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Amyloid-beta and tau protein beyond Alzheimer's disease

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Abstract

The aggregation of amyloid-beta peptide and tau protein dysregulation are implicated to play key roles in Alzheimer's disease pathogenesis and are considered the main pathological hallmarks of this devastating disease. Physiologically, these two proteins are produced and expressed within the normal human body. However, under pathological conditions, abnormal expression, post-translational modifications, conformational changes, and truncation can make these proteins prone to aggregation, triggering specific disease-related cascades. Recent studies have indicated associations between aberrant behavior of amyloid-beta and tau proteins and various neurological diseases, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, as well as retinal neurodegenerative diseases like Glaucoma and age-related macular degeneration. Additionally, these proteins have been linked to cardiovascular disease, cancer, traumatic brain injury, and diabetes, which are all leading causes of morbidity and mortality. In this comprehensive review, we provide an overview of the connections between amyloid-beta and tau proteins and a spectrum of disorders.

Key Words: amyloid-beta; cancer; cardiovascular diseases; diabetes; neurodegeneration; Tau; traumatic brain injury

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Introduction

Extracellular amyloid plaques or senile plaques composed of the amyloid-beta (A β) and intracellular neurofibrillary tangles (NFT) comprising phosphorylated tau protein are known as the main pathological hallmarks of Alzheimer's disease (AD) since the early 1900s when Alois Alzheimer first published his historical treatise that formally introduced the disease (Zilka and Novak, 2006; d'Errico and Meyer-Luehmann, 2020). While senile plaques and NFT are well-established pathological hallmarks of AD, the presence of one or both of these has also been reported in other diseases. In this review, we provide an overview of the physiological role of amyloid-beta and tau proteins, mechanisms underlying their accumulation, and pathogenesis in

diseases including cardiovascular diseases (CVD), cerebral amyloid angiopathy (CAA) and stroke, cancer, diabetes, retinal diseases, Parkinson's disease (PD), traumatic brain injury (TBI) In addition, we briefly discuss the role of A β and tau protein in other conditions such as Autism, multiple sclerosis (MS), motor neuron disease, Huntington's disease (HD), Creutzfeldt-Jakob disease (CJD) and Wilson's disease (WD) where dysregulation of these two proteins has been reported (Figure 1).

Search Strategy

We conducted a comprehensive literature search using various search engines, such as PubMed, Scopus, and Web of Science. The search was performed without any year restrictions, and we utilized keywords such as "amyloid-beta", "amyloid plaques", "senile plaques", "tau", and "neurofibrillary tangles". Additionally, we manually screened the references of selected studies to identify potentially relevant articles for inclusion in this narrative review. Only English-language documents were considered.

Amyloid- β Formation and Aggregation

A β refers to peptides with 36–43 amino acids that derive from amyloid- β precursor protein (A β PP, APP), APP is a single-pass transmembrane glycoprotein expressed in many tissues, especially in the brain in both neuronal and non-neuronal cells (Marsden et al., 2011; Chen et al., 2017). APP is located on chromosome 21q21.3 and belongs to a larger gene family in humans which has two other members including the APP-like protein-1 (APLP1) and the APP-like protein-2 (APLP2). APP and APLP2 are expressed in several tissues, while APLP1 expression is limited to neural tissue (Pandey et al., 2016; Chen et al., 2017). These members have similar structures and are processed in the same manner; however, the A β sequence, which is involved in senile plaques is specific to APP (Chitranshi et al., 2021). Differential mRNA splicing of exons 7, and 8 results in the expression of three isoforms including the 695 amino acid isoform, which is the main isoform in the brain, and 751 and 770 amino acid isoforms that are mainly expressed in peripheral cells and platelets (Figure 2). APP is first cleaved by α - or β -secretase, which starts two different pathways, named non-amyloidogenic and amyloidogenic pathways, respectively (Kojro and Fahrenholz, 2005; Sun et al., 2015). In a non-amyloidogenic pathway, cleavage by α -secretase results in the amino-terminal fragment named secreted APP α (sAPP α) and the 83 amino acid long carboxyterminal fragments (CTF83 or C83), then CTF83 subjected to γ -secretase cleavage that produced P3 (3 kDa) and amino-terminal APP

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intracellular domain; however, in the amyloidogenic pathway, β -secretase particularly β -secretase 1 (BACE1) cleavage liberates the amino-terminal fragment named secreted APP β (sAPP β) and the 99 amino acid long carboxyterminal fragment (CTF99 or C99) that produced A β (4 kDa) and APP intracellular domain following cleavage by γ -secretase (Figure 3; Kojro and Fahrenholz, 2005; Zhang et al., 2011). Generated A β has 39–43 amino acids but A β with 40 amino acids is relatively more abundant (Murphy and LeVine, 2010), while A β 42 is the predominant protein component in senile plaques probably due to faster aggregation of A β -42 compared to A β -40, and might be more toxic (Meisl et al., 2014; Wang et al., 2021). Several factors, including aging, inflammation, renal dysfunction, ischemia, genetic polymorphisms, and drugs, increase tissue deposition of A β by augmenting APP production or by decreasing A β clearance and degradation (Mawuenyega et al., 2010; Sadigh-Eteghad et al., 2015; Abyadeh et al., 2023a).

Senile plaque formation is a four-step process including (1) primary nucleation, where A β monomers interact with each other molecules (lipids, alpha-synuclein) and form small soluble aggregates also called oligomers that are highly toxic and suggested to play a main role in cell and tissue toxicity; (2) elongation, in this step A β monomers add to existing soluble aggregates and increase aggregate length; (3) secondary nucleation, existing aggregates trigger the formation of new small soluble aggregates; (4) fragmentation, in which formed fibrils break down into several fibrils (Santos et al., 2016; Chen et al., 2017). Senile plaques have been observed in several diseases as mentioned before, particularly in the brain of AD patients, however, these plaques have also been observed in some cognitively normal older individuals (Murray and Dickson, 2014; Mormino and Papp, 2018).

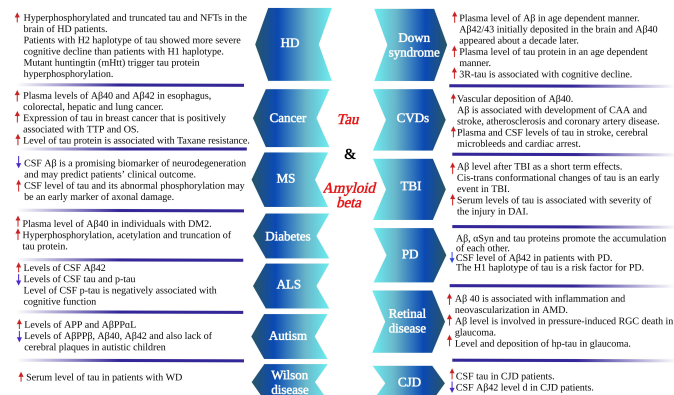


Figure 1 | Various diseases associated with tau protein and amyloid beta and some main related points.

Created with BioRender.com. A β : Amyloid-beta; ALS: amyotrophic lateral sclerosis; AMD: age-related macular degeneration; APP: amyloid precursor protein; CAA: cerebral amyloid angiopathy; CJD: Creutzfeldt-Jakob disease; CSF: cerebrospinal fluid; CVD: cardiovascular disease; DAJ: diffuse axonal injury; HD: Huntington's disease; MS: multiple sclerosis; NTF: neurofibrillary tangles; OS: overall survival; PD: Parkinson's disease; p-tau: phosphorylated tau; TBI: traumatic brain injury; TM2: type 2 diabetes; TTP: time to progression; WD: Wilson disease.

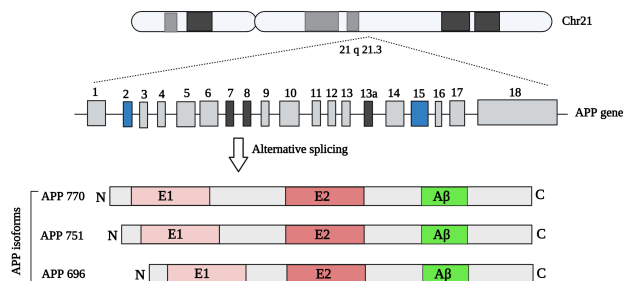


Figure 2 | APP gene and different isoforms resulted from alternative splicing. Created with BioRender.com. A β : Amyloid-beta; APP: A β precursor protein.

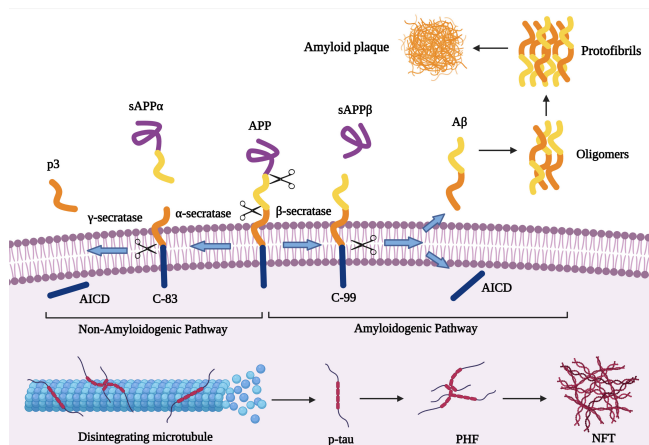


Figure 3 | Two main pathological hallmarks of AD include the amyloid plaque and the NFT formation process including APP proteolysis in the non-amyloidogenic and amyloidogenic pathway, and also tau protein aggregation and NFT formation. Created with BioRender.com. A β : Amyloid-beta; AICD: intracellular domain; APP: amyloid precursor protein; NFT: neurofibrillary tangles; PHF: paired helical filaments; p-tau: phosphorylated tau; sAPP: soluble APP beta protein.

