Alzheimer Disease

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Abstract

The most widely accepted hypothesis to explain the pathogenesis of Alzheimer disease (AD) is the amyloid cascade, in which the accumulation of extraneuritic plaques and intracellular tangles plays a key role in driving the course and progression of the disease. However, there are other biochemical and morphological features of AD, including altered calcium, phospholipid, and cholesterol metabolism and altered mitochondrial dynamics and function that often appear early in the course of the disease, prior to plaque and tangle accumulation. Interestingly, these other functions are associated with a subdomain of the endoplasmic reticulum (ER) called mitochondria-associated ER membranes (MAM). MAM, which is an intracellular lipid raft-like domain, is closely apposed to mitochondria, both physically and biochemically. These MAM-localized functions are, in fact, increased significantly in various cellular and animal models of AD and in cells from AD patients, which could help explain the biochemical and morphological alterations seen in the disease. Based on these and other observations, a strong argument can be made that increased ER-mitochondria connectivity and increased MAM function are fundamental to AD pathogenesis.

Keywords

ApoE • Cholesterol • Cholesteryl esters • Endoplasmic reticulum • Lipid rafts • MAM • Membranes • Mitochondria • Mitochondria-associated ER membranes • Neurodegeneration • Phospholipids

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11.1 Introduction

Beginning in primary school and continuing on through secondary school and university, the approach to teaching the structure of eukaryotic cells has been informed by what one might call the "pigeonhole" view. In other words, the cell is described not as a unitary entity, but rather as an object containing various discrete subcellular elements – for example, the nucleus, the endoplasmic reticulum, the Golgi body, mitochondria, peroxisomes, endosomes, and lysosomes – each with its own special place within the cell and each with its own special function. This view is so embedded in our thinking that we have even anthropomorphized many of these functions: the mitochondrion is the "powerhouse of the cell," the nucleus is the cell's "information center," the lysosome is the cell's "garbage disposal and recycling center," and so forth.

Of course, the reality is much more complex. Each subcellular compartment indeed has its own role to play, but to work properly, both spatially and temporally, the function of each organelle has to be coordinated with the function(s) of every other organelle. In addition, organelles can have multiple complementary and/or overlapping functions. For example, the synthesis of cholesterol requires the interplay of at least five organelles – endoplasmic reticulum (ER), the Golgi body, the plasma membrane (PM), mitochondria, and the nucleus – while calcium trafficking requires at least three, ER, mitochondria, and PM.

This interdependence is seen most clearly in the many functions of the ER, which makes physical connections with the nucleus (as the nuclear envelope), the Golgi body (at ER exit sites), the plasma membrane (at plasma membrane-associated membranes, or PAM), peroxisomes (in the "pre-peroxisomal" compartment), and even with lipid droplets (English and Voeltz 2013, Lynes and Simmen 2011). One other important ER connection point, and one that is relevant to the rest of our discussion here, is the association of ER with mitochondria, at mitochondria-associated ER membranes, or MAM. The role of MAM as a highly dynamic entity and its unexpectedly important association with neurodegenerative disease have been revealed only in the last ten years. We will discuss here a hitherto-unsuspected connection between MAM function and the pathogenesis of Alzheimer disease (AD).

