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Alzheimer's disease As an Autoimmune Disorder

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Abstract*—Alzheimer's disease could be an autoimmune disorder. Ceramide, the lipid molecules bound to Amyloid beta in cell membrane act as non - magnetic antigens and induce the activation of immune cells. The acid sphingomyelinase releases ceramide from sphingomyelin finally resulting in the formation of ceramide-enriched membrane. platforms. These membrane domains serve the clustering of receptor molecules for immune cells Receptor clustering is associated with cell death signaling pathway*.*

***Keywords*—** *Alzheimer's disease (AD), Amyloid beta (Aβ), Autoimmune Disorder (AD), Lipid Rafts, Ceramide (Cer), Tau protein*.

I. INTRODUCTION

There is no 100% treatment for Alzheimer's disease yet. There is no scientific evidence for the cause of Alzheimer's. There are many hypotheses, but oppositions still remain. One thing is clear that Alzheimer's disease is caused by the death of neuron cells. So far, several hypotheses are concerned with the cause of neuronal cell death. The most fundamental question can be raised here. Substances in Alzheimer's hypothesis for Alzheimer's disease are biomarkers not causative agents. By the year 2050, one out of 85 people around the globe is expected to suffer from cognitive impairment arising from Alzheimer's disease. South Korea is not an exception; baby boomer generation is soon to reach the threshold age 65. People are burdened with gigantic medical cost from Alzheimer's disease, not to mention the emotional devastation when they see their beloved people lose their bright minds. However desperate the cure for Alzheimer's disease is needed, pharmaceutical giants have started to give up on finding Alzheimer's disease treatment. Although tremendous amount of research funding has been, and still is, invested for Alzheimer's disease, the cause of such devastating disease is still vague. Amyloid hypothesis pinpoints the accumulation of Amyloid beta or Abeta, commonly represented as Aβ, the cause of neurofiber tangles and eventual degeneration of brain ability among AD patients. Abeta's physiological role is yet to be unraveled; some evidence shows Abeta lacks functional value, while the other supports otherwise. Abeta is cleaved from APP, Amyloid Precursor Protein, by beta-secretase and gamma-secretase. The Alzheimer's Association recently reported that a woman's estimated lifetime risk of developing Alzheimer's at age 65 is 1 in 6, compared to nearly 1 in 11 for a man (ie, female to male ratio 1.8)[1]. Based on female to male ratio, Alzheimer's disease could well be an autoimmune disorder. Like Alzheimer's, multiple sclerosis, an autoimmune inflammation of the central nervous system, has a female to male ratio of 2.3. Also based on female to male ratio[1], Alzheimer's resembles the autoimmune inflammatory disease rheumatoid arthritis, which has a female to male ratio of 2.7[1]. The reasons for the female preponderance in autoimmune disease are unclear, but anti-inflammatory drugs are widely and successfully employed to treat autoimmune anti-inflammatory disease and dramatically relieve symptoms.

Autoimmune diseases are caused by unusual activity of the body's own immune system. In these diseases the immune system, which usually protects the body from disease, attacks healthy cells in the body by mistake. The researchers are becoming increasingly aware of the important role the immune system plays in dementia, and this new study provides evidence to support link between the immune system and dementia. it is too far to draw firm conclusions from its findings, but it supports ongoing work into the contribution of the immune system to dementia. Autoimmune disorders – may be a trigger of dementia and Alzheimer's disease have pushed a person's immune system into overdrive, this can lead to immune cells attacking healthy brain tissue. Another study found that people with rheumatoid arthritis who were undergoing anti-TNF therapies were significantly less likely to develop Alzheimer's disease. Anti-TNF (anti-tumor necrosis factor) drugs including etanercept are commonly used to combat autoimmune diseases like rheumatoid arthritis. *In* this study, the incidence of Alzheimer's disease was found to be lower in patients with rheumatoid arthritis who had been treated with anti-TNF agents. Although the cause of Alzheimer's disease is not known, the results suggest that TNF may play a role in its development. The good news is that if Alzheimer's is, in fact, an autoimmune disorder, we could understand the disease better, and that may lead to better treatment options. This study aims to examine the possibility of autoimmune disease on the cause of Alzheimer's.