Tau Protein

Tau is a microtubule (MT) associated protein (MAP) that is involved in the assembly and stabilization of MTs and is also a key player in the DNA and RNA protection (Violet et al., 2014). Tau is encoded by the microtubule-associated protein tau (MAPT) gene with a size of about 50 kb located on chromosome 17q21 and contains 16 exons. Alternative splicing of exons 2, 3, and 10 leads to the formation of six different isoforms of 352–441 amino acids tau proteins, which can be divided into two groups namely 3E and 4R based on whether they have three or four carboxy-terminal microtubule-binding repeat domains (Figure 4; Kolarova et al., 2012; Huda and Pan, 2018; Barbier et al., 2019). All of these six isoforms can be found in the brain and are mostly expressed by neurons and to some extent by astrocytes and oligodendrocytes (Mietelska-Porowska et al., 2014; Maté de Gèrardo et al., 2021). Tau interacts with the C-terminus of tubulin and increases their assembly into the MTs, which are involved in the formation and stability of the neuronal cytoskeleton, axonal transport, neurite outgrowth, and cell division (Rodríguez-Martín et al., 2013; Barbier et al., 2019). Physiologically, tau is a soluble and unfolded protein; however, in pathological conditions, it becomes insoluble and aggregates into paired helical filaments and NFTs (Figure 3). MT binding ability and DNA protection feature of tau protein is affected by its gene mutation, conformational changes, and post-translational modifications (PTMs), particularly phosphorylation (Violet et al., 2014). Tau protein undergoes several PTMs including phosphorylation, acetylation, truncation, nitration, glycation, glycosylation, and ubiquitination; however, as the most abundant PTM, phosphorylation of tau protein has been more studied and suggested as the key PTM in the pathological aggregation of tau (Mietelska-Porowska et al., 2014; Abyadeh et al., 2020; Zhao and Zlokovic, 2021). Tau protein has about 85 serine (S), threonine (T), and tyrosine (Y) sites of potential phosphorylation and is mainly phosphorylated by glycogen synthase kinase (GSK)-3 β , cyclin-dependent kinase 5, mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), and c-Jun N-terminal kinase in both physiological and pathological conditions and also dephosphorylated by the protein phosphatase 2A. Tau phosphorylation at specific sites is required for its normal function, however abnormal phosphorylation or hyperphosphorylation (hp-tau) triggers its conversion to a form that plays a pathological role (Mietelska-Porowska et al., 2014; Hobday and Parmar, 2021; Samimi et al., 2021; Abyadeh et al., 2022a). Abnormal phosphorylation and toxic tau formation are believed to be affected by several proteins such as A β , Fyn kinase, peptidylprolyl cis/trans isomerase, NIMA-interacting 1 (Pin1), heat shock cognate 70, heat shock protein 90, immunophilins FKBP51 and FKBP52, α -synuclein (α -Syn) or actin interacting protein PACSIN1 (Prots et al., 2013; Mietelska-Porowska et al., 2014).

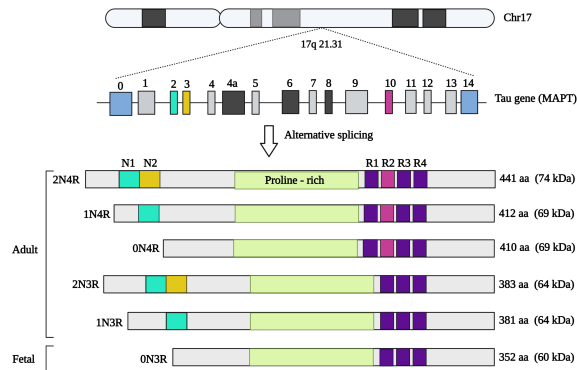


Figure 4 | Tau gene (MAPT) and different isoforms resulted from alternative splicing. Created with BioRender.com. MAPT: Microtubule-associated protein tau.

The pathological role of tau protein has been investigated in several disorders including brain neurodegenerative diseases, retinal diseases, PD, cancer, and TBI (Anderson et al., 2008; Baquero et al., 2011; Barbier et al., 2019). However, it has been studied more extensively in a group of neurodegenerative diseases termed tauopathies. These disorders are histopathologically characterized by tau protein aggregates in neurons or glial cells, or both (Samimi et al., 2021). Tauopathies are divided into two groups: primary and secondary tauopathies. In primary tauopathies, tau is the main

contributing factor of the neurodegenerative process such as Pick's disease, progressive supranuclear palsy, and chronic traumatic encephalopathy (CTE), however, in secondary tauopathies, tau aggregation is not the primary cause of neurodegeneration (Josephs, 2017; Chung et al., 2021). Interestingly toxic forms of tau protein have been suggested to spread from cell to cell in a prion-like fashion, and injection of tau aggregates obtained from AD brain into the mouse brain was shown to induce endogenous tau aggregation, which indicated that toxic tau can acquire the ability to self-propagate, like the prion proteins that are responsible for CJD pathology (Walker, 2018). However, prion-like propagation of tau protein was shown to require isoform pairing between the infecting prion and the recipient cells and even tau aggregates from AD and CTE patients that have two isoforms (3R and 4R) did not significantly infect either 3R- or 4R-expressing cells (Woerman et al., 2016; Wood, 2018).

Cardiovascular Diseases

CVDs are the leading cause of death globally, which takes over 17.9 million lives each year and is estimated to reach 22.2 million death annually by 2030 (Ruan et al., 2018). CVDs and AD share several risk factors (particularly aging) and pathological mechanisms. There is strong evidence indicating a causal association between CVDs and dementias; and individuals with CVDs are at higher risk of developing AD (Attems and Jellinger, 2014; Santos et al., 2017; Tini et al., 2020). A growing body of experimental and clinical evidence suggests that A β , the pathological hallmark of AD, constitutes a risk factor for CVDs (Tublin et al., 2019; Stakos et al., 2020). Here, we summarize current knowledge on mechanisms underpinning A β pathogenesis in CVDs that are currently centralized around the pathogenesis of A β in vascular components.

CAA is a specific cerebrovascular disease in which A β plays a key pathological role, CAA is a cerebrovascular disorder that is caused by deposition of A β peptide (mainly A β ₁₋₄₀) within the capillaries, arterioles, leptomeninges and small to medium-sized cerebral blood vessels. It is believed to result from a defective drainage of neuronal A β from these vessels and faulty A β clearance but not overproduction of A β (Biffi and Greenberg, 2011; Goulay et al., 2020; Stakos et al., 2020). The source of A β in CAA is mainly neuronal cells as observed in transgenic mice models and also blood plasma and the muscular layer of vessel walls (Herzig et al., 2006; Auriel and Greenberg, 2012; Goulay et al., 2020). A β ₄₀ is the predominant type of A β in vascular deposition. Although vascular deposition of A β ₁₋₄₂ is limited and it is the main A β species in parenchymal lesions of AD, its presence facilitates A β ₁₋₄₀ vascular deposition (McGowan et al., 2005; Schaich et al., 2019). A β deposition also impairs perivascular space drainage leading to perivascular space enlargement in the cortical grey matter and the underlying white matter, which can be seen in brain images and is a potential biomarker of neurovascular disease (Ramirez et al., 2016; Charidimou et al., 2017; Goulay et al., 2020). CAA results in hemorrhagic and ischemic lesions, blood-brain barrier breakdown, neurological deficits, cognitive impairment, stroke, dementia, and death (DeSimone et al., 2017; Goulay et al., 2020). While CAA increases the risk of stroke, in turn, stroke-induced hypoxia increases the expression of APP in vascular smooth muscle cells and thereby increases CAA development (Rensink et al., 2003; Goulay et al., 2020). Moreover, hypoxia condition stabilizes hypoxia-inducible factor-1 α , which bind to hypoxia-responsive element on the BACE1 gene promoter and leads to increased A β processing in both endothelial cells and macrophages and result in increased levels of A β particularly A β ₁₋₄₀ in patients with acute ischemic stroke (Schaich et al., 2019). Hypertension as a common risk factor between AD and stroke was shown to increase A β -induced neurovascular dysfunction, β -secretase activity, and amyloidogenic processing of APP (Faraco et al., 2016).

The presence of A β also has been reported in atherosclerotic plaque; atherosclerosis is a multifactorial disease and several risk factors contribute to atherosclerotic lesion formation (Mundi et al., 2018; Markin et al., 2020). Inflammation plays a central role in the initiation and progression of atherosclerosis and currently, this disease is also known as an inflammatory disease (Spagnoli et al., 2007; Raggi et al., 2018). A β presence has been reported in human atherosclerotic plaques in the vicinity of activated macrophages and platelets (Tibolla et al., 2010; Lathe et al., 2014). In this regard, an *in vitro* investigation using human and murine cells indicated that platelet phagocytosis by perivascular macrophages leads to the processing of platelet-derived APP towards A β production, as mRNA of β -secretase has been found in macrophages. Subsequently, A β evokes macrophage activation as indicated by up-regulation of inducible nitric oxide synthase (a marker of macrophage activation), while phagocytosis of platelets from APP knockout mice did not stimulate macrophage activation (De Meyer et al., 2002; Jans et al., 2006; Spitzer et al., 2020). Moreover, A β is shown to be involved in macrophage inflammatory responses including increased reactive oxygen species (ROS) production and tumor necrosis factor- α expression via CD36-dependent signaling cascade. CD36 is a cell surface receptor on macrophages, platelets, and microvascular endothelium that promotes inflammation and thereby atherogenesis (Canton et al., 2013). Further studies showed that A β ₁₋₄₀ is the major form of A β within the human aortic atherosclerotic lesions and plasma levels of A β ₁₋₄₀ are associated with atherosclerosis progression (Jans et al., 2006). Moreover, APP overexpression in transgenic mice causes endothelial dysfunction through increasing oxidative stress and reducing the availability of nitric oxide; however, activation of peroxisome proliferator-activated receptor-delta can prevent APP-mediated endothelial dysfunction and modulate the level of nitric oxide (Kokjohn et al., 2011). The association of A β ₁₋₄₀ with vascular aging has been reported by both *in vitro* and *in vivo* studies (Bonda et al., 2011; Laina et al., 2018). A β ₁₋₄₀ mediated vascular aging

is decreased by sirtuin 1, also known as NAD-dependent deacetylase, through increasing the expression of ADAM10 (ADAM metalloproteinase domain 10), which is an important α -secretase, and promoting the non-amyloidogenic pathway (Laina et al., 2018). Results of *in vivo* studies also showed impaired endothelial function, vascular development, angiogenesis, telomerase activity, and increased cellular senescence following exposure to A β (Donnini et al., 2010; Wang et al., 2015; Laina et al., 2018). However, increased circulating level of A β ₁₋₄₀ has been also observed in healthy elderly subjects, which might be due to decreased degradation of the peptide (Silverberg et al., 2010; Li et al., 2016). Current data are inconsistent with respect to the roles of A β in angiogenesis. While, *in vitro* studies indicate both anti- and pro-angiogenic features of A β in a dose-dependent manner, where higher concentration impairs angiogenesis and low concentration promotes angiogenesis through increasing cell proliferation, migration, and tube formation; *in vivo* studies showed increased cerebral vascularization in human AD brains and also APP transgenic animals (Biron et al., 2011; Cameron et al., 2012; Ristori et al., 2020).

There is also evidence indicating that A β interacts with endothelial cells of blood vessels and promotes the generation of superoxide radicals leading to impaired endothelial structure and function and a disrupted cerebrovascular autoregulation (Thomas et al., 1996; Niwa et al., 2002). In addition, a vasoactive role has been suggested for A β , which reduces acetylcholine-induced relaxation, enhances contraction of blood vessels, and reduces cerebral blood flow, and pretreatment with superoxide dismutase significantly resolved A β -related effects (Thomas et al., 1996; Iadecola et al., 1999). Interestingly, NADPH oxidase 2 (Nox2) inactivation also resulted in reduced APP-mediated vascular dysfunction without changing brain A β load and amyloid plaques, which indicated the key role of Nox2-derived ROS in APP pathogenesis (Park et al., 2008). Plasma concentration of A β ₁₋₄₀ is reported as an independent marker of aortic stiffness and also is associated with the severity of coronary artery calcium deposition score and coronary artery disease (Stamatelopoulos et al., 2018a).