11.2 Mitochondria-Associated ER Membranes

As noted elsewhere in this volume, MAM is a dynamic subdomain of the ER that communicates with mitochondria, both biochemically and physically (Csordas et al. 2006, Hayashi et al. 2009, Raturi and Simmen 2013, Rusinol et al. 1994). It is a distinct biochemical/biophysical entity within the overall ER network: as opposed to "free ER," "MAM ER" is a lipid raft-like domain rich in cholesterol and sphingomyelin (Area-Gomez et al. 2012, Hayashi and Fujimoto 2010) and is enriched in approximately 1,000–1,200 proteins, as determined by proteomic analyses of MAM derived from mouse liver (Sala-Vila et al. 2016) and mouse brain (Poston et al. 2013); of these, approximately 165 have been verified in the literature, and of those, mutations in about 65 are associated with human disease. Among the proteins associated with MAM-related functions are those involved in calcium homeostasis (e.g., IP3 receptors (Mendes et al. 2005, Szabadkai et al. 2006)), in phospholipid metabolism (e.g., phosphatidylserine synthase (Stone and Vance 2000, Vance et al. 1997)), in cholesterol metabolism (e.g., acyl-CoA/cholesterol acyltransferase (Rusinol et al. 1994)), in lipid transfer between mitochondria and ER (e.g., fatty acid transfer protein 4 (Jia et al. 2007)), and in the regulation of mitochondrial morphology (e.g., dynamin-related protein 1 and mitochondrial fission factor (Friedman et al. 2011)). MAM is also associated with proteins that regulate and/or stabilize the apposition of mitochondria to ER (at an estimated interorganellar distance of ~10–30 nm (Csordas et al. 2006)), such as

mitofusin 2 (de Brito and Scorrano 2008) and phosphofurin acidic cluster sorting protein 2 (Simmen et al. 2005), but the exact "tethering" mechanism is not known.

11.3 Alzheimer Disease

The main histopathological hallmarks of Alzheimer disease (AD), a neurodegenerative disorder characterized by progressive neuronal loss in the cortex and hippocampus, are the accumulation of extracellular neuritic plaques and intracellular neurofibrillary tangles (Querfurth and LaFerla 2010). The plaques are composed of numerous proteins, most prominent among them β-amyloid (Aβ). The tangles consist mainly of hyperphosphorylated forms of a single protein, the microtubule-associated protein tau (Reitz 2012). The majority of AD (>99% of patients) is sporadic (SAD), but genetic variations in *APOE*, encoding apolipoprotein E, a component of circulating lipoproteins, confer an increased risk of developing the disease (Holtzman et al. 2012, Huang 2010). At least three genes have been identified in the far rarer autosomal-dominant familial form (FAD): the amyloid precursor protein (APP), presenilin-1 (PS1), and presenilin-2 (PS2). From a clinical point of view, the two disorders are essentially identical, differing only in the earlier age of onset in FAD (Querfurth and LaFerla 2010).

Disturbances in APP processing play a critical role in both forms of the disease. Full-length APP (which is 695–770 aa in length, depending on the isoform; APP-695 is the predominant isoform in brain) is cleaved near its C-terminus by β-secretase (BACE1) to produce a long soluble N-terminal fragment (sAPPβ) and a shorter membrane-bound C-terminal fragment (APP-C99). APP-C99 is then cleaved by the γ-secretase complex (an aspartyl protease containing PS1 and/or PS2 in its catalytic core; both presenilins are produced as full-length, relatively inactive, precursors that are cleaved autocatalytically to produce the active enzyme) to produce Aβ (~40 aa [$A\beta_{40}$]) and the APP intracellular domain (AICD) peptide (~50 aa). Pathogenic mutations in PS1, PS2, or APP that cause FAD result in the production of aberrantly processed forms of Aβ (and especially an increase in the ratio of $A\beta_{42}/A\beta_{40}$) that accumulate in the neuritic plaques. The accumulated Aβ, and especially $A\beta_{42}$, is toxic to cells, promoting tau hyperphosphorylation. This chain of events has been called the "amyloid cascade" (Hardy and Higgins 1992, Selkoe 2011) and is the most widely accepted hypothesis to explain the pathogenesis of AD.

