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Opinion

A Possible Neurodegeneration Mechanism Triggered by Diabetes

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Several conditions result in neurodegeneration; among which diabetes mellitus (DM) is of crucial importance. Tau (τ) malfunction is a major pathological process participating in neurodegeneration. Despite extensive considerations, the actual causative link between DM and τ abnormalities remains uncertain thus far. Phosphorylated (p)-τ at Thr–Pro motifs can exist in the two distinct *cis* and *trans* conformations. *cis* is neurotoxic, and is accumulated upon various stress conditions, such as nutrition depletion. We assume that pathogenic *cis* p-τ is the central mediator of neurodegeneration in DM, and propose why different brain areas give various responses to stress conditions. We herein juxtapose recent approaches in diabetic neurodegeneration and propose a therapeutic target to stop neuronal loss during DM.

Highlights

DM is a major metabolic disorder that may result in neurodegeneration.

Disrupted insulin signaling pathway or glucose metabolism deficiency can induce τ hyperphosphorylation.

τ is a microtubule-associated protein. It is moderately phosphorylated under physiological conditions but its hyperphosphorylation reflects pathogenicity and is a major pathological hallmark of neurodegeneration.

Phosphorylated τ at Thr231 exists in the two distinct *cis* and *trans* conformations. *cis* p-τ is neurotoxic and drives neurodegeneration. *cis* p-τ is accumulated in cultured neurons upon oxidative stress as well as nutrition depletion.

DM and Neurodegeneration

DM is a metabolic syndrome with broad clinical phenotypes. There are abnormally high blood glucose levels in DM due to either inadequate insulin secretion or insulin resistance [1]. Anomalies in glucose metabolism or any dysfunction in the insulin signaling pathway lead to a vast spectrum of systemic complications and pathologies in different organs, among which the central nervous system (CNS) shows a severe response [1,2]. Dementia, the most prevalent neurodegenerative disorder, is one of the common complications of DM [3,4]. DM and dementia are common age-related diseases globally. More than 422 million adults and 50 million patients around the world suffer from DM and dementia, respectively[i,ii]. DM results in memory disorders, loss of attention, and deregulated information processing [5]. Epidemiological studies have established DM as one of the main risk factors for dementia, whose incidence in diabetic patients is increased up to 70% [4,6]. Furthermore, the severity of dementia appears to correlate with DM progression [6,7]. Dementia can cause brain-specific DM as well. Type 3 DM (T3DM) has been introduced as another type of diabetes in Alzheimer's disease (AD) patients (Box 1) [8,9].

Tubulin-associated unit (τ) (see Glossary) hyperphosphorylation (p-τ) and aggregation along with **amyloid β (Aβ) plaque** formation are the most common pathological hallmarks of neurodegeneration that are also observable in diabetic patients [10–13]. Moreover, some studies showed that these hallmarks are detectable in cerebrospinal fluid (CSF) of DM patients with no neurodegenerative-dependent mutation (Table 1) [11,14,15].

Neurofibrillary Tangles (NFTs): Fundamental Hallmark of Neurodegeneration

The function of τ is predominantly controlled by its phosphorylation status but its hyperphosphorylation reflects NFT formation [13,16]. DM may result in increased CSF p-τ levels in those patients without any particular age-related neurological disorder, such as AD [11], which is consistent with reports demonstrating that NFTs are found in DM mouse models with no age-related neurodegenerative disorders [17,18]. Thus, NFTs observed in DM could be irrespective of aging and neurological disorders, leading to neurodegeneration [17–19]. Despite extensive research, it has remained uncertain how DM can induce p-τ and NFTs. There are several reports describing the molecular mechanisms of tauopathy in DM [2,20,21]. Notably, a disrupted insulin signaling pathway and glucose metabolism can induce p-τ formation [2,17,22]. Mitochondrial dysfunction, oxidative stress, inflammation, and τ-related kinase overactivation, are also some key mechanisms in p-τ induction in DM [21,23,24]. Although some studies have concluded that p-τ is the main pathological hallmark for dementia in diabetic patients [11,15], the relevant phosphorylation sites on τ protein linking to disease progression remain to be clarified.