In acute coronary syndrome, A β metabolism is increased and associated with clinical presentation, moreover, A β peptides possibly derived from platelet also accumulate in the myocardium with ischemic heart failure (Kitazume et al., 2012; Stamatelopoulos et al., 2018b; Inyushin et al., 2020). Interestingly, A β ₁₋₄₀ but not A β ₁₋₄₂ was reported to be increased and associated with coronary artery disease, and diabetes mellitus (DM) type 2 (Roeben et al., 2016). Moreover, increased A β metabolism, inflammation, and cognitive dysfunction were observed in mice models of myocardial infarction induced by ligation of the left anterior descending artery, which indicated a causal association of infarction with AD (Hong et al., 2013). This hypothesis also has been confirmed in another study that showed increased ROS, A β deposition, tau protein phosphorylation, and activated microglia in the brain of myocardial infarction mouse models (Zhang and Luo, 2020). Intriguingly, a retrospective cross-sectional study found the intramyocardial aggregates of A β ₁₋₄₀ and A β ₁₋₄₂ in AD patients, in addition, these patients showed diastolic dysfunction, suggesting AD as a systemic disease that may lead to failure of several organs (Troncone et al., 2016).

The expression of tau protein has been reported in the heart, and mouse modeling studies have shown that loss of this protein impaired cardiac function leading to elevated blood pressure, cardiac hypertrophy, and decreased left atrial contractility that was exacerbated with aging (Gu et al., 1996; Betrie et al., 2017). However, like A β , dysfunctional tau protein is also reported in vascular disease, especially cerebrovascular disease, and in this regards several tau protein modifications have been reported including tau hyperphosphorylation, de-phosphorylation, and truncation. The association of plasma and cerebrospinal fluid (CSF) levels of tau protein has been reported to be associated with the risk of developing, severity, and outcome of stroke and the presence of cerebral microbleeds, which increase the risk of stroke and dementia (De Vos et al., 2017; Romero et al., 2020). Furthermore, its serum level was also shown to be elevated in patients with cardiac arrest, possibly released into the serum due to brain hypoxia, and was negatively associated with neurological outcomes after 6 months (Mörtberg et al., 2011; Randall et al., 2013). Overexpression of tau protein-induced blood vessel abnormalities in the mouse cortex such as abnormal and spiraling morphologies, increased density, and reduced size of blood vessels; these changes were associated with cortical atrophy and overexpression of angiogenesis-related genes including *Serpine1*, *Vegfa*, and *Plau* in CD31-positive endothelial cells (Bennett et al., 2018). Collectively, these results indicated that tauopathy adversely affects brain endothelial cells and the integrity of the brain's microvasculature, resulting in hypoperfusion of the cerebral cortex (Thomas et al., 2015; Bennett et al., 2018). In turn, hypoperfusion may increase p-tau through the down-regulation of neuroglobin, a scavenger of ROS, increased free radicals, and the induction of neuroinflammatory cascade, ultimately leading to blood-brain barrier compromised permeability and neuronal cell death (Raz et al., 2019).

Moreover, dephosphorylation and differential re-phosphorylation of tau protein in the canine brain has been observed after CA-induced ischemia and subsequent reperfusion. Immediate dephosphorylation of tau protein was observed after CA-induced cerebral ischemia, which was almost restored 24 hours after reperfusion, apart from phosphorylation of Ser262/356, which is involved in microtubule binding ability of tau protein (Mailliot et al., 2000). Furthermore, accumulation of tau protein and NFT-like formations have been observed in the brain of rodent stroke model that was associated with aberrant activation of Cdk5 and phosphorylation of GSK3, indicating the key

role of Cdk5 and GSK3 in ischemia-induced phosphorylation and subsequent aggregation of tau protein (Morioka et al., 2006; Wen et al., 2007).

These studies collectively provide valuable insights into the complex relationship of A β and tau protein with cardiovascular and cerebrovascular diseases. They highlight the need for further research to understand the precise mechanisms underlying A β and tau protein dysregulation and its implications for cardiovascular and cerebrovascular health. Investigating the effects of A β and tau protein accumulation, modifications and their potential as diagnostic markers or therapeutic targets could help develop strategies for early detection and intervention in these diseases and also AD.

Cancer

Cancer is the second leading cause of death globally, which has caused around 10 million loss of lives in 2020 (Sung et al., 2021). APP, APLP2, and gamma synuclein are reported to be overexpressed in gastrointestinal, breast, prostate, and lung cancers (Hansel et al., 2003; Wu et al., 2007; Takagi et al., 2013; Pandey et al., 2015; Pandey et al., 2016; Ito et al., 2019).

Increased expression of APP has been observed in mice and human breast cancer cell lines, particularly in those with higher metastatic potential, moreover, a level of APP was shown to be associated with tumor development. Accordingly, APP knockdown cancer cell lines showed reduced cell growth, migration, and invasion ability through modulating insulin-like growth factor 1/AKT signaling pathway and subsequently AKT/FOXO signaling, and also increased p27^{kip1} and caspase-3-mediated apoptosis and sensitivity to chemotherapeutic agents (Lim et al., 2014). However, there are also reports indicating intact levels of AKT and p-AKT upon silencing APP in bladder cancer cells, and a significant decrease in levels of RAS, RAF, and phosphorylated-mitogen-activated protein kinase kinase. Moreover, silencing APP resulted in cell cycle arrest in the G2/M phase and inhibited cancer cells proliferation, migration, and invasion (Zhang et al., 2018).

Furthermore, the presence of APP in human prostate cancer cell lines was shown to be triggered with copper, as levels of this metal ion were increased in several cancer tissues. APP mitigates copper-induced growth inhibition possibly through a mechanism mediated by its copper-binding domain located in the E1 extracellular domain and phosphorylation of tyrosine residues within the cytosolic domain (Gupte and Mumper, 2009; Gough et al., 2014). In this regard, APP was shown to play a key role in liver cancer resistance to 5-fluorouracil (5-FU), an important anti-cancer drug; the level of APP in liver cancer cells showed an increase following treatment with 5-FU, and cell lines overexpressing APP were resistant to 5-FU. They showed decreased apoptosis possibly through increasing the expression of two apoptosis suppressor genes such as Bcl-2 and Bcl-xl and down-regulation of mitochondrial apoptotic pathways genes such as BAX and BID, while APP knock-down cells were more sensitive to 5-FU with a higher rate of apoptosis compared to the control cells (Wu et al., 2020a; Sethy and Kundu, 2021).

In prostate cancer cells, increased level of APP was associated with increased proliferation and migration possibly through increasing the expression of metalloproteinase (MMP) genes such as ADAM10 and ADAM17, and epithelial-mesenchymal transition (EMT)-related genes, including VIM, and SNAI2. Interestingly ADAM10 and ADAM17 are reported to act as α -secretases for APP, and increased expression of these metalloproteinases has been found in several cancers, such as breast cancer; Increased expression of ADAM10 and sAPP α has been reported to be associated with worst outcome in non-luminal breast cancer. Moreover, similar functional effects were observed upon the down-regulation of APP or ADAM10. Interestingly, knockdown of ADAM10 resulted in reduced cell migration, which was reversed by adding sAPP α but not APP, suggesting the key role of ADAM10 in APP-mediated toxicity (Tsang et al., 2018; Wozniak and Ludwig, 2018). In addition, high expression of ADAM17 was shown to be associated with a shorter survival rate for breast cancer patients, and blocking this enzyme resulted in reduced proliferation of breast cancer cells (McGowan et al., 2008; Tsang et al., 2018). EMT is a necessary step for tumor metastasis; up-regulation of some other mesenchymal markers including MMP-9, MMP-2, MMP-3, N-cadherin and vimentin, and down-regulation of epidermal-associated markers such as N-cadherin and cytokeratin were also observed in breast cancer cell lines upon treatment with A β . In addition, A β affected the phosphorylation level of MAPK signaling pathway components including, mitogen-activated protein kinase kinase 11 (MLK3), mitogen-activated protein kinase kinase 4 (MEK4), and mitogen-activated protein kinase 10, interestingly MEK inhibitor significantly reduced the phosphorylation level of MAPK signaling pathway components and expression of EMT genes, suggesting that A β activates MAPK signaling pathway. The downstream transcription factor of this pathway may trigger the expression of EMT genes, leading to enhanced migration and invasion of human breast cancer cells (Shi et al., 2014; Zhao et al., 2019; Wu et al., 2020b). In nasopharyngeal carcinoma cells, also inhibition of APP expression caused down-regulation of the MAPK signaling and subsequently decreased expression of EMT genes and resulted in decreased cell viability, migration, and invasion (Xu et al., 2019).

In pancreatic cancer cells, blocking β -secretase activity results in reduced growth and viability, however, did not affect the non-transformed pancreatic cell line (Peters et al., 2012; Pandey et al., 2016). Accumulation of both extracellular and intracellular A β in human glioma cells has been reported (Zayas-Santiago et al., 2020). Moreover, plasma levels of A β ₄₀ and A β ₄₂ were found to be significantly higher in several cancer types including esophagus cancer, colorectal cancer, hepatic cancer, and lung cancer compared to

normal controls, although were slightly lower than AD samples (Jin et al., 2017). Accordingly, in AD patients with a cancer history, no differences were observed compared to AD patients without any history of cancer, but a significantly lower level of paired helical filament was observed in patients with a cancer history compared to control subjects (Yarchoan et al., 2017). Unlike the reported negative association of APP in cancer, increased levels of A β ₄₂ in tumor cells lead to telomere DNA damage, telomere uncapping, chromosome fusion, and telomere shortening, downregulation of telomerase reverse transcriptase and subsequently cell senescence and apoptosis (Qin et al., 2019). Furthermore, A β oligomers showed anti-proliferative effects on different cancer cells including human acute promyelocytic leukemia, human lung cancer, and human breast cancer (Pavliukeviciene et al., 2019).

