed to Aβ42, together with inhibition of Aβ42 aggregation (Alhebshi et al., 2013). Neuroprotective effects of honokiol and magnolol from *Magnolia officinalis* were also observed in PC12 cells. They decreased Aβ-induced cell death by inhibition of caspase-3 activity (Hoi et al., 2010). Δ^9-tetrahydrocannabinol (THC), the active component of *Cannabis sativa*, also exerts interesting effects. At extremely low concentrations, it lowered Aβ levels in N2a/AβPPswe cells via direct interactions (thereby inhibiting aggregation), and depleted total and phosphorylated GSK-3β levels without evident cytotoxicity (Cao et al., 2014). Although studies targeting the relationship between THC, Aβ and p53 are missing, it was shown that endocannabinoids prevent Aβ-mediated upregulation of p-p53$^{Ser\text{-}15}$ and association of p-p53$^{Ser\text{-}15}$ with the lysosomes (Noonan et al., 2010).

Finally, accumulating cell culture and animal model data indicate that dietary curcumin, a curcuminoid of turmeric (*Curcuma longa*) from the ginger family, is a strong candidate for use in the prevention or treatment of AD (Cole et al., 2007; Venigalla et al., 2015). In the brain of AD animal models curcumin inhibits Aβ deposition and oligomerization, reduces tau phosphorylation, improves behavioural impairments, and alleviates cognitive deficits (Yang et al., 2005; Ma et al., 2009; Hamaguchi et al., 2010). Curcumin also possess strong antioxidant, metal-chelating and anti-inflammatory properties that contribute to beneficial effects of curcumin (Baum and Ng, 2004). In SH-SY5Y cells overexpressing APPswe curcumin upregulated PI-3K/Akt/NF-E2-related factor-2 (Nrf2) pathway, and decreased ROS content and Aβ expression (Yin et al., 2012). It also may decrease expression of GSK-3β at the mRNA and protein levels, activate pro-survival Wnt/β-catenin signalling

and attenuate Aβ-induced tau hyperphosphorylation (Zhang et al., 2011; Huang et al., 2014). Curcumin has already been included in clinical trials, which revealed outstanding safety profile of curcumin (Gupta et al., 2013). However, clinical or biochemical evidence of curcumin efficacy against mild-to-moderate AD were limited, probably due to poor bioavailability and absorption (Hamaguchi et al., 2010; Ringman et al., 2012; Goozee et al., 2016). Fortunately, extensive research on curcumin found some potential ways to overcome these delivery problems that hopefully will enable identification of prophylactic and therapeutic potential of curcumin in future studies (Prasad et al., 2014). Again, caution is required as curcumin may dephosphorylate Akt and prevent its downstream inactivation of GSK-3β, inhibit PP2A and induce cytochrome c release and caspase-3 activation in p53-dependent manner in tumour cells (Hussain et al., 2006; Liu et al. 2007).

3. Conclusions

Despite much research efforts and scientific progress over the past few decades, molecular mechanisms underlying neurodegenerative diseases, including AD, still remains a challenge in many ways, which has been a hurdle to accelerate the development of effective and safe therapeutic approaches. A substantial body of evidence points to the fact that targeting p53, or targeting amyloidogenic pathway resulting in AICD reduction and p53 decrease, could be a promising therapeutic approach as it is a major player in influencing many pathological processes. The p53 protein exerts diverse biological functions and generates structurally and functionally different isoforms whose roles are further modulated by numerous posttranslational modifications. The role of these different isoforms in AD pathology is still not revealed. The existence of a functional link between p53 and Aβ- and tau-related pathology appears to be likely in AD. Although evidence *in vitro* is promising, studies *in vivo* are needed to strengthen and support the potential of p53 targeting for translation into the clinic. p53 is one of the most studied proteins but its intracellular pathways and activities are still not fully elucidated, particularly in neuronal cells where p53 assumes different roles compared to other cell type, probably as a result of the permanent post-

mitotic nature of neurons. Encouraging results indicate that modulation of intracellular pathways impacted by p53 is a realistic approach in AD. The further investigation of the interactions of p53 with tau and Aβ might help in the development of p53-based therapeutics that will act as disease-modifying agents and bring novel therapeutic options for AD patients.