II. LIPIDS RAFTS

Lipids are fundamental organic molecules that are utilized by the human body for a number of essential cellular processes. Broadly speaking, lipids can be classified into five major subcategories. These include fatty acids, triglycerides, phospholipids, sterol lipids and sphingolipids. 5% of all human genes are devoted to lipid[2] The brain makes great use of all five classes of lipids, and contains the second highest concentration of lipids in the human body[3]. Fatty acids are an essential class of lipids. All fatty acids consist of a carbon chain that terminates in a carboxylic acid functional group, and they are categorized into different subclasses based on the length of the carbon chain. Fatty acids with 2–4 carbons are classified as short-chain fatty acids, medium-chain fatty acids have 6–12 carbons, long-chain fatty acids have 14–18 carbons,

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and very long-chain fatty acids have 18+ carbons. The length of the fatty acid introduces significant variation in function and subcellular localization[4]. The structural role of sphingolipids in membranes facilitates their role in signaling processes. The hydrophilic head groups contain a number of hydroxyl groups, which allow for extensive hydrogen bonding between individual head groups[5]. This creates a flexible surface membrane that is largely impermeable. The fatty acyl groups that are associated with sphingolipids allow for thicker and more closely packed membranes. As a result, sphingolipids act as determinants of membrane fluidity and permeability[6]. A concentration gradient of sphingolipids is observed in cellular membranes. The ER (endoplasmic-reticulum) has a low concentration, the Golgi has an intermediate concentration, and the plasma membrane and endosomes have a high concentration. This gradient is in place to align with cellular function. The ER has a low concentration since a more fluid membrane allows for easier protein insertion and folding, whereas a high sphingolipid concentration in the plasma membrane and endosomes creates thicker and less permeable barriers to outside molecules[7]. Another structural component that sphingolipids take part in are lipid rafts. These lipid rafts are the result of the strong intermolecular forces between individual sphingolipid molecules, driving a phase separation of the sphingolipids from the phospholipid-rich outer membrane[8]. Present on membranes with high concentration of sphingolipids and cholesterol, lipid rafts act as major anchoring sites for proteins. Proteins that integrate with these rafts have been implicated in a host of processes, ranging from endocytic pathway sorting to antigen-responsive signaling[9]. In the present, it is under study on the efflux of cholesterol, sphingolipids, and glycerophospholipids from cells and the changes in the composition of membrane lipid domains after treating rat cerebellar granule cells differentiated in culture with methyl-β-cyclodextrin (MCD)[10]. This data would provide a new scenario, in which the membrane lipid domains appear as dynamic structures whose existence strongly influences cell membrane properties such as lipid rafts which specialized plasma membrane microdomains highly enriched in cholesterol, sphingolipids, sphingomyelin, [SM], gangliosides (GM) and glycosylphosphatidylinositol (GPI) anchored proteins[11]. Lipid rafts are involved in intracellular trafficking of proteins and lipids, secretory and endocytic pathways, inflammation and in cell-surface proteolysis. In the brain, there has been substantial interest in lipid rafts, with respect to both normal functioning and certain neurodegenerative diseases. It is well accepted that lipid rafts play an important role for signaling processes in the central nervous system (CNS). Synaptic proteins such as synaptophysin or synaptotagmin associate with lipid rafts and lipid rafts play a role in the control of post synaptic membrane viscosity. Moreover, BDNF (brain-derived neurotrophic factor), which exerts multiple biological functions in the CNS increased the levels of presynaptic proteins in lipid rafts of neurons[12]. Regulation of the glutamateric neurotransmission, which is involved in the formation of spatial memory, represents one example for the impact of lipid rafts on classical signaling processes. Lipid rafts have been attracted attention in neurodegeneration, such as Prion diseases, Parkinson`s disease and especially in AD. Recently, alterations in lipid rafts isolated from AD brain were reported[13], including the localization of active γ-secretase in lipid rafts in human brain. Active γ-secretase is involved in the pathological processing of the AD related amyloid precursor protein (APP). Neurotoxic β- amyloid peptide (Aβ) is a product of the secretase cleavage of APP and both proteins have been located in lipid rafts. Moreover, it was demonstrated that the presenilin-1 protein, which is part of the γ secretase complex, induces lipid raft formation *in vivo*[13].