A growing number of epidemiological studies have indicated both positive and negative associations of tau protein level with the risk of development and progression of several cancers, for example, high tau levels were reported in patients with breast cancer, particularly in estrogen receptor-positive and low-grade cancers and to some extent in estrogen receptor-negative and high-grade tumors, showed to be positively associated with the longer median time to tumor progression and overall survival (Pusztai et al., 2009; Baquero et al., 2011). However, in contrast to breast cancer, the level of tau protein was shown to be negatively associated with overall survival in epithelial ovarian cancer and prostate cancer patients (Smoter et al., 2013; Sekino et al., 2020). Moreover, tau protein expression also affects the response to microtubule-targeting chemotherapeutic agents such as taxanes, a group of drugs that inhibit microtubule depolymerization through binding to the β -subunit of the tubulin heterodimer, leading to impaired microtubule dynamic and thereby inhibit the process of cell division; high levels of tau protein was reported to negatively affect drug response in patients with different types of cancer including ovarian, gastric, prostate, breast, and non-small-cell lung cancer (Mimori et al., 2006; Smoter et al., 2013; Maloney et al., 2020; Papin and Paganetti, 2020). *In vitro* studies indicated that taxanes have the same tubulin-binding site as tau protein, therefore tau protein interferes with the binding of taxanes to tubulin and showed that the presence of tau protein decrease paclitaxel, a member of taxanes agents, binding and paclitaxel-induced MT polymerization (Rouzier et al., 2005; Gargini et al., 2019; Maloney et al., 2020).

Tau and APP have two conformations including trans and cis-conformations, where trans-conformation is functional and "healthy", and facilitate their normal functions, while cis-conformation is pathogenic, formed in stress conditions after phosphorylation, is dysfunctional and prone to aggregation (Kondo et al., 2015; Wang et al., 2020). Conformational conversion between cis and trans is mediated by the Pin1 enzyme, which is down-regulated in AD (Wang et al., 2020). Pin1-knockout mice represent AD features such as hp-tau, A β accumulation, and neurodegeneration, surprisingly these mice models of AD were resistant to breast cancer induced by oncogene Ras or Neu over-expression (Wulf et al., 2004; Lanni et al., 2021). These results indicated the importance of tau and A β up-stream regulators in the development of cancer, as Pin1 was shown to be increased in several types of cancer and promote oncogenesis (Yu et al., 2020), therefore it may be at the crossroad between cancer and neurodegeneration and observed changes in tau and A β levels in cancer stem from Pin 1 alteration.

Diabetes Mellitus

In 2019, DM was reported to affect 463 million people worldwide and is estimated to hit 700 million by 2045. DM is also among the top 10 leading causes of death, and a major cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputation (Saeedi et al., 2019; Sinclair, 2021). Diabetes is a disorder characterized by insufficient insulin and resistance to its metabolic effects, with hyperglycemia leading to chronic damage in multiple organ systems (Kottaisamy et al., 2021; Yao et al., 2021). Patients with diabetes show cognitive decline and also brain changes similar to those observed in AD brains and an increased prevalence of AD (nearly 65%) has been reported in diabetic patients, particularly in those with diabetes mellitus type 2 (DM2) (Arvanitakis et al., 2004; Stanciu et al., 2020). AD and DM share many risk factors and pathological changes such as the apolipoprotein E4, higher cholesterol, oxidative stress, mitochondrial dysfunction, inflammation, and resistance to insulin that comprises the core mechanism of DM2, which gave rise to a new term for AD named, type 3 diabetes (Stanciu et al., 2020; Diniz Pereira et al., 2021; Abyadeh et al., 2022). Increased plasma levels of A β ₄₀ (28%) and A β ₄₂ (37%) also have been observed in individuals with DM2 (Peng et al., 2020). Insulin dysregulation may affect both the production and degradation of A β and lead to increased extracellular levels of A β through increasing the activity of β -secretase and decreasing the release of insulin-degrading enzyme (IDE; one of the major A β degrading enzyme) into the extracellular space via inhibition of the PI3K-Akt pathway, activation of which promotes non-amyloidogenic processing of APP, furthermore insulin competitively inhibits A β degradation via IDE (Gasparini et al., 2002; Shieh et al., 2020). Conversely, expression of IDE is shown to be reduced in both AD and DM2 mice models and the size of A β plaques was inversely correlated with IDE activity, therefore reduced levels of IDE in diabetes were suggested as a potential trigger of A β accumulation and cognitive decline in both AD and DM2 (Li et al., 2018; Delikkaya et al., 2019). A β oligomers were shown to make a substantial loss of neuronal surface insulin receptors (IRs) in hippocampal neuronal culture, which may contribute to insulin resistance condition and in turn insulin resistance increases A β production and deposition in cerebral blood vessels leading to increased AD pathology (Zhao et al., 2008). Moreover, BACE1 was shown to degrade IRs in the liver in

a glucose concentration-dependent manner and its plasma level and activity increase in diabetic conditions leading to a reduced amount of IRs; however, its effect on neuronal IRs is not still clear (Meakin et al., 2018; Bao et al., 2021). In addition, global deletion of *BACE1* was shown to be associated with reduced risk of diet-induced obesity and diabetes in mice, while neuronal *BACE1* knock-in resulted in A β accumulation, neuroinflammation, and more interestingly systemic diabetes in mice, which indicated the increased central *BACE1* activity in AD patients as the potential mechanism underpinning the higher prevalence of metabolic disorders in AD patients (Meakin et al., 2012; Plucińska et al., 2014; Plucińska et al., 2016). While studies showed the association of nutrient-induced insulin resistance with elevated A β deposition in the brain of both humans and diabetic AD model mice, genetically induced insulin resistance mice (deficient for either IRS-2 or neuronal insulin-like growth factor 1 receptor) showed a protective effect against brain A β deposition, suggesting that the increased A β pathology might be due to high-fat diet-induced metabolic stress or inflammation but not direct effects of insulin signaling dysfunction (Wakabayashi et al., 2019). Interestingly, early intranasal insulin administration was suggested as a therapeutic option to improve memory and cognitive performance in people with mild cognitive impairment or early AD. However, a recent report by the same group did not confirm their previous findings (Craft et al., 2012; Suzanne, 2012; Craft et al., 2020). A suggested mechanism for the beneficial effects of insulin on AD symptoms is through decreasing A β generation. Insulin was shown to decrease the endocytosis rate of A β PP and increase A β PP O-GlcNAcylation via Akt insulin signaling leading to decreased sA β PP β and increased sA β PP α production, collectively increasing non-amyloidogenic processing of the APP (Kwon et al., 2019).

There is a negative association between the level of tau protein phosphorylation and the insulin signaling pathway, which is interesting given the reports that patients with DM2 have increased CSF levels of p-tau (Moran et al., 2015; Lu et al., 2018). Moreover, the elevated level of tau hyperphosphorylation and its inability for binding to MTs have been observed in the brains of both DM1 and DM2 mice models (Chatterjee and Mudher, 2018).

Insulin regulates the phosphorylation of tau protein through the PI3K/AKT signaling pathway that leads to GSK-3 β phosphorylation and inactivation, therefore an impaired insulin signaling pathway results in GSK-3 β -mediated tau hyperphosphorylation. In addition, tau protein phosphorylation is also negatively regulated through modification by O-GlcNAcylation and impaired insulin-PI3K-AKT signaling may also lead to abnormal tau hyperphosphorylation through down-regulation of O-GlcNAcylation (Liu et al., 2011; Hobday and Parmar, 2021). In turn, tau hyperphosphorylation and aggregation could further contribute to insulin signaling impairment through interacting with phosphatase and tensin homolog deleted on chromosome 10 (PTEN) which is a negative regulator of insulin/phosphoinositide 3-kinase signaling. In combination these changes can lead to cognitive dysfunction (Hobday and Parmar, 2021), which can be limited by the inhibition of GSK-3 β (King et al., 2013). Moreover, tau acetylation and truncation resulted in disrupted tau-microtubule interactions and hastened aggregation of pathological tau in AD patients. In this respect, increased acetylation and truncation of tau protein have been also observed in diabetic mice models in hyperglycemic conditions, and this may lead to its dysfunction and aggregation (Kim et al., 2009; Chatterjee and Mudher, 2018). Another mechanism that affects tau protein hyperphosphorylation in AD is mTOR/S6K1 signaling, and its abnormal up-regulation is shown to be correlated with tau hyperphosphorylation and NFT formation in AD brains (Tang et al., 2013). mTOR/S6K1 signaling is also involved in glucose metabolism and required for memory formation (Sipula et al., 2006; Krebs et al., 2007; Lana et al., 2017). Interestingly up-regulation of mTOR/S6K1 signaling has been observed in the brain of diabetic mouse models and subsequent inhibition of mTOR signaling via rapamycin reduced the level of hp-tau and decreased DM-induced cognitive decline (Wang et al., 2014). Further analyses by the same group showed that caveolin-1, a transmembrane scaffolding protein that negatively regulates mTOR signaling, is down-regulated in chronic hyperglycemic conditions resulting in overactivity of mTOR/S6K signaling and subsequently tau hyperphosphorylation in neurons of diabetic rats (Wu et al., 2017a).

Interestingly, insulin accumulation as oligomers was observed in the brain of AD patients with hp-tau aggregations. In addition, insulin accumulation was independent of whether the patient had DM or not, indicating that peripheral and brain insulin levels are independently regulated. Further *in vitro* analyses showed that hp-tau-induced intraneuronal accumulation of insulin may lead to decreased IR levels (Craft et al., 2017). The identified shared risk factors and pathological changes, such as apolipoprotein E4, higher cholesterol, oxidative stress, mitochondrial dysfunction, inflammation, and insulin resistance, provide insights into the intricate interplay between DM and AD. Additionally, the observed increase in plasma levels of A β_{40} , A β_{42} , and p-tau in individuals with DM suggests a potential role of these proteins in the development and progression of both conditions.

Retinal Disorders

The retina is an extension of the central nervous system with both derived from the neural tube. They are partially protected from the vasculature via blood-retinal and blood-brain barriers respectively. Moreover, upon aging both the retina and the central nervous system show extracellular deposits associated with degenerative pathology such as the drusen and senile plaques respectively (Ratnayaka et al., 2015). The retina is affected by A β

accumulation in various neurodegenerative disorders. Visual impairment and retinal A β deposits have been reported in patients with early AD even before any significant neurodegeneration (Koronyo-Hamaoui et al., 2011; Criscuolo et al., 2018).

A β is produced in the retinal ganglion cells (RGC) which along with retinal pigment epithelium (RPE) monolayer and other retinal neurons has been suggested to be the main sources of A β generation and secretion (Ohno-Matsui, 2011). Retinal A β levels have been found to be increased with aging, for example, cultured RPE cells from geriatric mice showed a higher level of A β and β -secretase activity and a lower level of neprilysin (which clears A β), compared to the younger controls (Wang et al., 2012; Ratnayaka et al., 2015). In addition, increased accumulation of A β in the RPE-Bruch's membrane interface and retinal/choroidal blood vessels and decreased blood flow rates was observed in C57BL/6 mice with aging (Berisha et al., 2007; Hoh Kam et al., 2010). The above-mentioned changes seem to be more significant in age-related macular degeneration (AMD) and glaucoma.

