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Commentary

The ER stress-autophagy axis: implications for cognitive dysfunction in diabetes mellitus

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Unfolded protein response (UPR) often coordinates with autophagy to maintain cellular proteostasis. Disturbance of proteostasis correlates with diseases including diabetes and neurological complications. In a recent article in Clinical Science, Kong et al. highlighted the critical role of endoplasmic reticulum (ER) stress-autophagy axis in maintaining cognitive functions and provided pharmacological evidence with respect to cognitive improvements in a diabetic mouse model. These novel findings present new insights into the pathological mechanisms and therapeutic implications with the ER stress modulators in diabetes-related cognitive dysfunction.

The ever-increasing prevalence of diabetes mellitus worldwide has imposed a great burden upon public health [1]. Diabetes is a chronic and progressive metabolic disorder characterized by hyperglycemia, usually results from either insulin deficiency (Type 1 diabetes, T1D) or insulin insensitivity (Type 2 diabetes, T2D). Cognitive dysfunction has become an important comorbidity of diabetes. Particularly, both T1D and T2D increase the risk of cognitive dysfunction, from cognitive decrements, mild cognitive impairment (MCI) to dementia [2–4]. This co-occurrence increases with the progression and duration of diabetes. However, cognitive dysfunction can occur throughout the course of diabetes, even on prediabetic stage, in patients with impaired fasting glucose [5,6]. Of note, the incidence rate of both diabetes and cognitive dysfunction is increased upon aging, whereas the latter can also occur in youth with T1D or T2D [7–9]. In addition, diabetes accelerates the progression of MCI to dementia [10]. Importantly, patients with diabetes often display a group of comorbidities involved with multiple organ dysfunctions, including hyperlipidemia, hypertension, macrovascular and microvascular diseases. Together with the acute hypo- or hyperglycemia, these complications *per se* may also be risk factors for cognitive dysfunction in diabetes [11,12]. Thus far, understanding the mechanisms of underlying cognitive dysfunction merits further research efforts.

Proteostasis disturbance is a feature of many diseases such as diabetes and neurological complications. Many metabolic stimuli such as hyperglycemia can lead to accumulation of unfolded or misfolded proteins inside the endoplasmic reticulum (ER) lumen, a condition referred to as 'ER stress'. ER stress initiates unfolded protein response (UPR) by three ER membrane sensors, inositol-requiring enzyme 1α (IRE1α), protein kinase RNA-like ER kinase (PERK) and activating transcription factor 6 (ATF6). UPR is a cellular defensive process for relieving protein folding stress. The consequences of UPR involve perturbation of protein synthesis, trafficking, degradation or apoptosis under extreme conditions. Interestingly, macroautophagy (hereafter referred to as autophagy), a self-degradative cellular process, shares many features with UPR with respect to clearing unfolded or misfolded proteins and inducing apoptosis. UPR and autophagy are thus essential for cellular homeostasis. With this respect, these two pathways integrate a collection of mechanisms involved in multiple cellular functions, including inflammation, glucose and lipid metabolism and energy balance. As such, ER stress and autophagy are involved in a range of pathological processes.

In volume 132 issue 1 of Clinical Science [13], Kong and colleagues highlighted the role of ER stress and autophagy pathways in diabetes-related cognitive dysfunction (Figure 1). In streptozotocin (STZ)-induced

