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Golgi apparatus in Alzheimer's disease

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Editorial

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Abbreviations: AD: Alzheimer's Disease; GA: Golgi Apparatus; ER: Endoplasmic Reticulum; mDNA: mitochondrial DNA; CytOX: Cytochrome c Oxidase; PS1: Preseniline1; ROS: Reactive Oxygen Species; APP: Amyloid Precursor Protein; AβPP: Amyloid-β Precursor Protein; cdk5: cyclin-dependent kinase-5; UPR: adaptive mechanisms of the Unfolded Protein Response

Editorial

Alzheimer's disease (AD) is the most common cause of progressive and irreversible presenile and senile dementia of unavoidable tragic outcome, affecting millions of humans worldwide. Even from the last decades of the 20th century AD has become a serious medical challenge for aging population, inducing many ethical, legal, social, humanitarian, philosophical [1] and economic problems without an obvious perspective clarityfor the near future, despite the quotidian ongoing research [2].

The clinical phenomena of the disease are characterized by profound memory loss, visuo-spatial disorientation, loss of professional skills, learning inability, decline of speech fluency,gradual dysarthria,mood and behavioral disturbances and personality changes,phenomena which appear increasingly as the disease advances, complimented frequently by autonomic disorders and epileptic seizures, which progressively result in a final vegetative state, which is the common dark epilogue of the tragic life of the patients.

The neuropathological profile of AD is plotted many years prior to phenomenological appearance of the disease. It consists of (a) abnormal accumulation of Aβ peptide in the form of neuritic plaques or diffusely dispersed in the neuropile and (b) intracellular accumulations of hyper-phosphorylated tau protein in the form of neurofibrillary tangles and (c) selective neuronal loss. All these findings, which compose the main neuropathological diagnostic criteria, as key hallmarks of AD [3,4] are usually observed, been dispersed in the hippocampus, the cortex of the cerebral hemispheres, and in many subcortical neuronal networks, which play a substantial role in cognition.

Electron microscopy enlarged the horizons of morphological investigation in AD and revealed dendritic, spine and marked synaptic pathology, in association with substantial organelle alterations, involving mostly microtubules, mitochondria [5,6], Golgi apparatus (GA) [7] and endoplasmic reticulum (ER) [8] clearly observed even in areas of the brain, where dendritic plaques and neurofibrillary tangles are infrequent.

The alterations of ER and GA result inaccumulation of misfolded proteins and neuronal loss [9], given that failure of the adaptive mechanisms of the unfolded protein response (UPR) may result in chronic accumulation of misfolded proteins in the ER [10] and impaired amyloid precursor protein (APP) processing and trafficking [11].

In addition Tau protein, which is accumulated in ER, Golgi complexes, and mitochondria [12], may activate the unfolded protein response by impairing ER-associated degradation [13]. In addition all newly synthesized proteins, which are used for membranic processes, insertion or secretion, axoplasmic or dendritic flow and synaptic activity, including APP, are practically processed through the vesicles and the cisternae of Golgi complex [14].

Trafficking from the cell surface and proper sorting of APP and its cleaving involved enzymes require an intact and proper functioning Golgi complex [15]. APP, during its trafficking,in the GA and in the endocytic pathway, generates Aβ peptide, ranging in size from 37 to 43 amino acids, by cleavage of the APP C terminal fragment [16]. PS1, which is a component of γ-secretase and selectively increase the secretion of the Aβ (1-42) peptide, is mainly located in the ER and the cisternae of GA [17], trafficking to synapses, where it becomes component of synaptic and endothelial adherent junctions [18].

The GA in the majority of the early cases of AD is fragmented and atrophic in comparison with age matched normal controls [19]. The number of the vacuoles and vesicles, which are associated with the Golgi complex, are reduced in most of the Purkinje and granule cells of the cerebellum, the hippocampal neurons, the acoustic and visual cortices as well as the hypothalamus [20]. It must be emphasized that alterations of GA are also observed in the astrocytes, in endothelial cells as well as in pericytes in AD brains [21].

The normal structure of the cisternae and vesicles of the GA in the cell body is maintained by the proteins of the Golgi matrix [22]. It is reasonable that alteration of these structural proteins as an early phenomenon in AD may induce GA fragmentation and atrophy [23]. The accumulation of Aβ peptide in AD, at the subclinical period, may cause fragmentation of GA by phosphorylation of GM130 or GRASP65 (Golgi reassembly and stacking protein of 65 kD) [24,25] proteins by the activation of cyclin-dependent kinase-5 (cdk5), as it is well documented in transgenic mouse models [26].

In addition alterations of GA may influence protein glycosylation [27], which is among the major processing activities of the trans-Golgi network, occurring through numerous sequential steps, each of them requiring its own enzymes [28].

In the pathogenic chain of AD, the further fragmentation of GA induced by Aβ peptide overproduction [29] may reasonably affect dendritic protein trafficking, which is essentialfor dendritic remodeling and arbor stability, since microtubules are closely associated with Golgi outpost and trafficking of vesicles and proteins towards the terminal dendritic branches and spines [30]. At the same time the Aβ peptide which is accumulated in multivesicular bodies [31], in association with mitochondrial dysfunction [32] may induce disruption of the synapses [31], a fact which is closely related with the cognitive decline in AD.

The morphological alterations of GA, which are observed even at the initial stages of AD, plead in favor of the hypothesis that impairment of trafficking in Golgi cisternae and endosomes and ER stress may be one of the crucial factors in amyloidogenesis [27,33].

It is an undoubted ascertainment that there is no effective therapeutic intervention in AD for the time being. The majority of the current therapeutic attempts have temporal effects and induce symptomatic alleviation only.

A therapeutic philosophy aiming at protection from oxidative stress, mitochondrial damage [32] and hypoxic perturbations on one hand and protection of the endoplasmic reticulum [8] and Golgi complex from stress and fragmentation [34] on the other hand, may be beneficial in the initial stages of AD, promoting restoration and remodeling of dendrites [30], regeneration of spines, synaptogenesis and synaptic plasticity.

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