The amyloid cascade hypothesis helps explain why mutations in both APP and in the presenilins cause FAD. However, the amyloid cascade hypothesis does not address other features of AD that have received less attention in the field (Area-Gomez and Schon 2016, Schon and Area-Gomez 2010, Schon and Area-Gomez 2013). These include altered cholesterol (Stefani and Liguri 2009), glucose (Hoyer et al. 1988, Liu et al. 2009), fatty acid (Fraser et al. 2010), and phospholipid (Pettegrew et al. 2001) metabolism, perturbed calcium homeostasis (Bezprozvanny and Mattson 2008), and mitochondrial dysfunction (Wang et al. 2009). It is notable that these "other" features of AD are the very ones that are implicated in MAM function and that are often associated with proteins enriched in the MAM. This potential connection has given rise to the hypothesis that perturbed MAM function plays a role in the pathogenesis of AD (Area-Gomez and Schon 2016, Schon and Area-Gomez 2010, Schon and Area-Gomez 2013).

11.4 The MAM Connection in AD

In the last few years, a number of groups have found that presenilins and γ-secretase activity itself, while present in the ER (in agreement with the findings of others (Busciglio et al. 1997, Walter et al. 1996)), are *not* present there homogeneously, but rather are enriched heterogeneously in the MAM subcompartment of the ER (Area-Gomez et al. 2009, Newman et al. 2014, Schreiner et al. 2015). The finding that MAM is an intracellular lipid raft (Area-Gomez et al. 2012, Hayashi and Fujimoto 2010) is

consistent with the observation that PS1 and γ-secretase activity reside in lipid rafts (Vetrivel et al. 2004) and supports the emerging view that rafts are located not only at the cell surface (Lingwood and Simons 2010, Vieira et al. 2010) but can also be found inside the cell (e.g., at the MAM).

Furthermore, alterations in the processing of APP result in MAM dysfunction, and *vice versa* (Area-Gomez et al. 2012, Hedskog et al. 2013), which links abnormalities in γ-secretase function to the metabolic alterations found early in the course of the disease. On the morphological side, the area of ER-mitochondria appositon is increased significantly in FAD and SAD fibroblasts and in presenilin-mutant cells, compared to controls (Area-Gomez et al. 2012). On the biochemical side, it has long been known that calcium homeostasis, which is in large part a MAM-mediated process (Csordas et al. 2010, Hayashi et al. 2009, Patergnani et al. 2011), is perturbed in AD patients (Gibson et al. 1997, Liang et al. 2015, Mattson 2010, Peterson and Goldman 1986, Sims et al. 1987, Supnet and Bezprozvanny 2010) and in animal models of AD (Sun et al. 2014). Another MAM-mediated process, mitochondrial bioenergetics and dynamics (e.g., organellar localization, fusion, and fission), is also perturbed in AD (Ferrer 2009, Gibson and Huang 2004, Peterson and Goldman 1986, Riemer and Kins 2013, Stokin et al. 2005, Wang et al. 2008).

Another important early feature of AD is disturbed lipid homeostasis (Di Paolo and Kim 2011), which may be behind some of the synaptic alterations seen in the disease (Rohrbough and Broadie 2005). As alluded to above, MAM serves as a regulatory hub for lipid regulation, including that of cholesterol and phospholipids (Vance 2014). Both of these functions are altered in AD (Area-Gomez et al. 2012, Stefani and Liguri 2009, Pettegrew et al. 2001), which can explain the altered lipid profiles seen in the disease (Chan et al. 2012) and the still-controversial connection to cholesterol (Chan et al. 2012).

Early alterations in MAM can also explain the prominent role of ApoE4 as a major genetic risk factor in sporadic AD (Holtzman et al. 2012). As noted above, ApoE is a component of lipoproteins that traffic lipids – mainly cholesterol, cholesteryl esters, and phospholipids – through the circulation, including the brain (where astrocytes, but not neurons, synthesize ApoE). There are a number of naturally occurring variants of ApoE in the population, with the most common being ApoE3 (it has a cysteine at amino acid position 112). ApoE4, with an arginine at that position, confers a significantly increased risk of developing AD compared to that conferred by ApoE3, via a currently unknown mechanism (Holtzman et al. 2012). Notably, ApoE4 has been shown to increase the intracellular concentration of cholesterol compared to the effect of ApoE3 (Heeren et al. 2004).