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Box 1. Type 3 Diabetes Mellitus

DM can cause insulin signaling pathway deficiency and glucose metabolism abnormalities in the brain. Examination of the postmortem brain of patients with AD has shown that the disease can cause biochemical and molecular abnormalities that overlap with DM [9]. While serum insulin and glucose levels are normal in AD, there are fewer IRs in the CNS and consequently, insulin resistance in the brain. AD may disrupt glucose metabolism as well as gene expression of insulin-like growth factors, insulin, and IRs [77]. Aβ plaque deposition, τ protein aggregates, inflammation, mitochondrial dysfunction, and oxidative stress are some of the pathological features of AD, which can induce insulin resistance in T3DM [9]. Moreover, there are increased microglial and astrocytic inflammatory factors at the early stages of sporadic AD, which would result in T3DM [9]. Furthermore, neurotoxic Aβ oligomers destroy synaptic networks and neuronal membranes, which in turn modify IR sensitivity and distribution and induce insulin resistance in the neurons. Toxic oligomers would result in oxidative stress, which triggers diabetic cascades [78].

It has been proposed that phosphorylation of τ at specific sites correlates with its functional abnormalities [10,16]. In particular, p-τ at Thr–Pro domains exists in distinct *cis* or *trans* conformations, and the *cis* p-τ conformers are almost exclusively pathogenic and prone to aggregation. Notably, recent studies have found that phosphorylated *cis* pThr231-τ is neurotoxic and leads to

Studied groups/ No. of patients	No. and % of APOEε4$^+$ (DM/control)	Analyzed biomarkers in CSF	Results	Refs
T2DM/124 control/692	ND	Total τ/p-τ	Association of T2DM with level of total τ/p-τ	[11]
		$Aβ_{42}$	NS[a] association of T2DM with level of $Aβ_{42}$	
IR/28 non-IR /30	10, 35.7% / 13, 43.3% (ns)	Total τ/p-τ	NS difference in total τ/p-τ and between IR /non-IR groups	[76]
		Aβ	NS difference in Aβ level between IR/non-IR groups	
Diabetes/11 Control/18	ND	p-τ	NS difference in p-τ level between DM/ control groups	[14]
		$Aβ_{40,42}$	NS difference in $Aβ_{40}$ and $Aβ_{42}$ level between DM/control groups	
T2DM/77 Control/735	39/327 (ns)	$Aβ_{1–42}$	Significant difference in $Aβ_{1–42}$ level between DM/control groups	[12]
T1DM/37 Control/15	35.1% / 46.7% (ns)	p- τ	Significant difference in p-τ level between T1DM/control groups	[15]
		Aβ	The significant difference in Aβ level between T1DM/control groups	

Table 1. Clinical Studies Investigating Correlative Biomarkers between DM and Neurodegeneration

[a]Abbreviations: ND, no data; NS, not significant.

Glossary

Advanced glycation end products (AGEs): high glucose levels can induce nonenzymatic protein glycation, named AGEs. AGEs may have endogenous (inside the body) or exogenous (dietary) origin. AGE accumulation may result in different diabetic related complications; likely through oxidative stress and inflammation. AGEs may trigger different signaling pathways, through interaction with their specific receptors.

Amyloid β plaques (Aβ): amyloid precursor protein is a transmembrane protein, whose misprocessing reflects Aβ polypeptide formation. Aβ is one of the major pathological hallmarks accumulating in the extracellular matrix and forms Aβ plaques. Aβ plaques may additionally induce inflammation and oxidative stress, reflecting synapse disruption and neurodegeneration.

Glycogen synthase kinase 3β (GSK3β): GSK3β is a member of the proline directed serine–threonine kinase family playing a central role in insulin signaling pathway. It also phosphorylates τ protein. GSK3β function is controlled by phosphorylation at different sites. AKT is a major GSK3β inhibitor being activated upon disturbed insulin signaling pathway in different diseases, such as AD and DM.