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Figure legends

Figure 1: **Contribution of ApoE4 isoform to Aβ and tau pathology**. In comparison to its other two isoforms, ApoE4 is related to enhanced accumulation of soluble oligomeric forms of Aβ that impairs synaptic functioning, triggers apoptotic cascade and promote tau pathology through various mechanisms as it increases the likelihood of GSK-3β-mediated tau hyperphosphorylation.

Figure 2. **Downstream effects of Aβ on tau pathology**. Through various mechanisms Aβ oligomers promote tau pathology in AD. Aβ-induced inhibition of PI-3K/Akt and Wnt signalling, ER stress, enhanced expression of RCAN1 and decrease in sirtuins contribute to enhanced GSK-3β activation and promote tau phosphorylation. In addition, RCAN1 contributes to tau pathology by inhibiting phosphatase calcineurin.

Figure 3**. p53-dependent mechanisms affecting neuronal survival and death**. p53 exerts transcription-dependent and transcription-independent activities in neurons. In the nucleus, it binds to target DNA sequences and promotes or represses expression of genes that mediate its functions. Some of p53-target genes are involved in synaptic functioning and regulation of neurite outgrowth and axonal regeneration, indicating a potential neuroprotective role of p53. The pro-death mode of p53 requires transcriptional activation of p53-upregulated modulator of apoptosis (PUMA) that triggers Bax-dependent cell death. Transcription-independent apoptotic pathways include a direct p53 interaction with Bax that likewise ends in neuronal death.

Figure 4. **Regulation of p53 expression**. In physiological conditions, p53 expression is kept at low levels by its negative regulator Mdm2. During oxidative stress, p53 undergoes posttranslational modifications that promote its apoptotic activities. HIPK2 phosphorylates p53 at Ser46, which stabilizes p53 and enhances transcriptional activities towards repression of anti-apoptotic and

activation of pro-apoptotic targets. These include proteins PUMA and Bax whose increased expression drives cells into detrimental apoptotic cascade.

Figure 5. **Aβ-mediated effects on neuronal survival via p53 signalling**. Very low concentrations of soluble Aβ may promote misfolded p53 conformation that induces increased resistance to oxidative stress. This effect is mediated by kinase HIPK2 that in physiological conditions ensures conformational stability of p53 and promotes its apoptotic action. However, small Aβ amounts induce HIPK2 depletion and increase in metallothionein 2A (MT2A), resulting in p53 protein misfolding and subsequent abolishment of transcriptional p53 activity. When present in higher amounts, Aβ peptides promote direct transcriptional activation of p53 and FOXO3a (through PI-3K/Akt inhibition) that enhances PUMA expression and leads to neuronal death via apoptotic machinery.

Figure 6. **Cooperation of p53, tau and Aβ in AD pathology**. p53 and GSK-3β cooperate as partners in regulating cellular response to DNA damage. When the levels of p53 are elevated, it regulates GSK-3β, whereas GSK-3β, in turn, stimulates transcriptional and mitochondrial p53 activities. In addition, GSK-3β regulates p53 activity via Mdm2 phosphorylation. If aggregates of Aβ are formed, this leads to increased ROS production and more DNA damage, stimulating further activation of p53 and GSK-3β. Furthermore, APP-derived AICD fragments directly stimulate p53 expression and promote GSK-3β activity, whereas GSK-3β by phosphorylating AICD ensures its trancriptional function.

