Alzheimer's disease via enhanced calcium signaling caused by the decrease of endoplasmic reticulum–mitochondrial distance

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ABSTRACT

It has long been recognized that Ca^{2+} dysregulation is relevant to the initiation of Alzheimer's disease (AD), and most recent works have suggested that increased cross-talk between endoplasmic reticulum (ER) and mitochondria plays an important role in the pathogenesis of the disease. However, the detailed mechanism involved has not been fully elucidated. Owing to its importance in the regulation of Ca^{2+} signaling, ER–mitochondrial distance in the neurons is tightly controlled in the physiological conditions. When the distance is decreased, Ca^{2+} overload occurs both in the cytosol and mitochondria. The cytosolic Ca^{2+} overload can (1) hyperactivate Ca^{2+}-dependent enzymes, which in turn regulate activities of pro-apoptotic BCL-2 family proteins, causing mitochondrial outer membrane permeabilization and thereby resulting in the release of cytochrome c to activate caspase-3; (2) indirectly activate caspase-3 through the activation of caspase-12; and (3) promote the production and aggregation of β-amyloid. The three pathways eventually trigger neuronal apoptotic cell death. The mitochondrial Ca^{2+} overload can lead to increased generation of reactive oxygen species, inducing the opening of the mitochondrial permeability transition pore and ultimately causing neuronal apoptotic and necrotic cell death. The resultant death of neurons which are responsible for memory and cognition would contribute to the pathogenesis of AD. Therefore, we propose that the reduction in the distance between ER and mitochondria may be implicated in AD pathology by enhanced Ca^{2+} signaling, which provides a more complete picture of the Ca^{2+} hypothesis of AD.

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Introduction

Alzheimer's disease (AD) is the most common human neurodegenerative disorder, and is characterized by the accumulation of β-amyloid and the progressive impairment of memory and cognition that is strongly correlated with death of neurons in the hippocampus and neocortex [1–5]. Neuronal cell death may occur through apoptosis and necrosis [6,7], the former being the predominant form in AD [3,8]. Despite extensive research into the etiologies of AD, the underlying pathogenic mechanisms involved remain obscure and no scientific explanation has gained total acceptance [9]. The main hypotheses that have been put forward to explain the causes of AD include amyloid cascade hypothesis [10], endoplasmic reticulum (ER) stress hypothesis [11,12], mitochondrial cascade hypothesis [13,14], and Ca^{2+} hypothesis of AD [15–17].

A proper increase of cytosolic Ca^{2+} concentration plays a pivotal role in regulating many neuronal functions, such as information processing, learning and memory [17]. The progressive decline in cognition is intimately linked to neuronal death that can be driven by the marked and sustained elevation of Ca^{2+} signaling [18], which forms the basis of the Ca^{2+} hypothesis of AD [19,20].

Neuronal Ca^{2+} homeostasis depends critically on the Ca^{2+} transfer from ER to mitochondria, which is ascribed to the close connection between both organelles [21,22]. Such a connection is maintained by several tethering proteins such as presenilin 2 (PS2) [23], phosphofurin acidic cluster sorting protein-2 (PACS2) [24], and mitofusin-2 (MFN2) [25]. It was revealed experimentally that a proper spacing between ER and mitochondria plays a regulatory role in Ca^{2+} signaling and that tightening of the gap facilitates mitochondrial Ca^{2+} overload and commits the cells to a cell-death pathway [26]. Most recently we demonstrated that there is an optimal distance between ER and mitochondria for the physiological Ca^{2+} signals and proposed that apoptosis induced by elevated cytosolic Ca^{2+} may be observed when the optimal distance is disturbed [27].