Long term potentiation/long term depression (LTP/LTD): LTP/LTD are the two important synaptic activities, involved in learning and memory. LTP is a long-lasting synapse strengthens primarily identified in rat hippocampus. Disruption of LTP can induce different cognitive decline diseases; such as AD and PD. LTD is the opposite of LTP and can decrease persistent synapse strengthens.

Peptidyl-prolyl *cis-trans* isomerase (Pin1): Pin1 is an enzyme that catalyzes *cis/trans* isomerization of serine/threonine–proline motifs. Pin1 has two distinct domains including the WW domain at the N terminus and PPIase domain at the C terminus. WW domain binds to specific serine/threonine–proline motifs on target proteins and the PPIase domain can induce *cis/trans*

neurodegeneration; a process termed cistauosis [25,26]. The neurotoxic form is induced by several stress conditions, such as nutrition depletion [27].

We herein summarize possible causative links between diabetic pathways and neurodegeneration process; highlighting *cis* p-τ as a key intermediate factor. Moreover, we review the pathological effects of DM in different brain areas.

Destructive DM Complications in CNS: Possible Mechanisms

In general, DM induces stress in neurons through the following mechanisms: (i) disruption of glucose metabolism and (ii) impairment of the insulin signaling pathway. These two pathogenic processes induce various cascades inside the neurons; eventually resulting in oxidative and inflammatory stresses [28]. Due to high oxygen consumption and accumulation of free radicals in the CNS, the brain is susceptible to oxidative stress [29]. It has been reported that different glucose transporters (Gluts) and insulin receptors (IRs) are not evenly distributed in the CNS (Box 2) [30,31]. This in turn, manifests as different responses in various brain areas under diabetic conditions [31]. Below are some proposed mechanisms of stress-induced brain damage in patients with DM.

Insulin and the Insulin Signaling Pathway

It has been shown that insulin has several roles in the CNS, including neurotransmitter synthesis, protein and glucose metabolism, brain development, synaptic plasticity, and the learning process [32]. It may also affect the localization of both the γ-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors [33]. Furthermore, it directly regulates memory formation and synaptic plasticity through **long term potentiation/depression (LTP/LTD)** control [34]. Thus, either insulin resistance or deficiency can suppress insulin-related processes. Notably, insulin administration, for the control of blood glucose, improves memory function in AD patients [35].

Insulin deficiency [type 1 (T1)DM] and insulin resistance (T2DM) can result in impaired insulin signaling pathway in the brain. The abnormal insulin signaling pathway can induce stress in IR-rich neurons through different mechanisms, including phosphoinositide 3-kinase/AKT (PI3K/AKT) inhibition and **glycogen synthase kinase 3β (GSK3β)** activation (Figure 1A) [36]. GSK3β could be phosphorylated by several kinases, among which AKT is of crucial importance [37]. Under the healthy condition, insulin signaling activates AKT, which in turn phosphorylates GSK3β at serine 9, leading to its inactivation [17]. It has been demonstrated that intracerebroventricular streptozotocin (STZ) injection is associated with desensitization of IRs and impaired insulin signaling, resulting in GSK3β activation in the brain [38]. Impaired insulin-like growth factor-1 signaling and increased GSK3β activity in the brain has been reported in T2DM mouse models [17,18]. Notably, treatment of diabetic mice with the appropriate dose of insulin significantly restores GSK3β phosphorylation [18]. Beside insulin, blood glucose can regulate

conformational changes in target proteins. Pin1 can affect localization, phosphorylation, interaction, stability, and activity of target proteins. Deregulation of Pin1 activity has contributed to different diseases such as AD, cancer, and DM. Pin1 plays different roles in the insulin signaling pathway. Pin1 can modulate the insulin signaling pathway by affecting activity of proteins such as AKT and GSK3β. Pin1 is suppressed differently under various stress conditions. It is phosphorylated at Ser71 upon traumatic brain injury, down-regulated in AD, or oxidized at Cys113 upon oxidative stress; resulting in *cis* p-τ accumulation.