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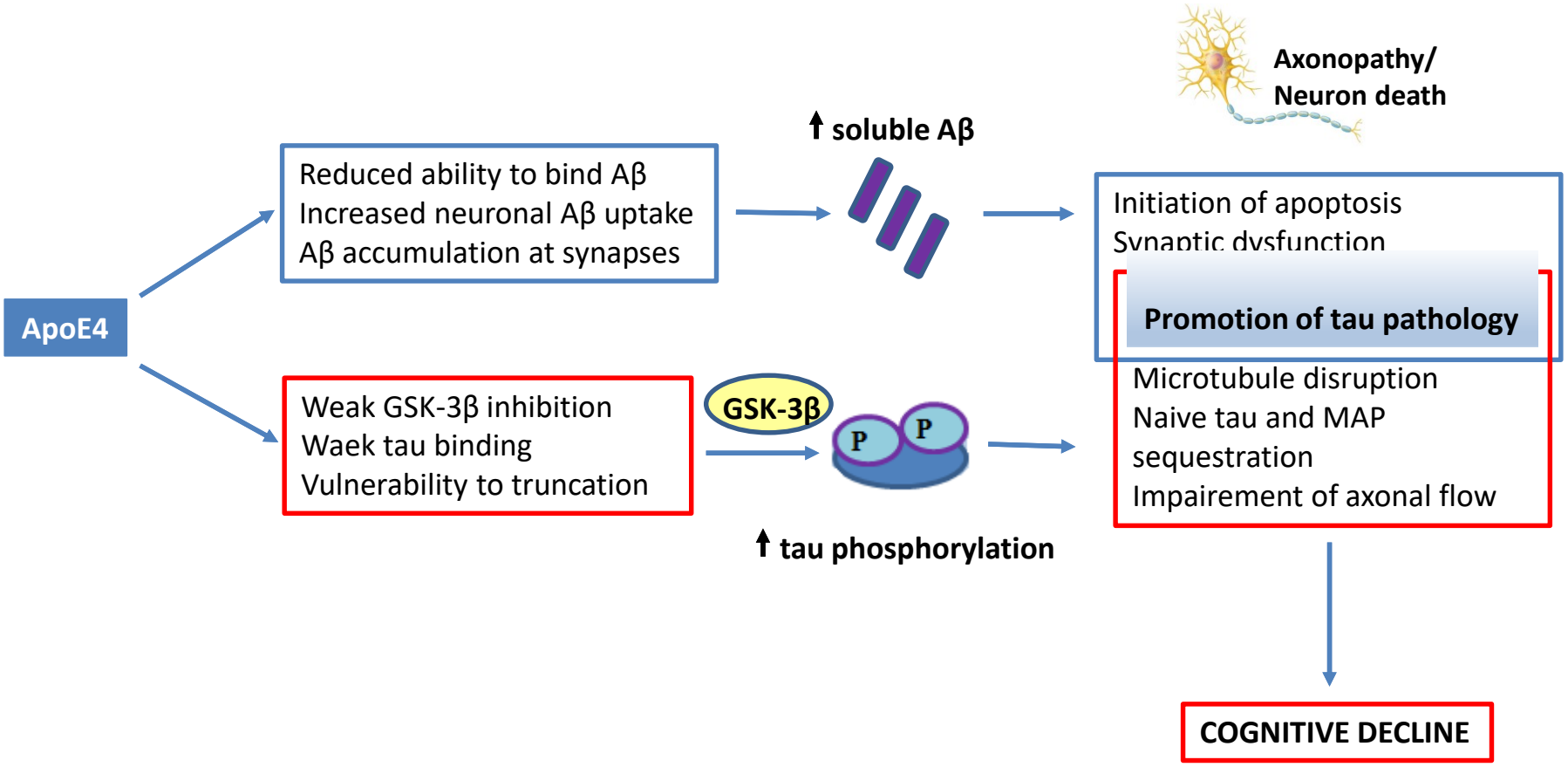

Figure 1

Jazvinšćak Jembrek et al. - Progress in Neurobiology - The interactions of p53 with tau and Aß represent potential therapeutic targets for Alzheimer's disease