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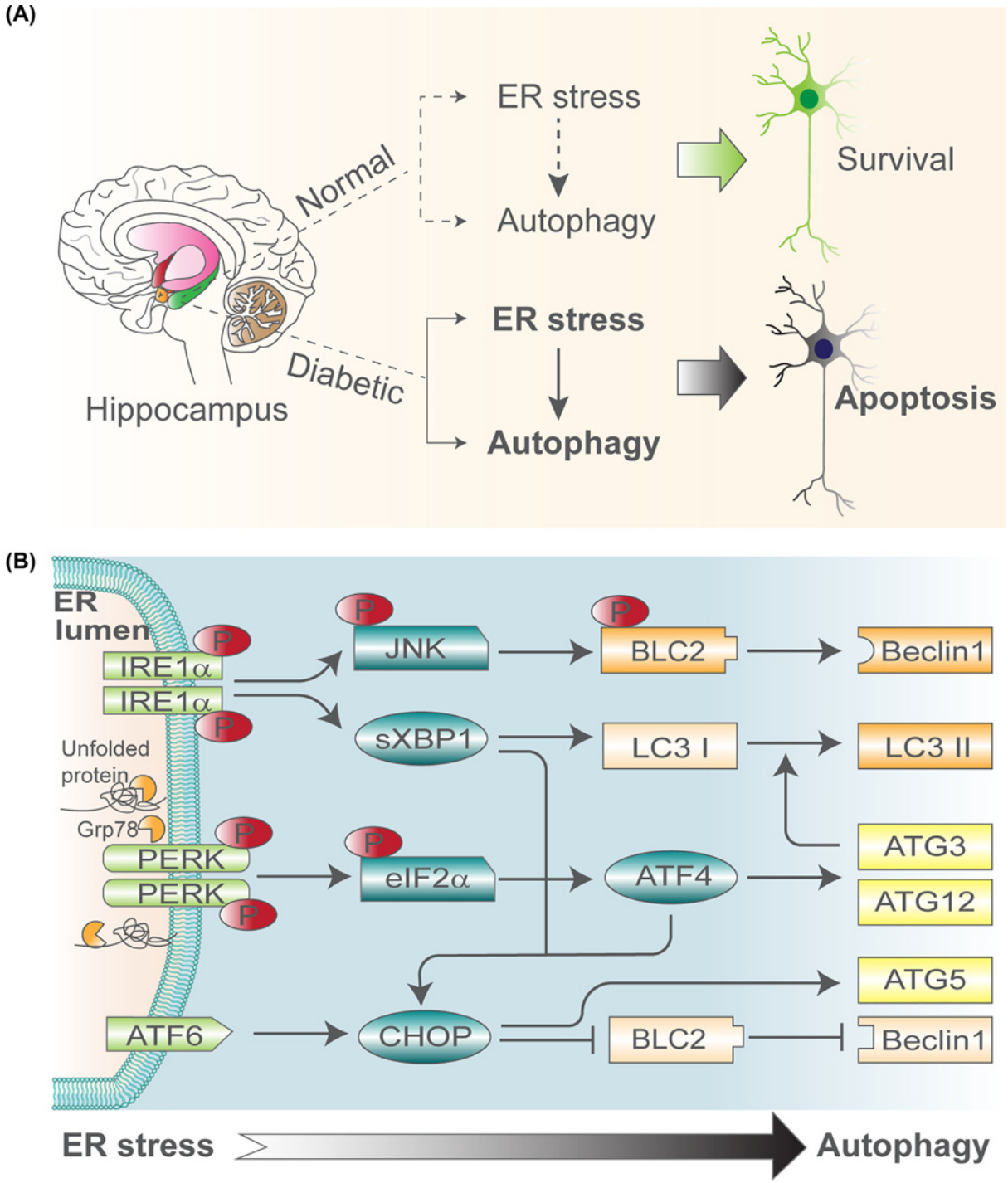

Figure 1. The ER stress-autophagy axis regulates diabetes-related cognitive dysfunction

(**A**) At normal state, hippocampal neurons survive with low levels of ER stress and autophagy, whereas in diabetes, unresolved ER stress further enhances autophagy and ultimately lead to apoptosis, and thus declines cognitive functions. (**B**) Cross-talk of ER stress-autophagy axis. Details presented in the text.

diabetic mice, they demonstrated that neuronal injuries mainly occurred in hippocampus rather than the cerebral cortex region, with pathologic alterations including less neuronal density, dysfunctional synaptic plasticity, damaged mitochondria and elevated apoptosis. Concomitantly, they observed remarkable increase in ER stress with high phosphorylation levels of IRE1α, PERK, JNK and high levels of GRP78 and CHOP, together with autophagy markers