Tubulin-associated unit (τ): τ is a microtubule-associated protein, whose function is to stabilize microtubule structure in axonal cytoskeleton. It is a phosphoprotein whose functions are thought to be controlled by phosphorylation but its abnormal hyperphosphorylation reflects pathogenicity. Abnormal τ hyperphosphorylation can induce τ dissociation from microtubules, resulting in its aggregation, NTF, and eventually neurodegeneration. There are over 80 phosphorylation sites on τ, and most of them are considered to be physiological sites. It has been demonstrated that phosphorylated τ at Thr–Pro domains may exist in the two distinct *cis* and *trans* conformations; whose conversion is mediated by Pin1 isomerase.

Box 2. IR and Glut Distribution

Glucose is the major source of energy for the brain. Glucose transporters mediate the availability of glucose for neurons in the brain. There are two different types of glucose transporters: (i) insulin-independent glucose transporters (GLUT1, 3) and (ii) insulin-dependent glucose transporters (GLUT4) [22,30]. The pattern of distribution of these transporters is heterogeneous in different parts of the brain [30]. The two main insulin-independent glucose transporter isoforms in the brain are GLUT1 and GLUT3. The former one is expressed in blood–brain barrier endothelial cells and glial cells. GLUT3 is expressed in the cortex, hippocampus, and glial and endothelial cells [30]. GLUT4 is an insulin-dependent glucose transporter located in the hippocampus, hypothalamus, and olfactory bulb [55]. In hyperglycemic conditions, insulin-insensitive transporters transfer glucose inside the neurons based on its concentration in blood [46]. Glucose neurotoxicity is the result of high glucose concentration in neural cells in hyperglycemic conditions [46]. In this condition, nutrition depletion happens in parts of the brain in which GLUT4 is dominant [30].

Furthermore, the same anatomical heterogeneous distribution pattern is shown for IRs in different parts of the brain. IRs are mainly located in olfactory bulbs, cerebral cortex, hypothalamus, cerebellum, and the choroid plexus. In both types of DM, these parts of the brain have stress complications secondary to disruption in insulin signaling pathway disorders [31,75].