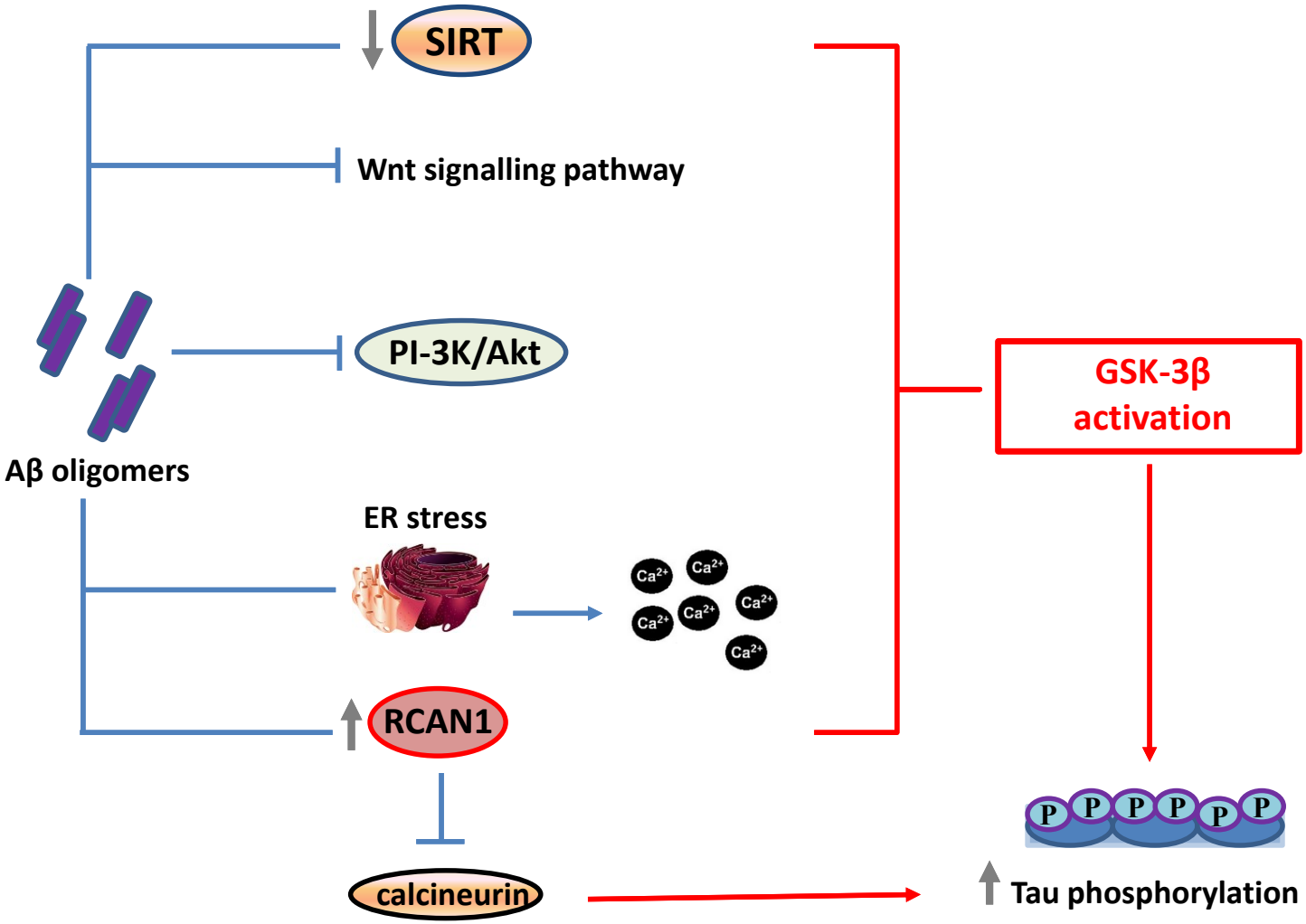

Figure 2
Jazvinšćak Jembrek et al. - Progress in Neurobiology - The interactions of p53 with tau and Aß represent potential therapeutic targets for Alzheimer's disease