AMD is the leading cause of severe, irreversible vision loss in people over age 60 with a global prevalence of 170 million, which is estimated to hit 288 million by the year 2040 (Kaarniranta et al., 2011; Pennington and DeAngelis, 2016). Glaucoma is among the top three causes of blindness, affecting about 76 million patients, and estimated to reach 111 million by 2040 (Allison et al., 2020). A pathological role of A β have been reported in AMD and glaucoma which share many pathological events with AD, including oxidative stress and neuroinflammation. Furthermore, increased levels of A β has been observed in the retina of AD patients (Ning et al., 2008; Kaarniranta et al., 2011; Song et al., 2017; Jonas et al., 2018). AMD, glaucoma, and AD are all age-related diseases and some epidemiological studies have reported that patients with AMD or glaucoma may be at higher risk of developing AD (Lee et al., 2019; Wang and Mao, 2021).

Drusen are one of the pathological hallmarks of AMD, comprising a complex of extracellular deposits of debris located between the basal lamina of the RPE and the inner collagenous layer of Bruch's membrane (Spaide and Curcio, 2010). Disruption of retinal RPE following drusen formation leads to degeneration of photoreceptor cells that results in central vision loss in AMD patients. Studies have reported A β to be one of the major constituents of drusen and also to be present in the RPE of AMD patients, suggesting it may be a key player in AMD progression (Prasad et al., 2017; Wang and Mao, 2021). Recent reports suggest that the most abundant A β species within the retina is A β_{40} (Wang and Mao, 2021). Late-stage AMD is associated with progressive RPE degeneration and can lead to either wet/exudative AMD with choroidal neovascularization or dry/non-exudative AMD with larger areas of RPE atrophy also known as geographic atrophy (Arya et al., 2018). Subretinal injection of A β_{42} was shown to be associated with RPE senescence, retinal degeneration, and AMD-like ocular pathology in mice (Liu et al., 2015a). Moreover, treatment of human RPE cells with A β_{40} showed RPE atrophy and basal deposit formation along with increased production of vascular endothelial growth factor, monocyte chemoattractant protein-1, and interleukin 8 (IL-8) by RPE that are key players in the growth of the abnormal blood vessels (i.e., choroidal neovascularization). There was also a significant decrease in pigment epithelium-derived factor, which is a potent inhibitor of neovascularization, thereby promoting choroidal neovascularization formation in AMD (Stellmach et al., 2001; Yoshida et al., 2005; Wu et al., 2017b; Tian et al., 2021).

A β -induced mitochondrial ROS were shown to be involved in A β -induced secretion of angiogenesis factor by RPE cells (Wu et al., 2017b). Proteomic analysis of RPE-choroid complex tissue samples from A β treated mice showed that A β impaired mitochondrial function and increased ROS production through up-regulating PU.1 (a transcription factor) which in turn activated NADPH oxidases, particularly NOX4-p22^{phox} (Sun et al., 2020). Impaired mitochondrial function following exposure to A β was also observed in photoreceptor cells, with ribosomal machinery and cytoskeletal organization found to be altered upon exposure to A β in a time and concentration-dependent manner (Deng et al., 2019, 2023).

RGC apoptosis is a key step causing irreversible vision loss in glaucoma. While elevated intraocular pressure is recognized as the main trigger for RGC death the underlying mechanism is multifactorial and far from clear (Guo et al., 2005). In a rat model of glaucoma, chronic ocular hypertension increased caspase-3 and caspase-8 activation which led to abnormal APP processing and increased A β level, which subsequently played a key role in pressure-induced RGC death. Treatment with A β antibodies significantly reduced RGC apoptosis (Guo et al., 2007). Moreover, β -secretase inhibitors showed neuroprotective effects against glutamate-induced RGC death *in vitro* and also on retinal damage induced by optic nerve crush *in vivo* (Yamamoto et al., 2004). A β also disrupts microvilli, the tight junctions, and adhesion of the RPE cells (Bruban et al., 2009).

The effect of A β_{40} and A β_{42} on retinal inflammation have been reported in several studies, highlighting the importance of inflammation in all age-related diseases. RPE, neuroretina, and vitreous analyses of animals (mouse and rat) that received intravitreal injections of A β showed overexpression of inflammation cytokines including IL-6, tumor necrosis factor- α , IL-1 β , IL-18, caspase-1, NLRP3, and XAF1, microglia activation and ultimately RGC loss, possibly through binding to microglial scavenger receptor CD36, TLR4, and NF- κ B signaling pathways (Liu et al., 2013; Chen et al., 2016; Lei et al., 2017; Simons et al., 2021).

Shared pathological events between AD and neurodegenerative diseases of the eye such as AMD and glaucoma, also warrant investigating the involvement of tau proteins, however, there is limited research on the role of tau deposition in AMD and glaucoma.

Tau protein is expressed in RGCs, however, a higher level of this protein can be found in the axons of developing RGCs. Tau protein also plays a key role in proper axon development and the survival of RGCs (Ho et al., 2012). Abnormal tau deposition and the presence of p-tau were observed in the retina of patients with uncontrolled primary and secondary open-angle glaucoma compared to healthy controls, while normal tau was found in the retina of healthy controls but not glaucoma patients (Gupta et al., 2008; Chan et al., 2021). An elevated level of p-tau also has been observed in the lateral geniculate nucleus of the monkey model of glaucoma following increased intraocular pressure (Yan et al., 2017). Interestingly, an *in vivo* study on a rat model of glaucoma showed both hyper and hypo-phosphorylation of tau protein and also mislocalization of tau protein in the somatodendritic compartment of RGCs, but not in axons. Subsequent down-regulation of tau by short interfering RNA resulted in an increased survival rate of RGCs, confirming the toxicity of tau protein (Chiasseu et al., 2016). Further results suggested the potential role of tauopathy in impaired autophagy and death of RGCs after optic nerve crush which can be ameliorated by silencing the tau gene via short interfering RNA (Oku et al., 2019). In rat RGCs, aggregation of tau protein impaired the anterograde axonal transport and transportation of mitochondria by kinesin-like motors toward the cell periphery leading to deficient energy production and accumulation of ROS (Stamer et al., 2002; Ho et al., 2012). Tau protein also interacts with the C-terminus of the P150 subunit of the dynein complex. Moreover, the tau protein enhanced the binding of the dynein complex to microtubules and co-localized with dynein. Therefore the abnormal distribution of tau in RGCs can result in the mislocalization of dynein in axons, which can lead to neurodegeneration (Magnani et al., 2007; Ho et al., 2012).

Collectively abnormal accumulation of both A β and tau protein appear to contribute to retinal disease pathogenesis, with aggregation of these factors inducing several down-stream events, including activation of retinal astrocytes and microglia and secretion of inflammatory cytokines such as IL-1 β , IL-6, and tumor necrosis factor- α , leading to inflammation (Ashok et al., 2020; Baudouin et al., 2020; Tan et al., 2020; Abyadeh et al., 2023b).

Parkinson's Disease

PD is the second most common brain neurodegenerative disease after AD. In 2016 about 6.1 million individuals had PD globally (Dorsey et al., 2018). It is pathologically characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the formation of Lewy bodies (LBs). LBs contain the protein α -Syn (Surmeier, 2018; Pan et al., 2021); however, it constitutes only about 9% of the LB (McCormack et al., 2016). α -Syn is a neuronal protein that is considered a major contributor to several neurodegenerative disorders known as synucleinopathies, including PD, dementia with LBs, and multiple system atrophy (Gonçalves and Outeiro, 2017). Recently a study reported using CSF α -Syn seeded assay as a novel biomarker for PD together with an olfactory test, producing a sensitivity of 98.6% (Siderowf et al., 2023).

There are multiple lines of evidence linking α -Syn and tau to Parkinson's disease. MAPT gene (tau protein) and SNCA (alpha-synuclein) have been identified as risk genes for PD in several genome-wide association studies (Wray and Lewis, 2010; Davis et al., 2016). Mutations in tau can result in FTD and Parkinsonism in a mouse model (Dawson et al., 2007). Consistent with the idea that the two proteins interact, mutations in SNCA A53T in humans exhibited exacerbated tau pathology (Markopoulou et al., 2008).

Interestingly α -Syn deposition is also observed in AD patients and increased deposition of insoluble α -Syn has been linked to cognitive dysfunction in a transgenic AD mouse (Clinton et al., 2010; Vasili et al., 2019). Coincident with this, elevated aggregation of A β and tau have been reported in PD patients, although the association of AD pathological hallmarks with PD is not consistently reported (Jendroska et al., 1996; Siderowf et al., 2010; Bäckström et al., 2015; Liu et al., 2015b; Winer et al., 2018; Melzer et al., 2019). Experimental studies have linked α -Syn mainly to tau hyperphosphorylation, however, some studies have indicated the role of A β in inducing aggregation of α -Syn and tau protein in synucleinopathies (Twhog and Nielsen, 2019; Bassil et al., 2020).

A β plaques have been found in PD patients along with the typical LB deposition and a direct association has been reported between these two pathological proteins (Lashley et al., 2008). Analysis of post-mortem brain from PD patients with dementia identified three pathologic types of PD, including (1) Predominant synucleinopathy; (2) Predominant synucleinopathy with A β plaques and minimal or no cortical tauopathy; (3) Synucleinopathy and A β plaques and at least moderate neocortical tau aggregations. This study also indicated A β deposition and synucleinopathy but not tauopathy as the main contributors to PD development and A β accumulation was shown to be associated with poor survival rate in PD patients with dementia (Kotzbauer et al., 2012). Early experimental studies indicated that α -Syn and A β have distinct and convergent pathogenic effects on brain function in a transgenic mouse model of AD with LBs. Further *in vitro* studies showed that A β , particularly A β ₄₂, even at low concentration, may promote the intraneuronal accumulation of α -Syn, but α -Syn did not affect overall A β level or plaque formation (Hamilton, 2000; Masliah et al., 2001; Köppen et al., 2020). These

results were confirmed in post-mortem analysis of PD brain, which showed the higher presence of LBs and increased level of insoluble α -Syn in brains with A β deposits compared to those without A β deposits, and suggested the A β enhanced development of α -Syn lesions in PD patients (Pletnikova et al., 2005). In addition, further studies indicated that A β , α -Syn, and tau proteins may interact synergistically to promote their mutual accumulation (Clinton et al., 2010). In this regard, *in vivo*, results showed that A β plaques promote α -Syn seeding and spread throughout the brain, and subsequently, α -Syn enhances tau aggregation (Bassil et al., 2020).

In summary, studies have reported a significant association between A β , tau, and α -Syn proteins that synergistically contribute to PD and AD pathogenesis. Interestingly, a meta-analysis in 2017 shows reduced CSF levels of A β ₄₂ in PD with cognitive impairment (Hu et al., 2017b). This is in agreement with more recent studies and suggested to occur because the A β ₄₂ may be sequestered away from CSF due to increased intracellular A β ₄₂ accumulation (Lewczuk et al., 2021; Nabizadeh et al., 2023).