Consistent with this difference, it was recently shown that lipoproteins containing ApoE4 (but not the free protein) upregulated MAM function to a significantly greater degree than did those containing ApoE3 (Tambini et al. 2016). These results imply that the negative effects of ApoE4 on MAM functionality may well be due to its function in lipoprotein-mediated cholesterol metabolism and trafficking. Thus, the contribution of ApoE4 to the risk of developing AD may be due to the effects of perturbed cholesterol homeostasis on MAM function. This finding is concordant with the discovery of genetic variants in a number of cholesterol metabolism-related genes (Wollmer 2010), such as *ABCA7* (Steinberg et al. 2015), which encodes a cholesterol and phospholipid transport protein (Abe-Dohmae et al. 2004), also predispose to developing AD.

Overall, these data and observations support a view of AD pathogenesis that departs from that afforded by the amyloid cascade hypothesis and is focused less on plaques and tangles and more on altered cellular metabolism as the underlying disturbance in AD. In particular, the "MAM hypothesis" proposes that the development and progression of the AD result from increased communication between ER and mitochondria at the MAM (Area-Gomez and Schon 2016,

Schon and Area-Gomez 2010, Schon and Area-Gomez 2013). This increase affects a panoply of cellular functions, both directly (e.g., alterations in MAM-localized enzymatic functions) and indirectly (e.g., alterations in cellular behavior in response to perturbed MAM behavior). The increased apposition between ER and mitochondria and the concomitant alteration in MAM function are consistent with the perturbed cholesterol homeostasis, the altered phospholipid profiles, the increased calcium trafficking between the two organelles, the changes in mitochondrial bioenergetics and dynamics, and the elevated ratio of $A\beta_{42}/A\beta_{40}$ (Schon and Area-Gomez 2013). Thus, it is possible that the functional cause of AD is an increase in the communication between ER and mitochondria and an associated upregulation in MAM function. What now remains to be elucidated is the biochemical cause of this ER-mitochondria hyperconnectivity and how APP processing plays a role in this process.

In this regard, the finding that ApoE4 impacts on MAM function may provide an important clue. Although the connection between ApoE4 and APP processing is at present unclear, one conceptual connection between the two is perturbed cholesterol homeostasis. Lipoproteins transport cholesterol and cholesteryl esters, and their components are recycled following binding to lipoprotein receptors on the cell surface and internalization into the cell. Interestingly, intracellular lipoprotein-derived cholesterol is recycled poorly in ApoE4-containing cells relative to ApoE3 (Heeren et al. 2004). Thus, one possible connection between APP processing and ApoE in general (and ApoE4 in particular) is the regulation of cholesterol homeostasis (Heeren et al. 2003), for two reasons. First, γ-secretase resides in the MAM (Area-Gomez et al. 2009), a lipid raft rich in cholesterol and sphingomyelin. Second, APP contains a cholesterol-binding domain at its C-terminus (Barrett et al. 2012) that may act as a cholesterol sensor (Beel et al. 2008). Thus, it may well be that in AD cholesterol levels are altered, either at steady state or dynamically (e.g., altered cholesterol turnover). In the case of SAD, this could be the result of aberrant cholesterol trafficking mediated by, for example, ApoE4 or mutated ABCA7. In the case of FAD, it could be the result of aberrant cholesterol sensing or homeostasis due to altered APP structure or amount (as is the case in subjects with Down syndrome, who are at elevated risk for developing AD, likely due to an extra gene dose of *APP*) or in the ability of mutated presenilins to cleave APP properly (Heilig et al. 2010). In either case, altered cholesterol metabolism somehow induces an increase in ER-mitochondria communication that then gives rise to the phenotypes seen in AD (Marquer et al. 2014).

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