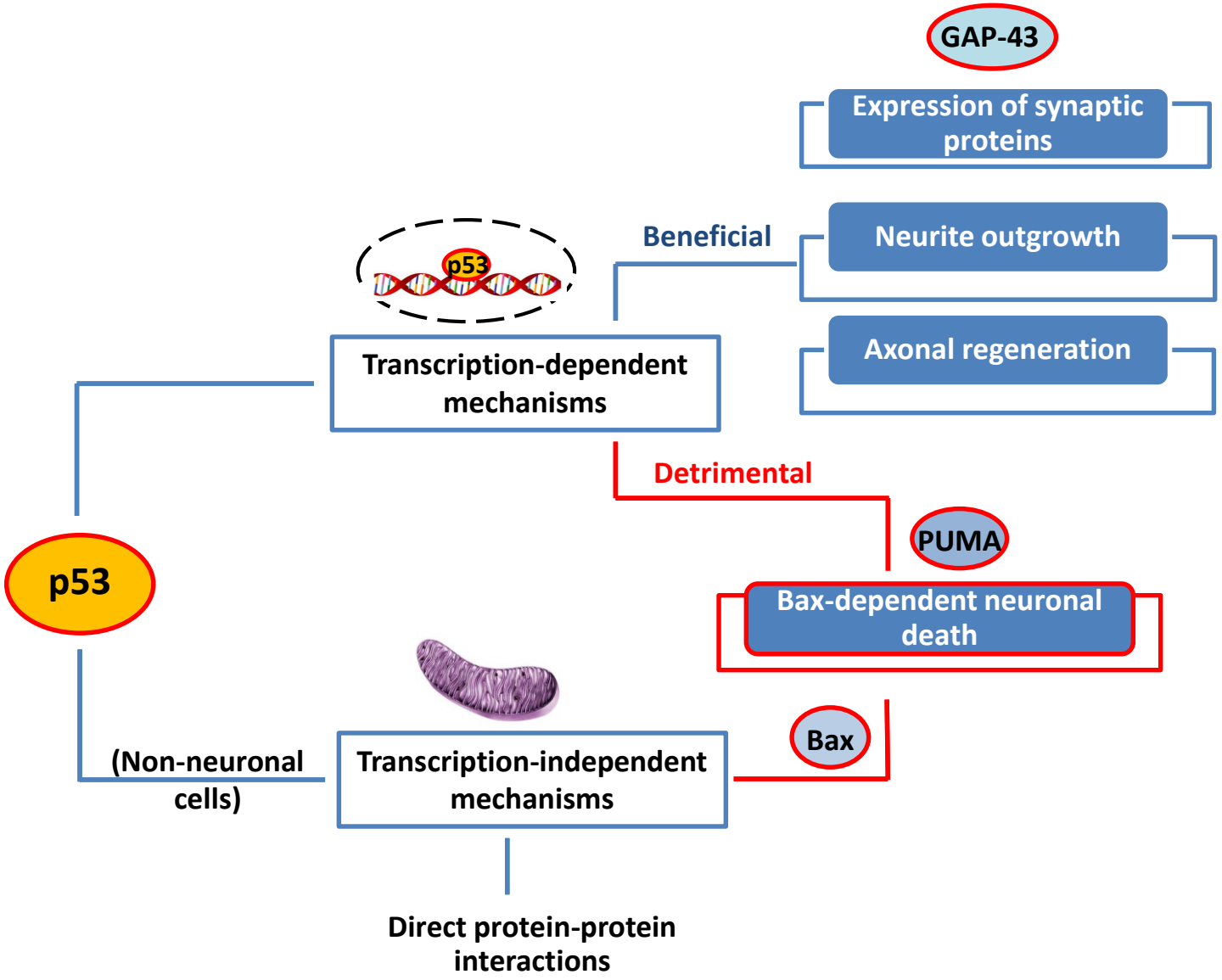

Figure 3
Jazvinšćak Jembrek et al. - Progress in Neurobiology - The interactions of p53 with tau and Aß represent potential therapeutic targets for Alzheimer's disease