Genetic studies have indicated the association of several gene polymorphisms with the risk of PD, including SNCA (synuclein alpha, encoding α -Syn), GBA (glucosylceramidase beta, encoding GBA protein), LRRK2 (leucine-rich repeat kinase 2, encoding LRRK2 protein), and MAPT (Bras and Singleton, 2009; Pan et al., 2021). MAPT that encodes tau protein has two haplotypes namely H1 and H2 and genome-wide association studies have repeatedly shown the association of H1 with increased risk of PD and AD, although results from different populations are not consistent. H1 is debated as a risk factor for PD and this inconsistency is possibly due to the effects of genetic background and environmental factors (epigenetic) (Sánchez-Juan et al., 2019; Pan et al., 2021). Meta-analyses of total tau (t-tau) and p-tau in CSF show increased levels in PD dementia cohorts (Liu et al., 2015b; Hu et al., 2017a).

Cell transplantation has emerged as a potential treatment for PD, interestingly p-tau and NFTs have been observed in transplanted cells 18 months to 21 years after transplantation (Cisbani et al., 2017; Ornelas et al., 2020). The presence of toxic tau in healthy transplanted cells is possibly through prion-like propagation (Clavaguera et al., 2017; Mudher et al., 2017). α -Syn accumulates and forms fibrillary assemblies in PD that play a key role in the pathogenesis of PD. Of interest is that tau is colocalized with α -Syn in LBs (Hu et al., 2010; Pan et al., 2021), and *in vivo* studies showed impairment and subsequent cognitive decline in a mouse model of familial PD (A53T mutant α -synuclein) shown to be mediated by tau protein (Teravskis et al., 2018; Singh et al., 2019).

Experimental studies have shown that tau monomers interact with the c-terminal region of α -Syn and promote its aggregation. In addition, α -Syn monomers and aggregates also increase tau aggregation (Dasari et al., 2019). Further studies showed that extracellular α -Syn increases the phosphorylation of GSK-3 β at Tyr216 and decreases its phosphorylation at Ser9. This enhances its activity and in turn, increases tau phosphorylation at Ser396 leading to microtubular destabilization (Giasson et al., 2003; Gąssowska et al., 2014; Credle et al., 2015). Conversely, GSK-3 β dysregulation contributes to Parkinson's-like pathophysiology with associated region-specific phosphorylation and accumulation of tau and alpha-synuclein (Credle et al., 2015). Another study indicated that aberrant expression of human P301L mutant tau increased phosphorylation and aggregation of α -Syn via GSK-3 β in rTg4510 mice (Takaichi et al., 2020). Overall, these studies highlight the intricate relationship between A β , tau, and α -Syn proteins in PD and AD. Understanding these interactions is essential to unravel the mechanisms underlying these neurodegenerative diseases and develop effective therapeutic strategies.

Traumatic Brain Injury

TBI, the "silent epidemic" is an increasingly recognized global health problem that is estimated to affect about 69 million people worldwide each year (Dewan et al., 2018). TBI is divided into two types: focal TBI, which affects only a specific area such as epidural or subdural hematoma and parenchymal contusions, and diffuse TBI which affects more widespread areas with traumatic axonal injury and diffuse cerebral edema (Andriessen et al., 2010). TBI is not isolated to a single event and has long-term consequences. Multiple concussions or even a single moderate to severe TBI increases the risk of developing several neurodegenerative diseases including CTE, AD, and PD at an early age (Katsumoto et al., 2019). Currently, no effective treatments are available for TBI or TBI-related dementia. Although the underlying mechanisms of the association of TBI with neurodegenerative disease remained unclear, the presence of hp-tau, tau aggregates, and A β have been reported in the brain months after TBI (Roberts et al., 1994; Smith et al., 2003; Katsumoto et al., 2019).

Increased levels of A β and its aggregation have been reported as a consequence of TBI and suggested as a major contributor to neurodegeneration and cognitive decline (Johnson et al., 2010; Acosta et al., 2017). In addition, increased level of BACE1 and γ -secretase following TBI has been reported in animal studies and suggested as two therapeutic targets for the treatment of TBI (Blasko et al., 2004; Loane et al., 2009). It has been reported that about 30% of individuals after a severe TBI with a survival time of between four hours and 2.5 years shows A β deposition and that presence of A β accumulation following TBI increased with age (Roberts et al., 1994). These findings also have been observed in another study that showed the presence of NFTs and A β plaques in the brain of single moderate to severe TBI cases after 1–47 years (Johnson et al., 2012). However, in contrast to these

results, the presence of A β plaques in short-term post-TBI cases but not long-term survivors (up to 3 years) was reported, suggesting that increased level of neprilysin after TBI may be the reason for the reduced level of A β plaques (Chen et al., 2009). Decreased level of A β plaque was also observed in aged plaque-forming APP transgenic mice 16 weeks after TBI, which indicated that plaque pathology may be reversible (Nakagawa et al., 2000). Although most of the animal studies have indicated that A β level was initially increased after TBI as a short-term effect but was resolved over time, and is not a long-term effect (Tsitopoulos and Marklund, 2013; Bird et al., 2016), there are some reports indicating increased A β accumulation as a long-term sequela after TBI. For example, the presence of A β plaques in injured axons without increased gene expression of APP was observed in a non-transgenic rat model of TBI even after 1 year (Iwata et al., 2002), and also increased levels of A β , BACE, presenilin-1 and caspase-3 in swollen axons of a non-transgenic pig model of TBI after 6 months (Chen et al., 2004). The discrepancy in these results may be attributed due to the studies being carried out in different TBI models.

The association of TBI with tauopathies has been suggested in several studies. A single incidence of severe brain trauma was shown to induce widespread hyperphosphorylated tau pathology in individuals surviving more than a year after injury (Zanier et al., 2018). Similar results were also observed in mice with a single severe TBI-induced tau pathology that reflected late post-TBI tau pathology in humans. Further analyses showed that induced tau toxicity can spread from the site of injury to other brain regions and also injection of toxic tau from TBI mice to wild-type mice can induce tau pathology, memory deficits, and synaptic alterations, which indicate prion-like behavior of tau protein (Woerman et al., 2016; Zanier et al., 2018). A proteome comparison between the frontal cortex of diffuse and focal TBI cases revealed a significantly higher level of proteins involved in neurodegeneration such as tau protein in diffuse TBI cases compared to focal TBI cases, however, no differences were found in the level of A β_{40} and A β_{42} between two types of TBI (Hamdeh et al., 2018). The results of this study indicated that even a single TBI can induce long-term progressive tau pathology and subsequent neurodegeneration, especially in the presence of diffused axonal injury. Further, repeated mild TBI also has been shown to be associated with NFT formation, neurodegeneration, and cognitive decline. In this regard, studies on American football players, boxers, and wrestlers that are repeatedly exposed to mild TBI, showed an increased level of hp-tau, NFTs, and cognitive impairment and developed CTE (Omalu et al., 2011; Katsumoto et al., 2019). Moreover, serum levels of tau protein were shown to be positively associated with the severity of the injury in a rat model of diffuse axonal injury, suggesting it as a potential diagnostic biomarker to assess the severity of diffuse axonal injury in the early phase (Tomita et al., 2020).

There are two conformational forms of phosphorylated tau at Thr²³¹ reported, including trans p-tau which is a physiological conformation, and cis p-tau as the toxic form which is more physiological, but is converted to trans p-tau by Pin1 (Figure 5; Nakamura et al., 2013; Kondo et al., 2015). In TBI reduced activity of Pin1 results in an increased level of cis p-tau which appears prior to tau oligomerization and aggregation, resulting in impaired axonal microtubule networks and mitochondrial transport. This toxic form can spread to other neurons and induce apoptosis leading to neurodegeneration and cognitive impairment, but this could be relatively ameliorated upon using a cis p-tau antibody (Kondo et al., 2015; Albayram et al., 2017). Thus, the results of these studies indicated that cis p-tau contributes to both short-term and long-term consequences of TBI that can be effectively neutralized by cis p-tau antibody treatment.

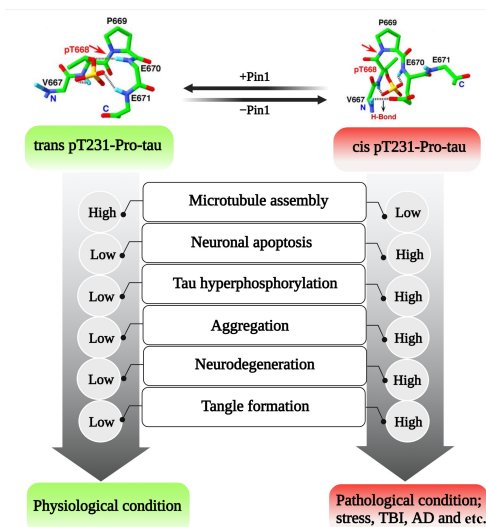


Figure 5 | Conformational changes of tau protein between trans and cis-conformations are mediated by Pin1; trans p-tau is considered as the physiological form of tau protein but cis p-tau is the toxic form that is increased in pathological condition due to impaired Pin 1 activity.

Created with BioRender.com. AD: Alzheimer's disease; Pin1: peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; TBI: traumatic brain injury.

These findings support the notion that TBI can initiate neurodegenerative processes resembling those seen in AD and CTE. The accumulation of A β and tau proteins, along with their pathological consequences, suggests a complex interplay between TBI, protein aggregation, and neurodegeneration. Further research is needed to unravel the intricate mechanisms underlying these processes, which can pave the way for the development of targeted interventions and improved management strategies for individuals with TBI, reducing the risk of long-term cognitive decline and neurodegenerative diseases.

Down Syndrome

Down syndrome (DS) is the leading genetic cause of intellectual disability with an incidence rate of about 14 in 10,000 live births in the United States (Dierrsen, 2012). The disorder is caused by trisomy of chromosome 21 and is therefore known as trisomy 21. Individuals with DS have common phenotypes such as short stature, muscle hypotonia, mental retardation, small head, short neck, protruding tongue, and flat faces; moreover, they are more prone to develop certain health conditions, such as AD, CVDs, and diabetes (Van Goor et al., 1997; Sobey et al., 2015; Antonarakis et al., 2020).