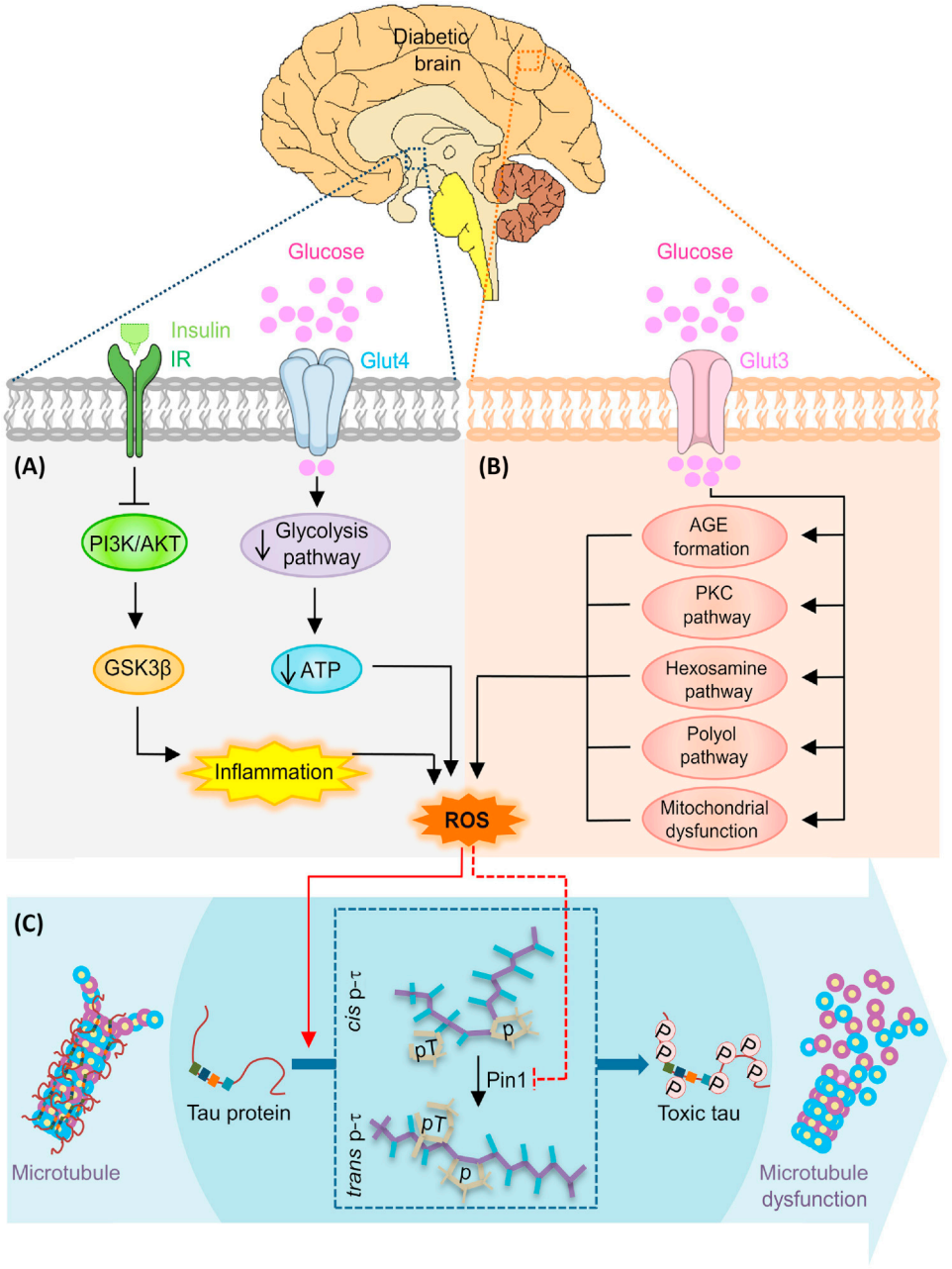

Figure 1. Induction of Tauopathy in Diabetes.

In insulin-receptor-rich areas of the brain, such as the hypothalamus, insulin resistance or lack of insulin can inhibit the phosphoinositide 3-kinase (PI3K)/AKT signaling pathway. Glycogen synthase kinase 3β (GSK3β) can be activated as a result of PI3K/AKT inhibition. GSK3β induces reactive oxygen species (ROS) production through the induction of inflammation. In addition, in neurons with insulin-dependent glucose transporters such as Glut4, less glucose enters the cells, and, so there is elevated ROS in neurons due to less ATP production (A). In insulin-independent glucose transporters (Glut3) rich areas, such as some parts of the cortex, more glucose enters the neurons. High intracellular glucose concentration inside the neurons induces different pathways such as advanced glycation end product (AGEs), protein kinase C (PKC), hexosamine, and polyol, and

(Figure legend continued on the bottom of the next page.)

GSK3β activity [39,40]. In particular, hypoglycemia, as a result of starvation, decreases GSK3β phosphorylation through AKT inactivation [39]. STZ-induced hyperglycemia in mice impacts GSK3β activity through its phosphorylation at serine 9 in the cortex and hippocampus [39]. It is clear that DM-associated metabolic anomalies induce oxidative stress and activation of GSK3β [24,41]. GSK3β is a key kinase in the insulin signaling pathway, playing different roles in the pathogenesis of the DM, such as p-τ formation [17]. GSK3β, a major τ kinase, plays several roles in CNS development and maturation, such as cell migration, neural progenitor proliferation, and neurogenesis [42]. Moreover, GSK3β may regulate LTP/LTD, inflammatory responses, and cytoskeleton dynamics through impacting τ phosphorylation [43]. There are several reports on GSK3β activation and p-τ formation in DM [17,18,38]. STZ administration suppresses AKT and activates GSK3β, which in turn phosphorylates τ protein [38]. Insulin resistance in the neuron-specific IR knockout of also results in GSK3β activation and τ phosphorylation [2]. It is notable that GSK3β overactivation is sufficient to induce τ aggregates. GSK3β overexpression in animal models resulted in p-τ formation as well as memory impairment [44]. GSK3β overactivation stimulates inflammatory transcription factors, including nuclear factor kappa enhancer of B cells *(NF-κB)*, signal transducer and activator of transcription (STAT)1–3, activator protein (AP)-1, and β-catenin [37]. Taking together, we believe insulin resistance or deficiency would result in p-τ accumulation through GSK3β activation and induction of inflammation in IR-rich areas.

