Review Article

The Potential Roles of Plasmalogens and Induced Microglial Cubic Membranes in Alzheimer's Disease Pathogenesis

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ABSTRACT

Cubic membranes (CM) are highly ordered 3D periodic phospholipid bilayer membrane structures. The literature survey revealed that CM often appeared in the eukaryotic subcellular organelles under multiple stress and diseased conditions. CM were found in the free-living "starved" amoeba Chaos carolinense (macrophage-like ancient protozoan) and microglia (brain-resident macrophages) of Alzheimer's disease (AD) patients. The amoeba starvation study reveals that plasmalogen is the key lipid module for CM formation, and this major brain lipid has been controversially discussed to be altered in AD. Here we propose a novel hypothesis that the presence of sufficient plasmalogen lipids may support the induced microglial CM formation in response to multiple stressors and further provide anti-inflammatory, antioxidant and cell protective functions to alleviate neuroinflammatory-oriented AD pathogenesis. In short, both plasmalogen and microglial CM are beneficial for the central nervous system (CNS) homeostasis and may point an effective remedy for AD.

CUBIC MEMBRANES

Cubic Membranes (CM) are highly ordered membrane structures described by 3-dimensional periodic minimal or level surfaces with cubic symmetry (Figure 1) [1-3]. CM are often found in the subcellular organelles (mitochondria and endoplasmic reticulum) of eukaryotes under stress and diseased conditions [3] including viral infections [4,5] and immunological disorders [6,7]. Without being appreciated the 3D nature of CM is probably due to the convoluted looks of their 2D expressions in thousands of published transmission electron microscopic (TEM) micrographs [8]. CM also appeared in brain microglia of Alzheimer's disease (AD) patients [Figure 1c] [9]. Microglia, the brain-resident macrophages as major innate immune surveillance cells in CNS play an important role in Alzheimer's disease and others involving brain inflammation [10,11]. Amoeba CM formation was induced by starvation and oxidative stress, and in turn, these stunning nanostructures may act as an alternative antioxidant system to reduce oxidative damage [12,13] and promote amoeba cell survival [14]. We thus speculate that the induced microglial CM in some AD brain might have similar implications in protecting brain cells under stressed conditions, based on the facts from a series of amoeba starvation studies [12-14] in addition to an extensive literature survey of TEM images [3], suggesting CM may act as cell self-defense system in response to multiple internal or external environmental cues. The stressors can be just a simple exposure to excess oxygen free radicals or certain cytokines (Type I Interferon) as manifestations of inflammatory response. In addition,

amoeba Chaos starvation study revealed that plasmalogen is the key lipid module in participating CM formation [3,15]. This bioactive ether lipid has been recognized to be actively participating in cell and tissue homeostasis and its deficit or deficiency is strongly associated with multiple diseases including AD [16].

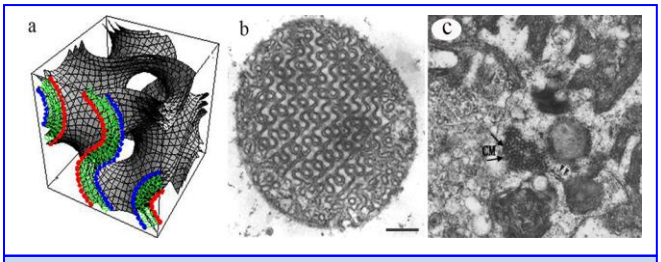

Figure 1: Cubic membrane (CM) architecture. (a) 3D mathematical model representing the lipid bilayer of CM organization. (b) TEM image of mitochondrial CM found in 10-day starved amoeba Chaos cells. Scale bar: 250 nm. (c) CM structure (indicated arrows) in some AD brain microglia, x36,000 [reproduced with permission from [9].

DOUBLE-FACED MICROGLIA

Microglia, the primary innate immune cells of CNS, are brain-resident macrophages [10]. The readily minor stimulation by micro-environmental changes of the brain would induce the conversion of resting microglia (M0) to an activated state, as pro-inflammatory phenotype (M1) or anti-inflammatory phenotype (M2). M1 microglia release a variety of pro-inflammatory factors as well as large amounts of nitrogen or oxygen free radicals, while M2 microglia release anti-inflammatory factors to maintain CNS homeostasis [10]. Microglia play an important role in chronic neurodegeneration and acute brain trauma and stroke [11]. Of particular importance, microglia also play roles in learning and memory by remodeling synapses through releasing cytokines and brain-derived neurotrophic factor (BDNF) [17]. In addition, microglia can reduce neuronal damage by removing β-amyloid and phagocytic debris or dead cells. Nevertheless, microglia also impair neuronal functions by excreting the toxic factors [18] as a dual player in neuro-inflammation and neurogenesis process [19]. A new study by Pluvinage et al. [20] using laboratory techniques to identify mouse genes whose activity either impairs or enhances microglial phagocytosis has put the senescent microglia again as spotlight in normal ageing brain and other neurodegenerative diseases including AD.