III. Ceramide in AD

The generation of Aβ mainly takes place in lipid rafts, membrane microdomains enriched with cholesterol, gangliosides and other sphingolipids, where APP and the β- and γ-secretases are together. Modulation of the membrane lipid composition might influence Aβ-generation. Spingolipids have an important role as structural components of cellular membranes, ceramides serve also as important bioactive lipids in a variety of cellular processes like cell growth and differentiation, inflammation and apoptosis[14]. Ceramide can also be formed through several lysosomal enzymes addressing complex sphingolipids such as glycosylsphingolipid, galactosylsphingolipid, sphingomyelin, and ceramide 1-phosphate. Ceramide can be further degraded to sphingosine, which upon entry into the ER(endoplasmic reticulum) can be salvaged into ceramide[15]. Ceramide can also be formed through the salavage pathway which involves the lysosomal degradation of complex sphingolipids into ceramide. The catabolism of the complex glucosphingolipids is predominantly located to the surface of internal membrane vesicles or at endocytosed lipoproteins. Receptor mediated endocytosis of low-density lipoprotein (LDL) delivers the glycosphingolipids to lysosomal lumen. The degradation of the simplest of the complex sphingolipids, glycosylceramide, is catalyzed through the action of glycosylceramide-beta-glucosidase (GBA1)[16]. Ceramides are also formed by degradation of more complex sphingolipids. Thus, sphingomyelinase is subject to activation through extracellular signaling pathways which leads to hydrolytic conversion of sphingomyelin to ceramide. Ceramide was the most effective lipid acceptor. Brain levels of the lipid ceramide are high in Alzheimer's disease, and it have been found increased levels of an antibody to the lipid in disease mice model[17]. Inside the brain, ceramide appears to increase beta amyloid production and help the iconic plaque kill brain cells in Alzheimer's[17]. Ceramide is as a risk factor for Alzheimer's. Amyloid triggers excess production of the lipid, although precisely how and why remain a mystery. Generating antibodies against ceramide would hamper plaque formation. Excessive ceramide works its way into the bloodstream, generating antibodies that supported disease progression, particularly in female mice. Alzheimer's disease, appears to support the theory that Alzheimer's is an autoimmune disease, which tends to be more common in women and is characterized by the immune system producing antibodies against a patient's tissue[18].

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Measuring blood levels of the lipid or some of its byproducts could be an early test for Alzheimer's since ceramide levels were elevated well before mice showed signs of substantial plaque formation. It's a chicken-egg situation. The anti-ceramide antibodies that may develop naturally during disease might be a result or a cause of the disease. Excess ceramide in the brain results in the production of vesicles, lipid bubbles, called exosomes, that start piling up around brain cells[19]. Exosomes trigger cell death, since ceramide contributes to neuro-degeneration in Alzheimer's[19]. The clearance system stops working, and toxic levels of amyloid and ceramide pile up. In mice model, when they gave more ceramide, it not only increased antibody levels, but levels of plaque and exosomes. Female Alzheimer's mice treated with more ceramide experienced about a 33 percent increase in amyloid formation and that serum exosome levels increased 2.4 times[20]. Ceramide antibodies maybe interrupt some good functions of exosomes. The mice genetically programmed to get Alzheimer's will produce less ceramide, less exosomes, and less plaques. In the face of more antibody, there is more plaque, but that is because there is more ceramide.

IV. Ceramide on Immune Responses

Inflammation is a tool to fight pathogens and the vertebrate immune system has a very complex network of cells to achieve this. However inflammation that goes awry is also the leading cause of several diseases ranging from cardiovascular diseases to diabetes. The cell membrane contains three main classes of lipids: Glycerolipids, sphingolipids and sterols. Ceramide (Cer) from mammalian membranes is composed of sphingosine, which is an amide linked to a fatty acyl chain, varying in length from 14 to 26 carbon atoms[19,20,21]. Ceramide constitutes the metabolic and structural precursor for complex sphingolipids, which are composed of hydrophilic head groups, such as sphingomyelin, ceramide 1-phosphate, and glucosylceramide. Ceramide formed in this compartment is transported to the Golgi, which is the site of synthesis of sphingomyelin and glucosylceramide (GlcCer). The Cer transport to the Golgi occurs either through the action of the Cer transfer protein, which delivers Cer for SMsynthesis[22]. or through vesicular transport which delivers Cer for the synthesis of GlcCer. The transfer of GlcCer for glycosphingolipid (GSL) synthesis requires the action of the transport protein. GlcCer appears to be synthesized on the cytosolic side of the Golgi, and needs to flip to the luminal side of the Golgi for the synthesis of complex GSL. Lipid rafts are cholesterol-rich domains found on the cell surface, and normally aggregation of lipid rafts appears especially at the site of TCR-antigen ligation. (T-cell receptor)[23]. Lipid rafts are plasma membrane microdomains enriched in cholesterol and sphingolipids that are involved in the lateral compartmentalization of molecules at the cell surface. Internalization of ligands and receptors by these domains occurs via a process defined as raft-dependent endocytosis. Lipid rafts are dynamic assemblies of phospholipids and glycosphingolipids that contain mostly saturated hydrocarbon chains which allow cholesterol to intercalate between the fatty acyl chains. Lipid rafts play both global and specific roles that contribute to control the conformation of amyloid proteins. When an Intrinsically disordered protein (IDP) comes close to a membrane, specific interactions with selected lipids (such as gangliosides in lipid rafts) will favor the efficient adhesion of the protein to this membrane[24]. Moreover, the repetitive head groups of raft lipids will induce α-helical folding of the protein through a typical chaperone-facilitated reaction. The reduction of dimensionality from 3D (extracellular milieu) to 2D (lipid raft surface) also favors the concentration of the protein on the membrane surface[24]. The Parkinson's and Alzheimer's disease–associated proteins α-synuclein and β-amyloid peptides (Aβ) are typical examples of such IDPs that acquire a helical structure when bound to lipid rafts of neural cells[24].