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Indeed, Area-Gomez et al. found that ER–mitochondrial communication is increased significantly in AD [28]. Based on this finding, they proposed that AD is a disorder of ER–mitochondrial communication [29]. It is compelling that the communication is involved in the transfer of Ca^{2+} between the two organelles to carry out the regulation of Ca^{2+} signaling. This raises the question of whether AD might result from changes in ER–mitochondrial distance.
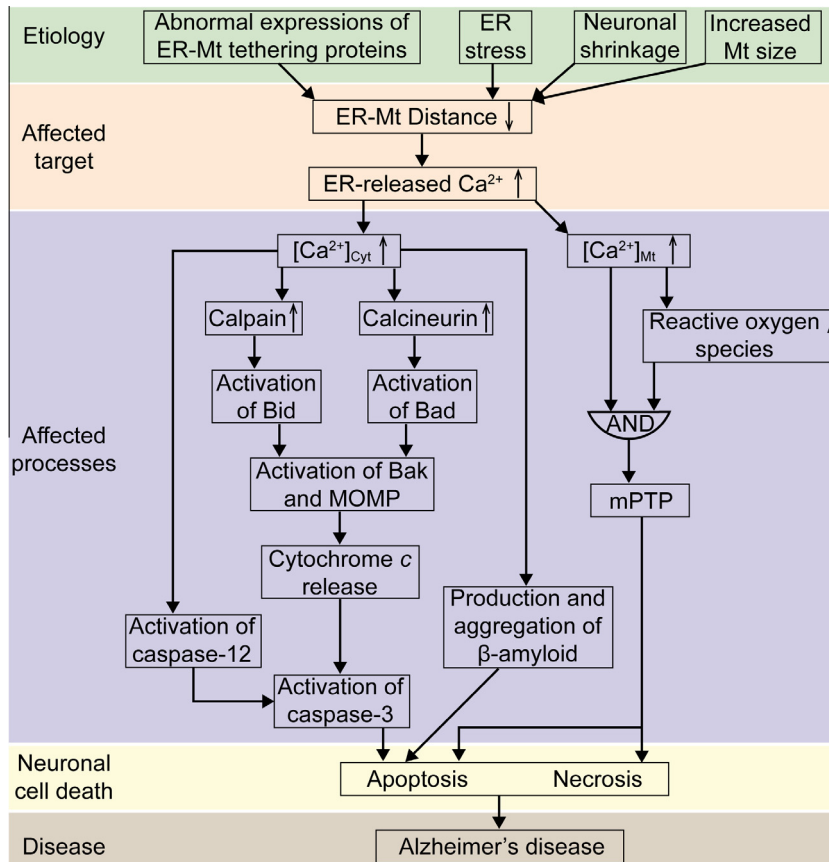
Hypothesis

The reduction in the ER–mitochondrial distance in neurons, which may be attributable to different causes (such as abnormal proteins expression, cellular stress, and aging), would result in excessive rises of Ca^{2+} within cytosol and mitochondria, which in trun activate their downstream cell death signals, contributing to the pathogenesis of AD.

Facts and evidences

Neurons have an elaborate ER network that extends throughout the cell [30]. A large portion of this network comes into close contact with mitochondria [24]. A huge body of literatures has addressed the dysfunction of ER, mitochondria and Ca^{2+} in AD. In the following, we list the facts and evidences to support our hypothesis (Fig. 1).

(1) A correct distance between ER and mitochondria is essential for their mutual interactions, which modulate key aspects of cell physiology [25]. However, reduction in the distance between them may occur in some pathophysiological conditions. First, ER–mitochondrial distance can be decreased by the abnormal expressions of tethering proteins: up-regulation of PS2 [23] or PACS2 [24], down-regulation of MFN2 [25]. Second, tight ER–mitochondrial coupling appears during early phases of ER stress [31]. Third, neuronal shrinkage [32,33] and increased mitochondrial size [34,35], which have been well-documented in AD brain [36,37] and are two concomitants of brain aging, may cause compact ER–mitochondrial juxtaposition, indicating that aging is the major risk factor for the development of AD [38].

(2) If ER–mitochondrial distance is shorter than the optimal value, the amount of Ca^{2+} ions released from the ER will increase, which in turn leads to elevated Ca^{2+} in both cytosol and mitochondria [27]. Although this conclusion was obtained by ignoring the contribution of extracellular sources of Ca^{2+} in theory, such transients have been observed experimentally in neurons [39]. In addition, changes in Ca^{2+} dynamics and levels are important features of AD pathology, including enhanced Ca^{2+} release from ER [40,41], exaggerated cytosolic Ca^{2+} [42–44] and overload mitochondrial Ca^{2+} [45,46].

