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Review

Mitochondrial control of autophagic lysosomal pathway in Alzheimer's disease

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ABSTRACT

When first described by Alois Alzheimer in 1907, AD was seen as a disorder that causes dementia and characterized by two defining neuropathological lesions, later associated with all forms of AD. While the etiology of AD remains largely unclear, there is accumulating evidence suggesting that mitochondrial dysfunction occurs prior to the onset of symptoms in AD. Mitochondria are exceptionally poised to play a crucial role in neuronal cell survival or death because they are regulators of both energy metabolism and apoptotic pathways. This review is mainly focused in the discussion of evidence suggesting a clear association between mitochondrial dysfunction, autophagy impairment and amyloid-β accumulation in Alzheimer's disease pathophysiology. The knowledge that autophagic insufficiency may compromise the cellular degradation mechanisms that may culminate in the progressive accumulation of dysfunctional mitochondria, aberrant protein aggregates buildup and lysossomal burden shield new insights to the way we address Alzheimer's disease. In line with this knowledge an innovative window for new therapeutic strategies aimed to activate or ameliorate macroautophagy may be opened.

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Contents

Introduction

Alzheimer disease (AD) is a progressive and fatal disorder of the central nervous system characterized by progressive memory loss, deterioration of cognitive functions and loss of synapses and neurons in the cerebral cortex and hippocampus. Two typical hallmarks of AD are intraneuronal neurofibrillar tangles (NFT) of hyperphosphorylated tau protein and extracellular senile plaques composed of fibrillar Abeta peptide. Abeta is a 40- to 42-amino acid peptide originating from the abnormal proteolysis of the amyloid precursor protein (APP) (Selkoe, 1993). Although fibrillar Abeta has been linked to the pathogenesis of AD for many years, recent studies have suggested a key role for soluble forms of the peptide in neuronal dysfunction (Klein et al., 2004). Studies from our group have reported that these peptides affect the electron transport chain, leading to the impairment of mitochondrial function (Cardoso et al., 2001; Pereira et al., 1999). Alterations of mitochondrial metabolism in AD patients have been well documented in the literature (reviewed in Moreira et al., 2006). Moreover, mitochondrial degeneration was shown to be an early sign of AD pathology appearing before NFT (Hirai et al., 2001). Several studies suggest that altered proteolytic processing of APP is synergistically related with impaired energy metabolism. First, brain glucose metabolism is decreased in cognition-related brain regions of APP mutant mice in association with increased amounts of Abeta (Dodart et al., 1999). Second, hypoxic tolerance is significantly decreased in presymptomatic Abeta APP mutant mice (Buchner et al., 2002). Third,

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caloric restriction protects neurons in experimental models relevant to AD (Mattson, 2003). Finally, impaired energy metabolism can induce amyloidogenic processing of APP, resulting in the accumulation of potentially neurotoxic forms of Abeta (Gabuzda et al., 1994).

Taken together, these data suggest that Abeta peptides translocate directly to the mitochondria may be responsible for the impairment of mitochondrial function that occurs in AD, at least for familial cases. The mechanism by which Abeta impairs mitochondrial function seems to involve enhanced reactive oxygen species (ROS) production (Cardoso and Oliveira, 2003), since several enzyme complexes of the respiratory chain are particularly vulnerable to damage by both Abeta and ROS (Cardoso et al., 2001; Pereira et al., 1999).

Protein oligomerization and aggregation are key events in age-related neurodegenerative disorders, causing neuronal disturbances that may include over-activation of macroautophagy. Macroautophagy, which is a lysosomal pathway for the turnover of organelles and long-lived proteins, is a key determinant of cell survival and longevity. During macroautophagy, an elongated "isolation" membrane sequesters a region of cytoplasm to form a double-membrane-limited autophagosome. The sequestered material within autophagosomes is digested by lysosomes upon fusion (autophagolysosomes) (Eskelinen, 2008). Recently, it was demonstrated that autophagy is constitutively active in neurons and is required for survival (Larsen and Sulzer, 2002). It has been described that the autophagosome–lysosome pathway (ALP) is compromised in AD brain and in animal AD models (Nixon et al., 2005; Yu et al., 2005). Neuritic dystrophy correlates with an increase in autophagic vacuoles (AV) induced early in AD before Abeta deposits extracellularly (Yu et al., 2005). It was demonstrated that Abeta peptides are degraded in normal conditions by the lysosome after autophagosome/endosome fusion. Subsequently, autophagosomes and late AV accumulate markedly in dystrophic dendrites, implying an impaired maturation of AV to lysosomes (Nixon, 2007).

In this review we will address mitochondria dysfunction as an initial cellular signalling pathway for AD etiopathogenesis. We will discuss how mitochondrial dysfunction may impair ALP and in turn endorse Abeta production.