Glucose Metabolism

There is impaired glucose metabolism in DM, resulting in a stress condition in the nervous system [45]. There is glucose toxicity in hyperglycemia, due to increased glucose uptake in insulin-unresponsive neurons [46]. Glucotoxicity as a consequence of hyperglycemia can disturb the glycolysis pathway in neurons, resulting in increased reactive oxygen molecules [47]. Hyperglycemia-triggered oxidative stress in neurons is mediated by different mechanisms, including protein kinase C (PKC) pathway activation, **advanced glycation end products (AGEs)** formation, mitochondrial dysfunction, and activation of polyol and hexosamine pathways (Figure 1B) [20,48,49]. For instance, in the polyol pathway, the production of sorbitol and NADH is higher than in normal conditions. Moreover, *reactive oxygen species* (ROS) production is higher than under normal conditions due to the excessive amount of NADH [50]. Hyperglycemia results in AGE accumulation, and in turn, reflects oxidative stress and p-τ formation [51]. AGEs can cause cell damage through different mechanisms, such as intracellular protein malfunctions, resistance to lysosomal degradation, as well as glycosylation of membranous and extracellular proteins [52]. In addition, AGEs interact with AGE receptors (RAGEs) expressed in neurons, astrocytes, and microglia, leading to neurodegeneration [49,52]. AGE–RAGE interaction also induces oxidative stress through NADPH oxidase and different kinase activation [52]. Therefore, the AGE–RAGE pathway contributes to DM-related neurodegeneration, mainly through inflammation and oxidative stress, which is causally linked to p-τ formation via τ kinase activation [51–53]. Nutrition depletion is another stress condition in those insulin-dependent Glut-expressing neurons [54]. Binding of insulin to its receptors can enhance the incorporation of insulin-dependent Gluts (such as Glut4) storage vesicles with the cell membrane [45]. Impaired insulin signaling can affect brain glucose metabolism, through its impact on Glut4 trafficking from the cytosol to the cell membrane [21]. Disrupted Glut4 function reflects energy deficiency and hypometabolism in the neurons [45]. Lesser glucose uptake would result in impaired glycolysis and AMP/ATP ratio [55]. Imbalance in AMP/ATP production in neurons can affect the downstream ATP-dependent pathways, resulting in oxidative stress [54]. Energy deficiency may also cause endoplasmic reticulum stress, mitochondrial dysfunction, disruption of the synaptic connection and neuronal cytoskeleton, and inflammation [21,45]. Finally, oxidative and inflammatory stresses can induce p-τ formation and neurodegeneration [17,24,45] (Figure 1C).

Apolipoprotein E (APOE) ε4 homozygous subjects are prone to abnormalities in glucose metabolism, reflecting a higher risk of neurodegenerative disorders. They have increased τ tangle formation, Aβ

Figure 1. *Continued*

mitochondrial dysfunction, leading to ROS accumulation (B). Elevated intracellular ROS can induce τ hyperphosphrylation. Phosphorylated τ can induce microtubule dissociation. ROS possibly can inhibit peptidyl-prolyl cis-trans isomerase (Pin1) activity and induce *cis* p-τ formation and microtubule dissociation (c). Abbreviation: IR, insulin receptor.

plaques, and brain atrophy, as well as lipid and glucose metabolism deficiency. Two independent studies showed that APOEε4 homozygous subjects are at high risk of T2DM compared with the normal groups [56,57]. Furthermore, it has been demonstrated that APOEε$4^{+/+}$ is significantly coordinated with AD incidence [58].

Despite extensive considerations on causative links between insulin signaling pathway, glucose metabolism anomalies, and p-τ formation, the actual molecular mechanism has remained uncertain thus far. It is of crucial importance to determine the causative links in order to find the right therapeutic targets to stop the pain of patients.