(3) When cytoplasmic Ca^{2+} concentration ($[Ca^{2+}]_{Cyt}$) exceeds the normal physiological level, apoptotic cell death can occur through three pathways. Firstly, elevated $[Ca^{2+}]_{Cyt}$ results in the activation of caspase-12 [47], which subsequently activates caspase-3 [48,49]. This pathway is important in ER stress-induced neuronal apoptosis [49]. Secondly, two Ca^{2+}-dependent proteases, calpain [50,51] and calcineurin [52,53], are hyperactivated under pathological conditions

Fig. 1. Decreased ER–mitochondrial distance hypothesis of AD pathogenesis. ER, endoplasmic reticulum; Mt, mitochondria; $[Ca^{2+}]_{Cyt}$, cytosolic Ca^{2+} concentration; $[Ca^{2+}]_{Mt}$, mitochondrial Ca^{2+} concentration; MOMP, mitochondrial outer membrane permeabilization; mPTP, mitochondrial permeability transition pore.

that involve sustained cytoplasmic Ca^{2+} overload, which in turn activates BH3-only family members Bid [54] and Bad [55], respectively. Either directly or indirectly, these two members can induce the activation of pro-apoptotic effector Bak [56,57], thereby enabling them to form pores that cause mitochondrial outer membrane permeabilization (MOMP) [58]. As a result of MOMP, cytochrome *c* is released from the mitochondrial intermembrane space into the cytosol, where cytochrome *c* promotes caspase-3 activation [56,57]. Caspase-3 cleaves a series of cellular substrates and orchestrates apoptosis [56,59]. Experimental evidences support the involvement of calpain [60] and calcineurin [53] as well as Bcl-2 family members [61] and caspase [62] in the neuronal apoptotic cell death that occurs in AD. Thirdly, high levels of $[Ca^{2+}]_{Cyt}$ induces apoptosis [63] by accelerating the generation [40] and aggregation [63] of β-amyloid.

(4) Mitochondrial Ca^{2+} overload has been associated with almost all forms of cell death [64], including apoptosis and necrosis [21]. Ca^{2+} transfer from the ER to mitochondria is required to maintain normal cell bioenergetics for survival [65]. However, excessive Ca^{2+} accumulation within mitochondria can enhance the generation of reactive oxygen species [66], which form a coherent feed-forward loop with an AND input function [67], controlling the opening of mitochondrial permeability transition pore (mPTP) [66] and ultimately leading to cell death either by apoptosis or necrosis [68,69]. In other words, mPTP is capable of translating mitochondrial Ca^{2+} into a death signal only if mitochondrial Ca^{2+} overloads and results in ROS over-production. There is evidence that the absence of cyclophilin D (an integral part of mPTP) protects neurons from cell death and ameliorates learning and memory in AD [70].

(5) Both apoptosis and necrosis can significantly contribute to massive neuronal cell loss, which is a cardinal feature of AD. Apoptosis has not only been documented in studies of animal and cell-culture models of AD [1], but also of post-mortem brain tissue in AD [7]. Although many neurons may die by apoptosis in AD [3], other modes of cell death, such as necrosis, are relevant for the ultimate progression of the disease [71,72]. It has been proved that brain regions involved in learning and memory processes, including hippocampus and neocortex, are reduced in size in AD patients as the result of neuronal demise [3].

Conclusions and future perspectives

Emerging evidence suggests that AD-linked PS2 mutation also modulates the physical interaction between ER and mitochondria [23] and the increased cross-talk between the two organelles may play an important role in AD pathology [24,28]. Furthermore, considering the profound impact of ER–mitochondrial distance on Ca^{2+} signaling as well as Ca^{2+}-mediated cell death on AD pathology, it is logical to hypothesize that the decreased distance may sensitize neurons to Ca^{2+}-induced cell death, and therefore contribute to the pathogenesis of AD.

Our hypothesis can be tested by measuring and comparing the distance between ER and mitochondria, the Ca^{2+} levels within the cytosol and mitochondria, and the activities of cell death-related protein in healthy humans and AD patients. Overall, our hypothesis provides deeper insights into how Ca^{2+} dysregulation plays an early proximal and central role in AD [40,73] and clarifies a possible role of ER–mitochondrial distance in AD pathogenesis, which may suggest directions for treating the disease at an early stage.

Conflict of interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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