Beclin1 and LC3 II/LC3 I ratio in diabetic hippocampus. These findings suggest the vulnerability of hippocampus and the critical role of ER stress and autophagy in hippocampal neurons in diabetic disease. Next, Kong and colleagues found pharmacological inhibition of ER stress by 4-phenylbutyrate (a chemical chaperone enhancing protein folding efficiency) or JNK inhibitor SP600125 reduced autophagy and apoptosis induced by high glucose in primary hippocampal neurons. In contrast, inhibition of autophagy by bafilomycin A1 aggravated ER stress and apoptosis. Indeed, autophagy is essential for structural and functional synaptic plasticity in hippocampal neurons [14]. Thus, ER stress evokes autophagy in a coordinated way to alleviate cellular stress upon glucotoxicity, and especially, this mechanism could be a cell autonomous effect in hippocampal neurons. Of note, although ER stress and autophagy can function independently, a growing body of evidence suggests an intensive cross-talk exists between these two pathways in many cell types including pancreatic β-cells, adipocytes, cardiomyocytes and hippocampal neurons, especially under diabetic status. Moreover, this cross-talk has been shown in multiple ways [15]. For example, IRE1α undergoes autophosphorylation upon ER stress, which then phosphorylates JNK via TRAF2-ASK1 complex. JNK further phosphorylates BCL2 and leads to the dissociation of Beclin1 from BCL2/Beclin1 complex, and thus activates Beclin1 and stimulates autophagy. Moreover, IRE1α also initiates sXBP1 splicing and subsequently LC3 II conversion to promote autophagy. Whereas PERK phosphorylates eIF2α, which further induces ATF4 and CHOP to release Beclin1 from the inhibition of BCL2. In addition, ATF4, sXBP1 and ATF6 can stimulate autophagy-related gene expression including Atg3, Atg5 and Atg12 (Figure 1B). The cross-talk, however, could be cell type-specific and dependent on pathological conditions. Taken together, Kong and colleagues shed light on this cross-talk in diabetic hippocampal neurons, and thus provided exciting clues with modulators targeting ER stress-autophagy axis in diabetes-related cognitive dysfunction.

Importantly, Kong and colleagues further examined ER stress inhibitor in STZ-induced diabetic mice. They found administration of 4-phenylbutyrate improved cognitive function such as spatial learning and memory abilities, whereas emotional and locomotor activities are not affected. Several other studies also support the efficacy of ER stress inhibitors, including Guanabenz that enhances eIF2α phosphorylation [16] and ISRIB that inhibits ATF4 induction [17], in cognitive improvements in different rodent models. In contrast, activation of autophagy often displays cognitive improvements [18,19]. To date, existing clinical treatments of dementia including cholinergic neurotransmitter modifying agents (donepezil, galantamine and rivastigmine) and noncholinergic agent (memantine) are largely limited to Alzheimer's dementia, with only improvement or delay of the symptoms [20], whereas no treatments of MCI are available. Management of diabetes seems to be beneficial for cognitive improvement, as indicated in a short-term study of metformin combined with rosiglitazone or glyburide in diabetic elderly [21]. However, other large and randomized trials fail to see any long-term benefits of cognitive improvement after intensive glycemic control in both T1D [22] and T2D patients [23,24]. Moreover, the recurrence of cerebral hypoglycemic episodes is also a challenge in diabetic population. Thus, diabetes-related cognitive dysfunction may have distinct underlying mechanisms due to the marked pathological differences. Of note, modulators by targeting ER stress-autophagy axis have shown benefits not only in insulin sensitivity, but also in cerebral ischemia and cognitive function, at least in rodent models [13,18,19,25]. However, studies with more specific compounds and genetically modified mouse models by targeting the distinct signaling components are still major needs. Collectively, these research efforts may offer new opportunities for developing more effective and safer pharmacological treatments against diabetes-related cognitive dysfunction.

Competing Interests

The author declares that there are no competing interests associated with manuscript.

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Abbreviations

ATF6, activating transcription factor 6; ER, endoplasmic reticulum; IRE1α, inositol-requiring enzyme 1α; MCI, mild cognitive impairment; PERK, protein kinase RNA-like ER kinase; STZ, streptozotocin; UPR, unfolded protein response.

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