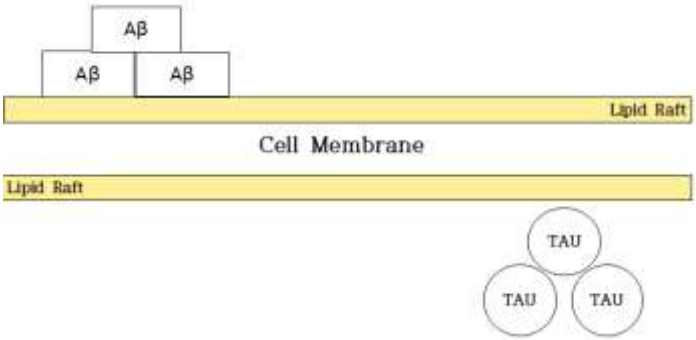

Fig. 1. Lipid Rafts in Neuron Cell.

However, when the proteins fall on the 2D surface of the membrane, this distance is significantly decreased[24]. The effect is potentiated by the fact that the attachment of the amyloid protein on the membrane is not stochastic. Indeed, a common feature of amyloid proteins is that they have a marked preference for glycosphingolipids that are concentrated in relatively small microdomains of the plasma membrane (lipid rafts). Thus, landing on a lipid raft result in an important concentration of the amyloid protein, and Tau protein accumulates inside the neurons (Figure 1). Moreover, the head groups of glycolipid clusters will exert a chaperone effect that forces the amyloid protein to adopt a secondary structure, which, depending on the protein–lipid stoichiometry, can be either an α-helix or a β-rich structure. The accumulation of Aβ has been observed to be related to cholesterol and lipid rafts. In a transgenic mouse model with double-mutant mice overexpressing APP involved in AD pathogenesis, a high-cholesterol diet led to a significant increase in Aβ formation[25]. Furthermore, in cholesterol-depleted hippocampal neurons Aβ formation is inhibited, and β-secretase was localized to lipid rafts. These findings imply that cholesterol-rich regions of hippocampal cell membranes are associated with increased Aβ formation, and that a lower cholesterol content of these membranes could lead to a decreased Aβ production. Ceramides, the major molecules of sphingolipid metabolism and lipid second messengers, have been associated with AD progression and pathology via Aβ generation. Enhanced levels of ceramides directly increase Aβ through stabilization of β-secretase, the key enzyme in the amyloidogenic processing of Aβ precursor protein (APP). Ceramides are a class of sphingolipids that are