Individuals with DS also showed higher blood levels of A β and tau protein and its phosphorylation forms compared to healthy individuals at young ages. Plasma level of A β showed a progressive age-dependent manner that almost all individuals with DS show sufficient neuropathology for a diagnosis of AD by the age of 40 (Head and Lott, 2004; Lee et al., 2017). As described above, the APP gene is located on chromosome 21 and thus triplicated in DS, resulting in an increased level of APP. In addition, increased activity of β -secretase and decreased activity of α -secretase especially after 40 years of age have been reported in individuals with DS. It is reported that A $\beta_{42/43}$ is initially deposited in the brain with A β_{30} appearing about a decade later (Iwatsubo et al., 1995; Mori et al., 2002; Head et al., 2018). Interestingly intracellular A β accumulation has been reported in DS that appeared prior to extracellular A β aggregation and NFTs and was shown to be accumulated in endosomes causing endocytic pathway abnormalities. These could be prevented in a mouse model of DS by partial inhibition of BACE1 (Cataldo et al., 2000; Jiang et al., 2016). However, it is important to note that BACE1 inhibition reduced the level of APP- β c terminal fragment but did not alter A β_{30} and A β_{42} peptide levels. Therefore, endocytic abnormalities may be due to a higher level of APP- β CTF but not A β levels (Jiang et al., 2016). Although the exact mechanism of intracellular A β aggregation is not still clear, it has been suggested that A β PP overexpression in DS may disrupt mitochondrial function, which in turn triggers intracellular A β aggregation that can further contribute to mitochondrial dysfunction (Busciglio et al., 2002; Abyadeh et al., 2021). Both intracellular and extracellular A β may contribute to NFTs formation and trigger caspase activation and accumulation of caspase cleavage products resulting in apoptotic pathways activation and neuronal loss in the DS brain. These observations were found in the brain of DS individuals aged over 40 years (Head et al., 2002; Head et al., 2018). In addition, age-dependent deposition of phosphorylated A β at serine residue 8 has been observed in extracellular plaques and within the vasculature of the brain of DS (Kumar et al., 2020).

The presence of an insoluble and phosphorylated form of tau protein and also NFTs have been reported in the brain of individuals with DS, even in the presence of low A β burden (Hanger et al., 1991; Zammit et al., 2021). Similar to A β , the plasma level of tau protein is higher in DS patients and showed a progressive age-dependent manner (Kasai et al., 2017; Lee et al., 2017). Although like AD, deposition of tau protein is observed in the DS brain, it may occur in different brain regions of adult DS compared to AD (Lemoine et al., 2020).

The balance between 3R-tau and 4R-tau levels is critical for proper neuronal function and increased expression of either 3R-tau or 4R-tau was shown to be correlated with several tauopathies such as Pick's disease (3R-tau), corticobasal degeneration and progressive supranuclear palsy (4R-tau) (Barron et al., 2020). Expression of 3R-tau is increased in the DS brain and shown to be related to increased expression of dual-specificity tyrosine-phosphorylated and regulated kinase 1A (Dyrk1A), located on the chr21 and triplicated in DS. In this regard, inhibition of Dyrk1A expression resulted in decreased expression of 3R-tau and improved impaired general behaviors in mice models of DS (Shi et al., 2008; Yin et al., 2017). Further studies have indicated that PI3K/Akt/mTOR axis is hyper-activated in DS, resulting in decreased autophagy, IRS1, and GSK3 β activity. However, tau was found to be hyperphosphorylated and associated with elevated expression of Dyrk1A, also enhanced expression of regulator of calcineurin 1 (RCAN1), which is linked to tau hyper-phosphorylation (Perluigi et al., 2014; Di Domenico et al., 2018). Collectively these results suggested the key role mTOR pathway and RCAN1 in the hyper-phosphorylation of tau protein in DS (Figure 6). Consistent with the hypothesis of prion-like behavior of tau protein, injection of plasma-derived neuron-derived small extracellular vesicles of DS-AD cases into the dorsal hippocampus of wild-type mice resulted in an increased level of hp-tau even in the corpus callosum and the mediolateral axis (Ledreux et al., 2021). Therefore, these results indicated prion-like behavior of tau protein that can spread within the brain. These findings collectively shed light on the complex neuropathological mechanisms underlying DS and its association with AD. Understanding these mechanisms may help in the development of targeted therapeutic approaches for DS-related cognitive decline and neurodegeneration.

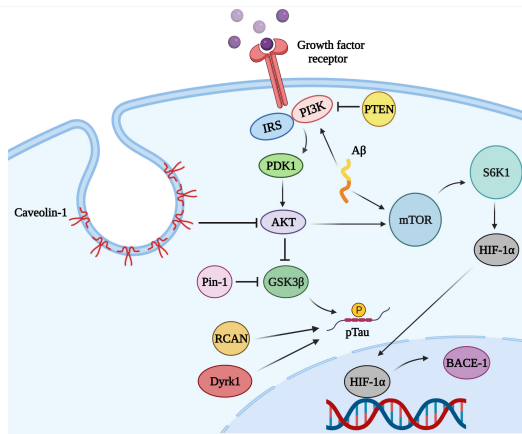


Figure 6 | Interplay between mTOR, A β , and Tau.

Created with BioRender.com. A β : Amyloid beta; AKT: protein kinase B (Akt); BACE-1: beta-secretase 1; BCAN: brevacin; Dyrk1: dual-specificity tyrosine-phosphorylation-regulated kinase 1; GSK3 β : glycogen synthase kinase 3 beta; HIF-1 α : hypoxia-inducible factor 1 alpha; IRS: insulin receptors substrate; mTOR: mechanistic target of rapamycin; PDK1: phosphoinositide-dependent kinase-1; PI3K: phosphoinositide 3-kinase; Pin-1: peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; p-tau: phosphorylated Tau protein; PTEN: phosphatase and tensin homolog deleted on chromosome 10; S6K1: ribosomal protein S6 kinase 1.

Motor Neuron Disease

Motor neuron disease including amyotrophic lateral sclerosis (ALS), the eponymous Lou Gehrig's disease, is a fatal progressive neurodegenerative disorder characterized by the degeneration of both the upper motor neurons of the motor cortex, and the lower motor neurons of the brainstem and spinal cord (Shadfar et al., 2022). The most distinguishing symptoms of ALS are muscle atrophy and weakness, and progressive paralysis (Masrori and Van Damme, 2020). The pathogenic mechanisms leading to neurodegeneration in ALS are not fully defined. Hence, at present, there is no effective cure for the disease, and patients have an average lifespan of three years following diagnosis, with death occurring due to respiratory failure (Masrori and Van Damme, 2020). The only currently approved Food and Drug Administration (FDA) therapeutics for ALS are riluzole (AMX0035), riluzole, and edaravone, although these drugs only extend the life span of patients by two to three months. Furthermore, they do not halt the neurodegenerative process in ALS (Mora, 2017). Therefore, there is an urgent need to develop novel therapeutics for the treatment of ALS, which target the underlying disease mechanisms.

A growing body of evidence indicates the role of A β and tau in ALS pathology. Increased levels of APP have been observed in ALS patients' spinal cord anterior horn neurons even with moderate motor neuronal loss (Calingasan et al., 2005). Similarly, compared to controls, increased levels of A β in the skin of ALS patients were demonstrated using enzyme-linked immunosorbent assays (Tamaoka et al., 2000).

The Caspase family is known to mediate alternative proteolysis of APP (Salvesen and Dixit, 1999). Among the members of the Caspase family, Caspase-3 predominantly participates in APP cleavage (Francois et al., 1999). Caspase-3 can directly cleave APP through apoptosis, leading to increased formation of A β (Francois et al., 1999; Salvesen and Dixit, 1999). Accumulating evidence suggests that caspase-3 plays a significant role in initiating neurodegenerative processes in transgenic mouse models of ALS (Salvesen and Dixit, 1999; Pasinelli et al., 2000), which may contribute to the elevated levels of A β formation.

Higher A β_{42} immunoreactivity was observed in motor neurons in the anterior horn in the postmortem lumbar spinal cord of ALS patients (Calingasan et al., 2005). There was colocalization of the A β_{42} with the oxidative damage markers including heme oxygenase-1, 8-hydroxydeoxyguanosine, and nitrotyrosine in these tissues (Calingasan et al., 2005). Remarkably, enhanced cleaved caspase-3 immunoreactivity was observed within the neurons with intracellular A β_{42} accumulation (Calingasan et al., 2005).

Approximately 4% of fALS and approximately 1% of sALS cases worldwide are caused by mutations in *TARDBP*, the majority of which are missense and autosomal dominant mutations (Sreedharan et al., 2008; Renton et al., 2014). Importantly, however, almost all cases of ALS (97%) and FTD cases (50%) are characterized by the presence of TDP-43 pathology (Chou et al., 2018). TDP-43 pathology is one of the primary features of ALS and FTLD-TDP, and is characterized by loss of TDP-43 function in the nucleus and enhanced deposition into cytoplasmic inclusion bodies in the brain and spinal cord neurons (Arai et al., 2006; Konopka et al., 2020). Redistribution of TDP-43 from the nucleus to the cytoplasm is recognized as a key characteristic of ALS patient motor neurons (Chou et al., 2018). Significantly higher levels (200%) of TDP-43 were observed in cortical autopsies of late-stage AD patients (Herman et al., 2011). Additionally, TDP-43 inclusions have been found in up to 57% of AD cases (Josephs et al., 2014; James et al., 2016). Elevated

TDP-43 pathology was detected in the rat motor cortex, following lentiviral expression of A β_{1-42} (Herman et al., 2011). In addition, there was a correlation between A β_{1-42} expression and increased phosphorylation of TDP-43 and its accumulation in the cytosol (Herman et al., 2011). Compared to wild-type mice, TDP-43 modifications were detected in 3xTransgenic AD (3xTg-AD); however, these modifications were reduced in parkin-injected hippocampi, despite the presence of Tau pathology. This indicated that A β triggers TDP-43 pathology, even in the absence of Tau (Herman et al., 2011).

Modifications in tau metabolism have been also reported in ALS (Strong et al., 2020), the most conspicuous tau alteration is its pathological phosphorylation at Thr¹⁷⁵ (pThr¹⁷⁵tau) (Strong et al., 2020). pThr¹⁷⁵tau has also been identified in CTE with ALS and in both *in vivo* and *in vitro* experimental paradigms, emphasizing the key role of tau phosphorylation in the pathobiology of ALS (Strong et al., 2020). Experimental rodent models suggest the presence of phosphorylated tau and alterations in the metabolism of TDP-43 and tau act synergistically to deteriorate the pathology of either (Chornenkyy et al., 2019; Strong et al., 2020).

Furthermore, in extracts of both the brain and ventral spinal cord of sporadic ALS patients, neurotoxic tau fragment (tau⁴⁵⁻²³⁰) has been identified (Lang et al., 2014; Vintilescu et al., 2016). Pathological forms of phosphorylated tau, together with tau immunoreactive inclusions have been detected in ALS patients (Yang et al., 2003; Yang et al., 2005; Yang and Strong, 2012). Prominent tau deposition (pThr¹⁷⁵tau) was observed in motor neurons following TDP-43 pathology (Yang and Strong, 2012).