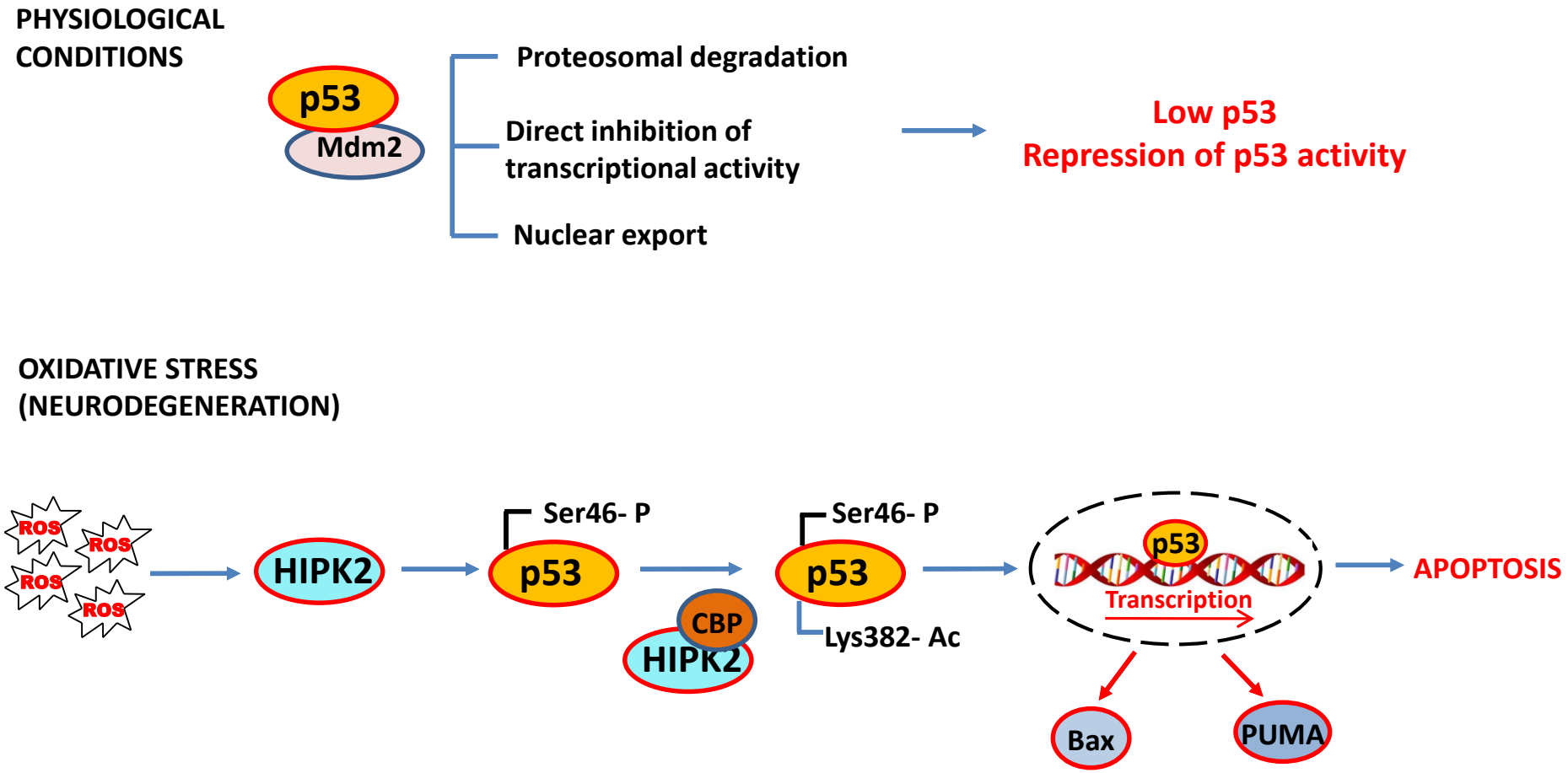

Figure 4

Jazvinšćak Jembrek et al. - Progress in Neurobiology - The interactions of p53 with tau and Aß represent potential therapeutic targets for Alzheimer's disease

