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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.

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], [2], [3], [4], [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], [16], [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].

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.

Section snippets

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 …

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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…

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.…

Acknowledgments

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2020, iScience

> *Citation Excerpt :*
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> ...A complete picture of the role of Ca2+ as a mechanistic trigger of apoptosis is still missing. Based on previous works (Albeck et al., 2008; Rehm et al., 2006) and our recent studies (Qi et al., 2018; Qi and Shuai, 2016; Yin et al., 2017), we developed an integrative signaling network comprising four modules

(Figure 1): (1) ER-involved Ca2+ oscillations, (2) Ca2+-activated proteins, (3) MOMP controlled by Bcl-2 family proteins on mitochondria, and (4) Cyt c-induced caspase cascade. The brief descriptions of each module are presented below (see details in Supplemental Information)....

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Citation Excerpt :

...Taking these results together, we concluded that neurodegenerative changes took place in our rat models exposure to Pb. Calcium ion, as an important second intracellular messenger, plays a vital part in regulating activities of learning and memory (Qi and Shuai 2016; Ludwar et al., 2017; Murali et al., 2017). Cognizing and learning are believed to be processes of a series of changes in the release intensity of neurotransmitters, a calcium-mediated biochemical process (Carafoli, 2002)....

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