DM Leads to Tauopathy

As discussed above, oxidative stress and inflammation in neurons, due to anomalies in either glucose metabolism or the insulin signaling pathway, may imbalance τ kinases and phosphatases such as GSK3β and protein phosphatase 2 (PP2A) [24,45]. Inhibition of GSK3β as a potent τ-related kinase by kinase inhibitors such as 6-bromoindirubin-3′ oxime can inhibit τ phosphorylation [59] of cultured neurons treated with H_2O_2 [41]. Furthermore, ROS can induce p-τ formation through other kinase activation including c-Jun N-terminal kinase and p38 mitogen-activated protein *kinase* activation [60].

p-τ can dissociate from microtubules and assemble into oligomers and NFTs [10,16]. Studies have shown that oligomers are more toxic than other forms of τ aggregates [61,62]. Oligomers can be spread to adjacent neurons and different brain areas by prion-like mechanisms, inducing stress in neighboring neurons [61,62]. τ oligomers, but not other forms of τ fibrils and aggregates, that were injected into the brain of wild-type mice can induce cognitive abnormalities and synaptic dysfunction [62]. There are some proposed mechanisms for the prion nature of oligomers, such as tunneling nanotubes, exosome related diffusion, endocytosis, and receptor-mediated endocytosis [63]. Transmitted oligomers can affect cell viability through mitochondrial dysfunction and microtubule instability, thereby affecting intracellular transport [62,63]. τ oligomers can decrease different mitochondrial complex activity and ATP production [62,63]. They may further disrupt mitochondrial membrane integrity, induce inflammation as well as oxidative stress, and activate apoptotic pathways [62–64]. Active and passive immunotherapies against p-τ tangles have been implemented [65]. However, their results have not been promising enough to be translated to the clinic. In addition, some chemicals have been used to block τ aggregation; such as rhodanines and N-phenylamine [66]. However, p-τ oligomers seem more neurotoxic than the aggregated forms [61,62]. Thus, it does not seem advisable to block aggregation [61,65].

p-τ oligomers have been recently recognized as pathogenic factors and drivers of neurodegeneration [61,62,65]. Since p-τ aggregates are detectable at the late stage of neurodegenerative diseases as well as in the diabetic patient's brain, their elimination may not have clinical implications, as mentioned earlier [13,67]. Instead, it is crucial to target pathogenic p-τ at early stages of neurodegeneration. In general, the high incidence of DM and neurodegenerative disorders that accompany this metabolic disease highlight the need for specific biomarkers for early detection of pathogenicity. Apparently, it is of importance to determine the pathogenic p-τ epitope, which drives the pathogenicity and neurodegeneration in DM, in order to find the right therapeutic strategy to prevent or even reverse disease progression at an early stage.

Cistauosis: Novel Neurodegeneration Mechanism Resulting from Stress

Inflammation and ROS can cause p-τ formation, likely through GSK3β activation and disruption of glucose metabolism in neurons [41]. Under stress conditions, τ-related kinases phosphorylate τ protein at different sites, including Thr–Pro domains [60]. It has been shown that τ phosphorylation at Thr231 results in the two distinct *cis* and *trans* conformations; conversion of which is mediated by **peptidyl-prolyl *cis/trans* isomerase (Pin1)**. Inactivated Pin1 in pathological conditions reflects *cis* p-τ accumulation [68–70]. *Cis* p-τ accumulates and makes aggregates inside the neurons and consequently, induces cell death upon either oxidative stress or nutrition depletion. *cis* p-τ has been introduced as an early biomarker in patients with mild cognition impairment without any other AD symptoms and bipolar disease, which is indeed helpful for the disease diagnosis [25,26,71]. In traumatic

brain injury, *cis* p-τ appears earlier than other p-τ epitopes such as, paired helical filament (PHF) and AT8. The monoclonal antibody against *cis* p-τ removes aggregates and suppresses neurodegeneration both *in vivo* and *in vitro* [26,27].