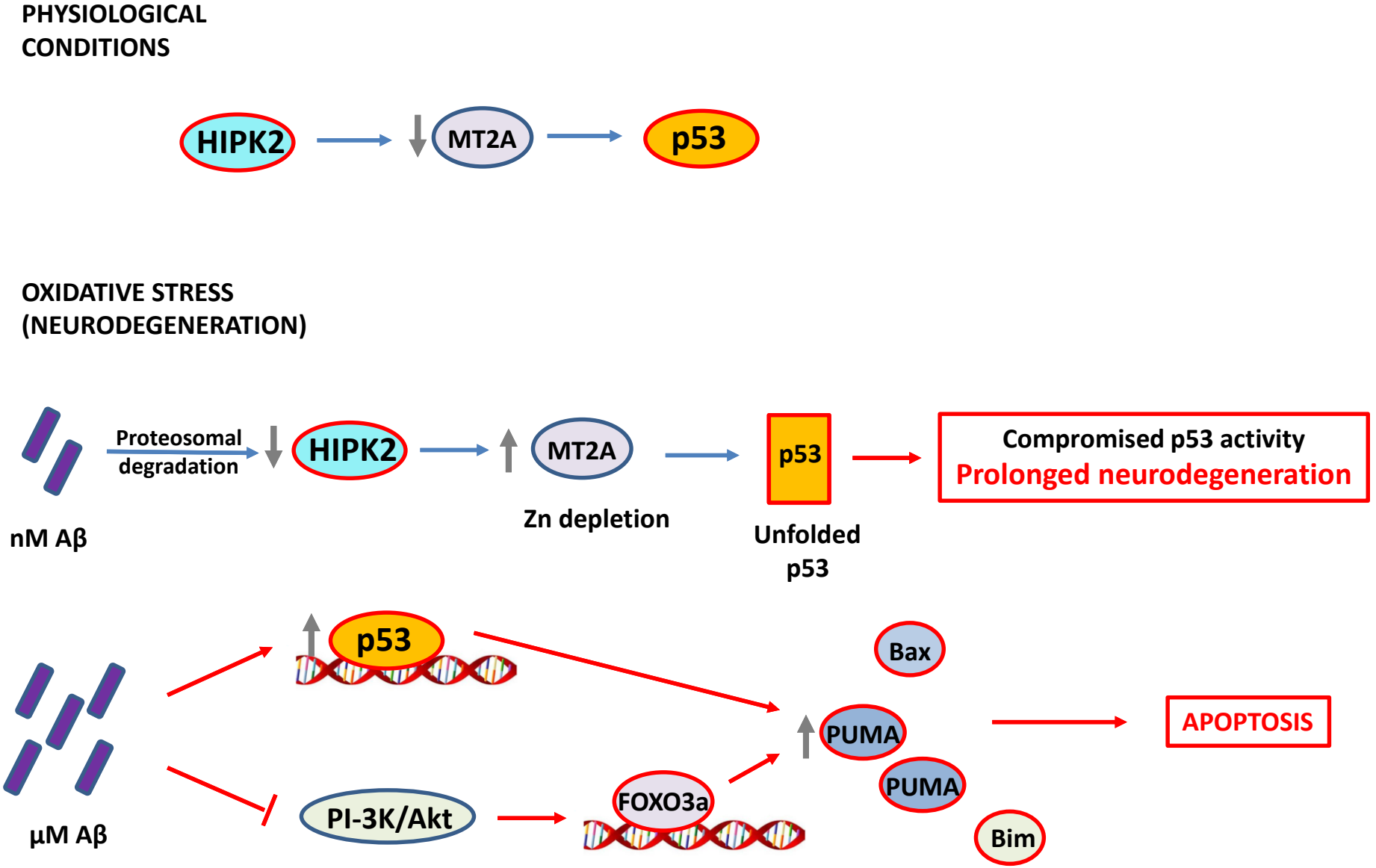

Figure 5

Jazvinšćak Jembrek et al. - Progress in Neurobiology - The interactions of p53 with tau and Aß represent potential therapeutic targets for Alzheimer's disease