Microglial studies from all aspects are therefore indispensable to provide fair explanations in AD pathogenesis. However, most of the microglia-related studies are at molecular level, and the approach to look at their ultrastructure in terms of 3D membrane shape of organelles is rare. A 60-years history of microglial ultrastructures by electron microscopic studies was recently reviewed [21], and surprisingly there are very few TEM studies on the intracellular membrane structures defining the microglial phenotypes. The lacking of TEM information on microglial intracellular organelle membrane structures has limited the full understanding of such important neuroglia. Of interest, the tubuloreticular structures (TRS) (CM subtype) [Figure 1c] discovered by Wegiel and Wisniewski (1992) were in the same region of brain microglia where β-amyloid (Aβ) was present [9]. β-amyloid has long been thought to have detrimental effects in microglial activation and neuro-inflammation [22]. The failure in the clearance of Aβ and aggregated plaques is considered to be the main cause of AD development. However, there are some opposite views on Aβ which is likely to have an antimicrobial property [23,24], in addition to its physiological role in memory protection [25]. Therefore, the actual role of Aβ as a protection or risk factor in AD brain remains controversial.

The level of type I interferon (IFN), a pleiotropic cytokine of innate immune system, is associated with microglial functions as manifestations in neuronal development, neuro-inflammation and neuro-degeneration [26]. Type I IFN is to be blamed for the innate immune response-mediated CNS disorders. By regulating type I IFN signaling, it is possible to delay cognitive decline and reduce neurotoxicity [27]. There is a significant increase in type I IFN-α level in the serum of systemic lupus erythematosus (SLE) patients [28], who have a higher risk of developing dementia than the normal ones [29]. Mak et al. reported that the peripheral blood mononuclear cells from SLE patients showed a distinct TRS membrane pattern (CM subtype), and an addition of IFN-α could directly induce CM formation in human B lymphocyte cell cultures [30]. Whether the microglial CM in AD brain as the manifestation of high level of type I IFN that may affect microglial phenotypes in terms of intracellular complex

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membrane organizations and the corresponding functions requires further studies.

CM AS EVOLUTIONAL SELF-DEFENSE SYSTEM SUPPORTS CELL SURVIVAL UNDER STRESS?

A series of studies of induced CM in amoeba Chaos carolinense and its potential function under starvation and oxidative stress have been reported by Deng and co-workers [12-14,31-32]. An ancient protozoan amoeba Chaos might have similar phagocytic behavior and functions as brain-resident macrophages (microglia). The previous studies showed that when Chaos cells were under starvation stress, their mitochondrial inner membranes folded into CM [12,13], and amoeba survival rate during long-term starvation period is much higher than the ones without CM [14]. In the presence of a large amount of reactive oxygen species (ROS), the starvation-induced amoeba CM protected bio-macromolecules (lipids and nucleic acids) from oxidative damage [13], suggesting CM might possess of antioxidant properties attributed to the 3D spatial arrangement of phospholipid-protein bilayer membranes [12]. Whether the presence of CM in AD brain microglia may play similar role as CM in starved amoeba Chaos? Whether the induced microglial CM is directly or indirectly associated with high level of type I IFN or ROS generation in the brain? or whether CM may protect both neuron and glial cells from oxidative damages during inflammatory process and further help in maintaining CNS homeostasis? All these intriguing questions require more studies to uncover the truth.

PLASMALOGENS: SMALL MOLECULES MATTER?

Plasmalogens (Pls) are a unique type of ether lipids containing a fatty alcohol with a vinyl-ether bond at the sn-1 position, and enriched in polyunsaturated fatty acids (PUFAs) at the sn-2 position of the glycerol backbone, found in numerous human tissues, with particular enrichment in the nervous, cardiovascular and immune system [16]. Pls are not only structural membrane components and a reservoir of lipid second messengers, but also known to facilitate membrane fusion and involved in ion transport, cholesterol efflux and storage of long-chain PUFAs. However, such important brain lipid has been ignored due to very little progress in plasmalogen research until 2006. There is a significant reduce in Pls level in the brain [33,34] and serum [35, 36] of AD patients, and the degree of decline in serum Pls level is related to the severity of the disease [35]. Pls extracted from Ascidian [37] and sea cucumber have been fed to AD mice [38] and AD rats [39], and the scallop-derived Pls (sPls) was fed to patients with mild AD and mild cognitive impairment [40]. The studies on the animal model showed that oral ingestion of Pls were able to attenuate the LPS-induced memory loss and microglial activation through NF-kB signal pathway [41,42]. Ifuku et al. also reported that Pls has both anti-inflammatory and anti-amyloidogenic effects [43]. Pls level also affects the activity of γ-secretase and is inversely related to the level of β-amyloid, a disease hallmark of AD [44,45].

Plasmalogen as major brain lipids has been controversially discussed to be altered in Alzheimer's disease (AD) and whether the changes of Pls as cause or consequence of AD pathology however remains elusive. Of significance, a number of animal studies [37-39,46] and a recent clinical trial [40] have shown that enhancing the level of Pls through oral intake or ingestion indeed improved cognitive function which was impaired in AD.