Mitochondrial dysfunction: a key indicator for AD pathology

The mitochondrial cascade hypothesis postulated by Swerdlow and Khan (2004) states that, in the sporadic late-onset AD, mitochondrial dysfunction is the primary event that causes Abeta deposition, synaptic degeneration and NFT formation (Swerdlow and Khan, 2004). The key difference between the sporadic and familial AD is that in the last case, Abeta seems to be the primary pathological event, causing a secondary mitochondrial dysfunction (the Abeta cascade hypothesis). However, there is accumulating evidence from *in vitro*, *in vivo* and human studies suggesting that mitochondrial abnormalities may be indeed the initial event that trigger sporadic AD.

In situ hybridization to mitochondrial DNA (mtDNA) and immunocytochemistry of cytochrome oxidase (COX) showed that mitochondrial abnormalities are intimately associated to AD (Castellani et al., 2002; Hirai et al., 2001). Indeed, it was shown that COX activity in post mortem AD brains was decrased (Kish et al., 1992; Cooper et al., 1993; Parker et al., 1994). Moreover, the cellular expression of COX subunit II and IV is reduced during aging and these age-related changes are more pronounced in AD (Ojaimi et al., 1999) suggesting that aging is a major risk factor for this disease. Furthermore, high levels of mtDNA mutations, linked to cytochrome oxidase deficiency, are observed more frequently in hippocampal pyramidal neurons of AD patients, compared to age-matched controls (Cottrell et al., 2002). Recently, it was described as a close association between an impaired respiratory chain function and Abeta deposition in dystrophic neuritis from AD patient's frontal cortex (Perez-Gracia et al., 2008).

Moreover, several studies are being performed in AD patients' peripheral cells, based on the hypothesis that AD might be a systemic disease that affects several tissues in the body. It was demonstrated in fibroblasts from sporadic AD patients an abnormal mitochondrial distribution as compared to normal subjects fibroblasts (Wang et al., 2008). Data from our laboratory (Cardoso et al., 2004) showed that isolated mitochondria from AD platelets have a decrease in COX activity despite the fact that COX subunits are present at normal levels. Furthermore, it was observed that platelet ATP levels are decreased in AD while reactive oxygen species (ROS) are increased. So, we concluded that COX diminished catalytic activity is associated with ROS overproduction and energetic failure (Cardoso et al., 2004). Moreover, it was also shown that COX activity is significantly decreased in AD platelets (Bosetti et al., 2002). In order to overcome COX defect the hydrolytic activity of F0F1-ATPase increases significantly in sub-mitochondrial particles obtained from AD platelets as compared to the control subjects (Mancuso et al., 2003). To address the relevance and potential causes of COX defect in AD, the cytoplasmic hybrid ("cybrid") technique, first described by King and Attardi (1989), has been applied (King and Attardi, 1989). The resulting AD cybrids showed a transferred COX defect and revealed a number of downstream consequences that recapitulate the pathology observed in AD brain (reviewed in Moreira et al., 2006). Results obtained with AD cybrids support the view that functionally relevant mtDNA mutation exists in AD subjects and accounts, at least partly, for the COX defect that is observed in multiple AD tissues.

Alternatively, the Abeta cascade hypothesis proposes that Abeta is the primary cause of AD pathophysiology (Hardy and Selkoe, 2002). Strong support for this hypothesis came from studies in familial AD clusters that are caused by mutations of APP, presenilin1 and presenilin 2 genes. These mutations lead to an increase in Abeta levels and to a relatively early onset of dementia. With this evidence, many groups have developed transgenic mice in order to address AD etiopathology. Studies where mitochondria were isolated from a double Swedish and London mutant APP transgenic mice revealed a pronounced mitochondrial dysfunction with a decrease in mitochondrial membrane potential, a decrease in ATP levels, an inhibition of COX activity and an increase in ROS production (Hauptmann et al., 2009). These mitochondria abnormalities correlated with an increase in intracellular Abeta and were evident before Abeta extracellular deposition. A study by Aliev et al. (2003) positively correlates Abeta deposition with mitochondrial abnormalities in the vascular walls of an overexpressing APP transgenic mice (Aliev et al., 2003). Furthermore, a gene expression profile was carried out in an APP transgenic mouse model (Reddy et al., 2004) in order to establish which genes may be critical for cellular changes in AD progression. The authors observed that genes related to mitochondrial energy metabolism and apoptosis are up-regulated before and during the appearance of Abeta plaques. These results indicate that mitochondrial energy metabolism impairment, possibly by intraneuronal Abeta, could lead to an up-regulation of mitochondrial genes as a compensatory response. In addition, Keil et al. (2004) demonstrated a decrease in mitochondrial membrane potential and a reduction in ATP levels in neurons of an APP transgenic mouse model when compared to littermate non transgenic mice (Keil et al., 2004).

Mitochondria versus Abeta

The modern era of molecular discovery in AD began in the mid-1980s with the isolation and characterization of amyloid beta (Abeta) peptide as the principal constituent of senile plaques. Initially it was thought that Abeta was generated only under abnormal conditions, but in the early 1990s it was discovered that all cells normally secrete Abeta. Although it is still hypothesized the pathological role of Abeta peptides deposition (Abeta cascade hypothesis) in the brain, it is now believed that intracellular Abeta is the major pathological cause of AD,

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