Considering the fact that nutrition depletion causes *cis* p-τ accumulation, it seems reasonable to conclude that DM, as the most common nutritional stress in neurons, causes *cis* p-τ formation. The possible mechanism for *cis* p-τ formation and neurodegeneration in DM may be attributed to ROS induction and Pin1 inhibition (Figure 1C).

Pin1 Modifications: Potential *cis* p-τ Inducer

It is clear that ROS can interact with macromolecules, such as DNA, RNA, and proteins; affecting their functions [72]. Metabolic anomalies, resulting in oxidative stress, can cause different neurodegenerative disorders, such as AD [29]. Reactive oxygen molecules can induce neuronal death by Aβ plaque, p-τ, and PHF formation. Oxidative stress can induce τ abnormalities through either direct interaction with τ-related kinases and phosphatases or Pin1 [41,68]. Phosphorylation, sumoylation, and oxidization of Pin1 are some mechanisms that regulate Pin1 function [69]. Hypoxia treatment of cultured neurons may result in Pin1 oxidation on Cys113, reflecting its suppression as well as subcellular mislocalization [68]. Redox proteomics analysis has demonstrated that Pin1 is oxidized on Cys113 in the hippocampus of AD patients [73]. It is now evident that hyperglycemia and nutrition-depletion-induced oxidative stress would likely oxidize and suppress Pin1, resulting in *cis* p-τ accumulation. Pin1 can inhibit τ phosphorylation by inhibiting GSK3β kinase activity, supporting the opposite effects exerted by Pin1 and GSK3β on τ phosphorylation [69]. As one of the Pin1 substrates, GSK3β activity can be suppressed through the binding of its T330-P motif with Pin1 [74]. Oxidative stress induction due to nutrition depletion, hyperglycemia, and insulin signaling pathway abnormalities, can be the leading cause of Pin1 inhibition, GSK3β activation, and *cis* p-τ accumulation [68]. There have been extensive investigations on Pin1 activities in AD and cancer. However, there is almost no report on Pin1 mediatory roles in DM. Pin1 suppression due to ROS activation, in patients with DM, is likely one of the mechanisms of *cis* p-τ formation and neurodegeneration.

Concluding Remarks and Future Perspectives

Altogether, clinical, epidemiological, and animal model studies have shown that DM can impair normal cognition and cause dementia [75]. It is clear that τ pathogenicity is a major leading cause of neural cell death upon DM, which could be caused by insulin dysregulation or disrupted glucose metabolism in different brain areas [17,51]. Apparently, early diagnosis is crucial in DM-related neurodegeneration treatment. While late-stage τ tangles are detectable in the brain and CSF of DM patients [11], detection of an early neurotoxic p-τ species has been out of reach thus far. We have introduced *cis* p-τ as an early pathogenic τ epitope that is detectable in stressed neurons, *in vivo* and *in vitro* [27]. We have shown that *cis* p-τ is neurotoxic and kills the neurons under various stress conditions [27]. Moreover, immunotherapy with a monoclonal antibody against *cis* p-τ suppresses neurodegeneration both in *in vitro* and *in vivo* models [27]. Thus, wherever *cis* p-τ accumulates, neurons are affected. This review summarizes possible relations between diabetic stress pathways and *cis* p-τ induction. One possible mechanism for the *cis* p-τ accumulation is Pin1 oxidation and inactivation. Finally, highlighting *cis* p-τ as a key intermediate between diabetes and neurodegeneration may guide the treatment of tauopathy at the early stages (see Outstanding Questions).

Outstanding Questions

Considering the heterogeneous distribution of insulin receptors and glucose transporters in the brain, which areas are more prone to diabetic stress?

What is the actual role of oxidative stress and inflammation in tauopathy upon DM?

How is tauopathy triggered by DM? Considering multiple phosphorylation sites on τ protein, which phosphorylation event drives τ hyperphosphorylation in DM?

Can *cis* p-τ be a consequence, cause, or be a part of the neurodegeneration process during DM?

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Resources

[i]www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html.
[ii]www.who.int/news-room/fact-sheets/detail/dementia.

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