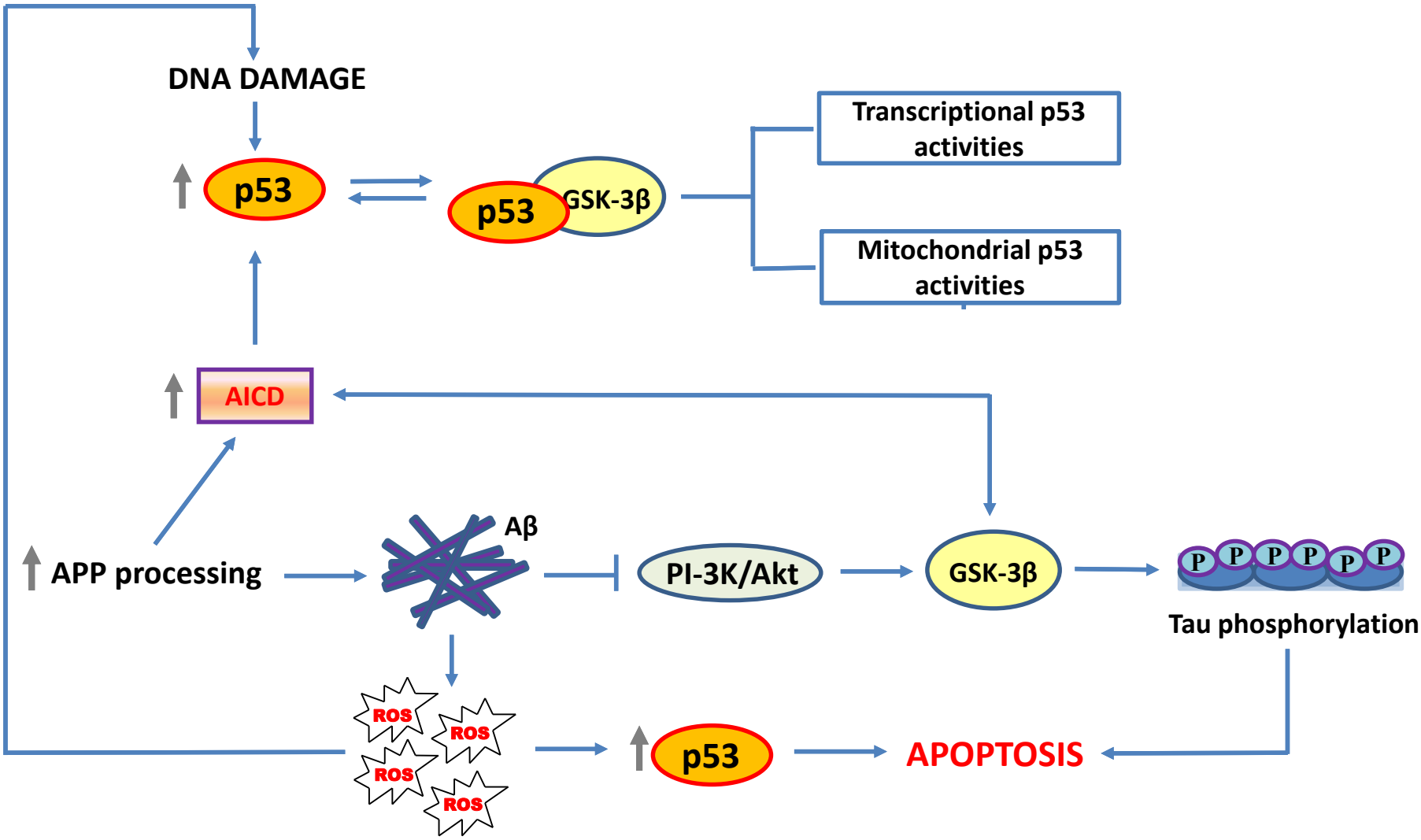

Figure 6

Jazvinšćak Jembrek et al. - Progress in Neurobiology - The interactions of p53 with tau and Aß represent potential therapeutic targets for Alzheimer's disease