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abundant in cell membranes and play an important role in regulation of the fluidity and structure of the lipid bilayer. Ceramides are a class of sphingolipids that are abundant in cell membranes and play an important role in regulation of the fluidity and structure of the lipid bilayer. Ceramides are composed of a sphingolipid base linked to a fatty acid of varying chain length carbons via an amide bond. Cell-permeable short chain ceramide, Ceramides were present naturally in the brain at low levels[20]. This mitochondrial failure evoked by ceramide leads to enhancement of oxidative stress, DNA damage and activation of nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP-1)[21]. It was reported previously that the formation of long-chain poly (ADP-ribose) (PAR) and the release of the apoptosis-inducing factor (AIF) from mitochondria to nucleus may accelerate cell death[9]. Ceramides have been indicated as key player in neuronal cell death. however, their role is not yet well understood. Ceramide can exert its physiological effects either through changes in membrane properties or through binding to specific target proteins[26]. Many studies indicate a critical role of ceramide in the reorganization of the cell membrane and membrane rafts. The generation of ceramide within the cell membrane alters its properties. Indeed, ceramide molecules spontaneously self-aggregate and are tightly packed in homodimers/multimers in association with other sphingolipids[14]. Leading to the formation of ceramide-enriched membrane domains that fuse to large ceramide-enriched membrane platforms[11]. These ceramide enriched-membrane platforms serve to the reorganization and clustering of receptor molecules such as CD95, CD40, DR5/TRAIL, CD20, CD28, TNF, interleukin-1 receptor, FC□RII and the PAF-receptor[15,16,19]. Ceramide syntheses play a critical role in inflammatory processes and are involved in many autoimmune diseases. However, how ceramide syntheses regulate activation and function of primary T cells is largely undefined. Ceramides are critical for inflammatory responses. Synthetic, short-chain ceramide molecules have proven to be much more soluble than endogenously produced long-chain ceramides and therefore have been used frequently in many different experimental systems. The functions of ceramide and ceramide-metabolizing enzymes in immune responses are only beginning to be understood. The ceramide-metabolizing enzyme acid sphingomyelinase has been shown to play a key role in the degranulation of T cells, a mechanism critical to their effector function. Moreover, it was shown that the cross-linking of CD28 activates acid sphingomyelinase, which enhances the transmission of the signal to NF-κB in Jurkat T cells[22]. In a recent lipidomic study, an increase in the production of 24-carbon ceramide has been demonstrated to occur during LPS-induced dendritic cell (DC) maturation, which again suggests roles for ceramide or ceramide-metabolizing enzymes during immune responses[27]. DCs are key regulators of immune responses. These cells efficiently transmit the pathogens' danger signal to pathogen-specific T lymphocytes. DCs sense pathogen-associated molecular patterns through highly conserved pattern-recognizing receptors such as TLRs. Following pathogen-associated molecular pattern recognition, DCs undergo maturation, which involves the upregulation of molecules for Antigen presentation and the co-stimulation of T lymphocytes. Ceramide may also play a critical role in regulating T cell responses in autoimmune diseases. Sphingolipids are known to play essential roles in the induction and progression of inflammation, but how specific ceramides regulate inflammation and immune responses is largely undefined. Ceramide contributes to inflammation by inducing T cell proliferation and IFN-γ production. it is plausible to predict that inhibition of Ceramide could specifically, or preferentially, suppress alloantigen-driven responses. The regulation of TCR expression is an important mechanism by which T cell responsiveness is controlled, and membrane rafts are the "effector" sites in T cell signaling. Upon stimulation, these rafts cluster into an immunological synapse that harbors key proteins, including TCR, CD3[25]. The synapse is believed to sustain TCR engagement and T cell signaling. Reports have shown that ceramides influence cell fate by participating in various signaling pathways through modulation of lipid rafts[28]. It is clear that Ceramide plays a critical role in regulating different immune cells, including macrophages and T cells, which in turn can modulate different autoimmune diseases, such as AD[29].

V. CONCLUSION

The lipid-rich domain of the cell membrane provides an accumulation space for the amyloid protein. Ceramide is a key component of the lipid domain. Ceramide molecules in the cell membrane are an attack target of dendritic cells that monitor non-magnetic antigens. The dendritic cells recognize the cell membrane domain, which contains ceramide and amyloid, as non-magnetic antigens, releasing inflammatory cytokines and inducing the activity of aggressive T cells.

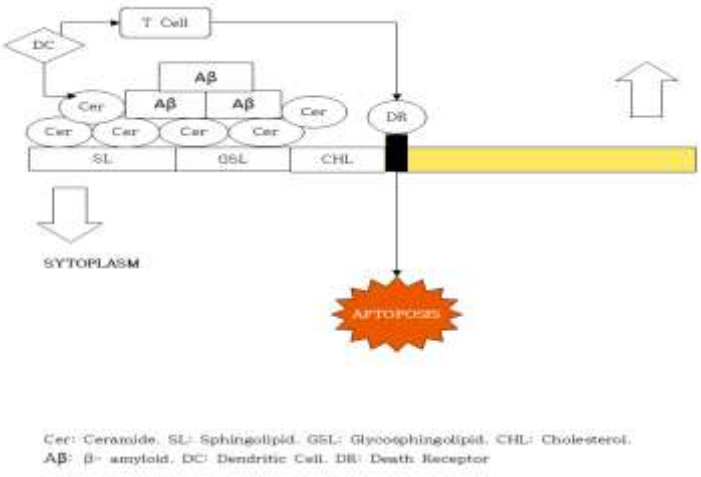

Fig. 2. Ceramide in Cell Death.

The amyloid protein, which undergoes intensive attack of immune cells, is destroyed by the N terminal structure to which the phosphate group binds and the ubiquitin is inhibited and accumulated one by one. As a result, in neurons, amyloid accumulates around the cell membrane and the neuron cell is killed by the activated T cell. This is a potent hypothesis demonstrating that autoimmune disease is a crucial cause of

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Alzheimer's induction (Figure 2). Further studies are needed to confirm the hypothesis by animal experiments.

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