Of our best interest, plasmalogen was recognized to be essential in amoeba CM formation induced by starvation stress [3,15]. Pls has been found to inhibit hippocampal neuron cell death upon nutrient deprivation in mice model [47,48]. This observation supported amoeba starvation study that when amoeba pre-fed with Pls-rich Paramecium they survived much better than amoeba pre-fed with Pls-poor Tetrahymena. The former food organisms can induce amoeba CM formation under starvation stress, while the latter cannot induce CM under same starvation stress and the lifespan of amoeba is significantly reduced [14].

The pioneer work of atomistic molecular dynamics simulations by Rog and Koivuniemi showed that Pls form more condensed and thicker lipid bilayers when compared to the corresponding diacyl bilayer system [49]. Along with this, Pls also play an important role in regulation of lipid rafts microdomain that is essential in the signal transduction of macrophage phagocytosis [50]. The integrity of membrane rafts that may modulate brain-derived neurotrophic factor (BDNF)-mediated neuronal synaptic plasticity, suggesting Pls may modify BDNF-mediated neurogenesis via rafts membrane structure [51]. An in-vitro study by Angelova et al. demonstrated that high loads of BDNF proteins promoted transformation of cubic phases [52], which has similar structural

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characteristics as CM whose lattice size is usually 10-fold larger than cubic phase structure [3]. Whether the overexpression of BDNF may induce CM formation in vivo requires further studies? The interplay between plasmalogen level, CM biogenesis and BDNF expression, and the effects of their interrelationship on microglial phenotypes and functions deserve more attentions.

ANOVEL HYPOTHESIS WITH PLASMALOGEN AND INDUCED MICROGLIAL CM AS CORE REGULATORS IN AD PATHOGENESIS

Although amyloid beta has long been the prime suspect in Alzheimer's diseases and as a sole hallmark and its presence in the brain helps define some of the clinical symptoms. Nevertheless why these healthy proteins in the brain turning to something aberrant or pathological or destructive in the brain remains a mystery.

The positive effect of CM formation in promoting amoeba cell survival under starvation-induced stress has encouraged a speculation that the induced microglial CM might possess of similar antioxidant and protective mechanisms in AD pathogenesis. The ability of inducing CM in microglia might be determined by plasmalogen level in the brain and serum. In short, if there is plenty of plasmalogen lipids, CM can be induced under starvation stress and act as an evolutionarily conserved self-defense system; if there is plasmalogen deficiency or deficit, CM formation cannot be supported, and this self-defense system might be weakened and CNS homeostasis is compromised consequently. If the stressors to brain sustain, the oxidative damage and cytotoxicity may proceed and lead to a vicious circle, AD may thus progress (Figure 2).

A novel hypothesis to be proposed to have plasmalogen and induced microglial CM as core regulators in AD pathogenesis, based on the assumption that CM (a highly ordered 3D membrane shape) may help lower the oxidative damages, reduce neurotoxicity, protect brain cells (both neuron and glia) and finally maintain CNS homeostasis. In short, plasmalogen amount is the key to determine whether CM may appear or not under stress conditions. The question is how to induce microglial CM? By simply providing functional food ingredients (plasmalogens) to prepare microglia to readily form CM in response to stress? The amoeba starvation study (food rich or poor in plasmalogens) [14] may support partly the reason why scallop-derived PIs supplements are effective in both animal studies [37,38,39] and clinical trials [40] of AD?

In summary, we propose to use microglia as cell model to study the roles of plasmalogen and induced CM and their potential anti-inflammatory, antioxidant and cell protective function in AD pathogenesis (Figure 2), to hopefully shed light on the still misty etiology of Alzheimer's disease: a global challenge for the 21st century.

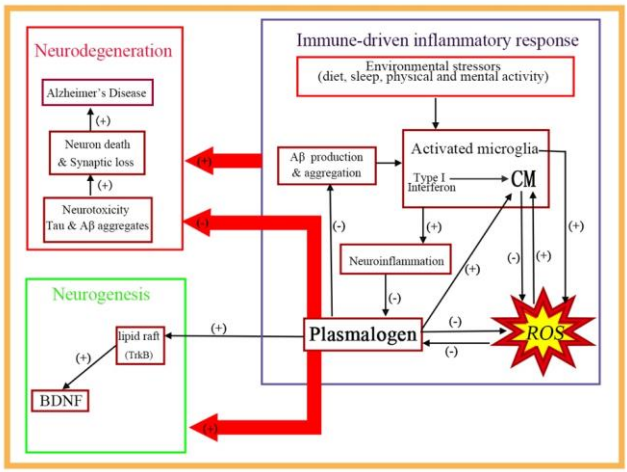

Figure 2: The potential roles of plasmalogen and induced CM in microglia-oriented neuro-inflammatory response. Type I IFN, amyloid beta (Aβ) are involved as promoter or inhibitor during neurodegeneration process. Plasmalogen may positively regulate BDNF-mediated neurogenesis. The CNS homeostasis is supported by inducing microglial CM which may help reduce neurotoxicity and neurodegeneration in response to multiple stressors caused by inappropriate lifestyles. Removing the stress factors may recover BDNF expression and adult hippocampal neurogenesis [53].

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