Alterations in tau metabolism were also detected in cortical and spinal motor neurons in sporadic ALS patients in antemortem or postmortem obtained tissues (McKee et al., 2009; McKee et al., 2016; Mez et al., 2017). pThr²³¹tau, pThr¹⁷⁵tau, and oligomeric tau (T22) were predominantly observed in the samples of sporadic ALS patients (Moszczynski et al., 2018). A recent study showed the increased levels of phosphorylated tau (p-tau) in CSF of ALS patients with or without cognitive impairment (Gong et al., 2022). Although the CSF p-tau level and p-tau:t-tau ratio were lower in patients with ALS than in ALS patients with cognition impairment, CSF p-tau could be used as a reliable index of cognition impairment in patients with ALS (Gong et al., 2022).

Amyloid- β and Tau Protein Signatures in Other Diseases

Autism

Autism spectrum disorders (ASD), are a diverse group of conditions characterized by challenges with social skills, communication, and repetitive behaviors. The prevalence of autism has increased in recent decades and according to the Centers for Disease Control and Prevention 2016 data, about 1 in 54 children in the USA are diagnosed with autism. Males have a higher risk of autism and related disorders than females (Palmer et al., 2017). The exact mechanism underlying autism is not clear, however, environmental and genetic factors are supposed to play a causative role (Palmer et al., 2017; Emberti Gialloreti et al., 2019). Children with autism commonly showed brain overgrowth, which is coincidental with the onset of symptoms. Initial studies in patients with severe autism observed an increased level of APP and A β PP α but decreased levels of A β PP β , A β_{40} , A β_{42} and also lack of cerebral plaques, therefore indicating the aberrant hyperactivity of non-amyloidogenic pathway (Bauman, 1994; Sokol et al., 2006; Ray et al., 2011). Data regarding the serum level of tau protein and its phosphorylation are inconsistent and both increased and decreased levels of this protein have been reported in both autistic humans and mice (Kadak et al., 2015; Barón-Mendoza et al., 2018; Ayaydin et al., 2020; Grigg et al., 2020). However recently it has been shown that genetically decreasing tau protein level prevents behavioral signs of autism in mice models possibly through the increasing levels of phosphatase and tensin homolog deleted on chromosome 10 (PTEN). This then suppresses the PI3K/Akt/mTOR signaling pathway that is overactivated in autism and is described as a shared altered mechanism between autism and AD (Tai et al., 2020; Mencer et al., 2021). The understanding of autism's underlying mechanisms is still evolving, and further research is necessary to uncover the complex interactions between genetic and environmental factors. Investigating the roles of amyloid metabolism, tau protein, and shared pathways with AD may provide further insights. The heterogeneity of ASD requires a personalized approach to diagnosis, treatment, and support, taking into account the individual's unique needs and characteristics.

Multiple sclerosis

MS is an autoimmune inflammatory disease of the central nervous system, that is the leading cause of acquired neurological disability in young adults worldwide and currently affects about 300,000 to 400,000 individuals in the US and over 2.5 million people worldwide (Van Schependom et al., 2019; Wallin et al., 2019). MS is pathologically characterized by the formation of demyelinating lesions in the brain and spinal cord, which induce inflammation and subsequently neurodegeneration (Filippi et al., 2018; Mirzaei et al., 2022). Myelin dysfunction also has been shown to drive the A β deposition in AD mouse models (Depp et al., 2023). Brain atrophy is extensively observed in MS patients and is recognized as an imaging marker of neurodegeneration in MS patients; however, early neurodegeneration may appear in the absence of brain atrophy (Van Schependom et al., 2019). The presence of amyloid plaques has been reported in MS patients; moreover, CSF levels of soluble A β_{1-42} were shown to be decreased and associated with cognitive decline in MS patients. It was suggested as a potential biomarker of neurodegeneration

that may predict clinical outcomes (Mai et al., 2011; Mori et al., 2011; Augutis et al., 2013; Pietroboni et al., 2017). In contrast to A β , the level of tau protein and its abnormal phosphorylation was found to be increased in MS patients in the neurodegenerative phase of tissue injury, which was associated with neuronal and axonal loss and suggested as an early marker of axonal damage in MS patients (Brettschneider et al., 2005; Terzi et al., 2007; Anderson et al., 2008). The presence of both amyloid plaques and abnormal tau protein levels in MS highlights the complex nature of the disease and suggests overlapping mechanisms with other neurodegenerative disorders such as AD. Further research is needed to fully understand the role of these biomarkers in the progression of MS and their potential implications for diagnosis, monitoring, and treatment of the disease.

Huntington's disease

HD is a rare genetic neurodegenerative disorder with a prevalence of 2.71 in 100,000 live birth globally (Pringsheim et al., 2012; Bates et al., 2015). HD patients commonly experience uncontrolled body movement, cognitive decline, and psychiatric disturbances (Li and Li, 2004; Żukiewicz-Sobczak et al., 2014). Patients with HD showed amyloid-like inclusions in their brain and heart that may cause neurodegeneration and cardiomyopathy (Melkani et al., 2013). Currently, available data about the level of A β in HD patients are inconsistent, while some researchers indicated a higher level of A β in HD patients, others failed to find significant differences with healthy controls (Jellinger, 1998; McGowan et al., 2000; Mollenhauer et al., 2006; Grätze et al., 2016). However, high levels of hyperphosphorylated and truncated tau and NFTs have been observed in the brain of HD patients (Masnata et al., 2020). Moreover, tau haplotype was shown to affect the cognitive function of HD patients, whereas patients with the H2 haplotype showed more severe cognitive decline than patients with H1 haplotype (Vuono et al., 2015; Grätze et al., 2016). In addition, mutant huntingtin, the HD protein, triggers tau protein hyperphosphorylation and alters its subcellular distribution (Blum et al., 2015). The level of caspase-2 is increased in HD patients and its inhibition improved cognitive and motor deficits in mice model of HD, interestingly a recent study suggested that caspase-2-mediated tau cleavage results in a soluble truncated tau that adversely affects synaptic function and cognitive performance in HD patients (Liu et al., 2019). Understanding the mechanisms underlying their interactions and contributions to disease progression is crucial for developing targeted therapies for HD.

Creutzfeldt-Jakob disease

CJD is a rare and fatal neurodegenerative disorder and the most common human prion disease with a prevalence of one individual per million per year worldwide (Iwasaki, 2017; Sitamagari and Masood, 2022). Prion diseases, previously known as transmissible spongiform encephalopathy are a group of neurodegenerative diseases that affect almost all mammals. In prion diseases, the pathological form of prion protein is able to transmit the disease (Gough and Maddison, 2010). A significantly increased CSF tau protein has been reported in CJD patients (58-fold) compared to healthy controls, while CSF A β 42 level was decreased in CJD patients (Kapaki et al., 2001). Moreover, abundant A β and marginal prion deposits (an inverse association) also have been reported in some CJD patients; in addition, CSF tau level showed a negative association with cognitive performance and a positive correlation with disease severity in CJD patients, indicating the potential use of CSF tau as a biomarker of neuronal damage (Debatin et al., 2008; Cohen et al., 2016). These findings indicate that while CJD shares some pathological features with other neurodegenerative diseases, such as the presence of tau pathology, it also exhibits unique characteristics, including decreased levels of A β 42. The abnormal accumulation of prion proteins and the associated neurodegeneration are the key hallmarks of CJD. Moreover, further research is needed to better understand the mechanisms of CJD and to explore the potential of CSF tau and other biomarkers as diagnostic and prognostic tools.

Wilson's disease

WD is a rare genetic disorder with a prevalence of 1 in 30,000 (based on limited available data) (Sandahl et al., 2020). WD is characterized by abnormal accumulation of copper (Cu) in the liver, brain, and other vital organs and with several symptoms ranging from fatigue to difficulty with speech, controlling movements, or muscle stiffness. Disordered Cu metabolism is also associated with other neurodegenerative diseases such as AD and PD (Bandmann et al., 2015). Studies reported that Cu binds to A β and decreases its clearance from blood-brain barrier, therefore leading to A β deposition; moreover, Cu also increases A β production and inflammation (Syme et al., 2004; Singh et al., 2013). Cu also can bind to tau protein and may induce its aggregation, moreover, serum levels of tau protein also have been found to be increased in patients with WD, and are believed to be a promising biomarker of axonal impairment and possible neuronal damage in patients with WD (Soragni et al., 2008; Lekontseva et al., 2019). These findings highlight the complex interactions between copper metabolism and the accumulation of A β and tau proteins in WD. Further research is needed to better understand the underlying mechanisms linking copper dysregulation to A β and tau pathology in WD, as well as its implications for disease progression and potential therapeutic interventions that may involve targeting copper homeostasis.

Conclusion

A β and tau protein are well-established pathogenic factors in several neurodegenerative diseases, particularly in AD; however, a growing body of evidence has indicated the presence of these factors in other diseases and provided molecular mechanisms underlying their aggregation and

pathogenesis. However, research about the role of these pathological factors in other diseases is limited. The reasons for the alteration of protein expression and modification in these diseases are multifactorial and may vary depending on the specific condition. One possible explanation is that A β and tau proteins are involved in various cellular processes beyond their roles in neurodegeneration. They participate in signaling pathways, synaptic function, and neuronal plasticity, and their dysregulation can contribute to pathological processes in different diseases. For example, in cardiovascular diseases, A β and tau may be involved in vascular dysfunction and contribute to cerebrovascular pathology. In diabetes, these proteins may contribute to neuronal damage and cognitive impairment associated with the disease. The presence of A β and tau protein alterations in these diseases may indicate the potential involvement of neurodegenerative mechanisms, but their presence alone does not appear to be specific. However, these proteins may play a critical role in cellular dysfunction and contribute to the progression of pathology specific to each condition.

Most studies are focused on altered levels of A β and tau protein and also phosphorylation of tau protein in disease; however, other PTMs such as acetylation and truncation also play a critical role. Moreover, conformational changes including trans and cis conformation may induce different levels of toxicity, which is not well investigated in these diseases. Regarding their potential as diagnostic and therapeutic biomarkers, further research is needed. While A β and tau have been extensively studied in the context of AD, their use as biomarkers in other diseases is still being explored. It is important to consider the specificity and sensitivity of these biomarkers in different conditions, as well as their correlation with disease progression and response to treatment. Utilizing A β and tau as diagnostic and therapeutic markers in non-neurodegenerative diseases may require tailored approaches and comprehensive evaluation to establish their clinical utility. Along with A β and tau protein, upstream regulators of these factors such as mTOR signaling and Pin1 have been suggested as other potential therapeutic targets to slow or prevent disease progression and ameliorate disease symptoms. Overall, the presence of A β and tau protein alterations in diseases beyond AD suggests shared mechanisms and potential contributions to pathogenesis. Further research is necessary to unravel the specific roles of these proteins in different conditions, assess their diagnostic value, and explore their potential as therapeutic targets.

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