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RESEARCH PAPER

Protective effects of vitamin E against hypercholesterolemia-induced age-related diseases

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Abstract Hypercholesterolemia is a major risk factor for age-related diseases such as atherosclerosis and Alzheimer's disease (AD). Changes in human plasma cholesterol levels results from the interaction between multiple genetic and environmental factors. The accumulation of excess cholesterol in blood vessels leads to atherosclerosis. Many studies on this field show that differential expression of oxidative stress-related proteins, lipid metabolism-related enzymes, and receptors response to atherogenic diet. Additionally, excess brain cholesterol has been associated with increased formation and deposition of amyloid-β peptide from amyloid precursor protein which may contribute to the risk and pathogenesis of AD. To consider genetically, more than 50 genes have been reported to influence the risk of late-onset AD. Some of these genes might be also important in cholesterol metabolism and transport. Epidemiological studies have shown an association between high intake and high serum concentrations of antioxidant vitamins like vitamin E and lower rates of ischemic heart diseases. It has been known that vitamin E also inhibits smooth muscle cell proliferation by non-antioxidant mechanism. On the basis of the previous results, vitamin E has been accepted as an important protective factor against hypercholesterolemia-induced age-related diseases.

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Introduction

Biological aging is a process, results in the loss of cellular functions that leads to the development of related neurodegenerative and cardiovascular diseases. Therefore, understanding the mechanisms underlying aging is necessary to develop therapeutic interventions against age-related diseases. Following several studies in many years, oxidative damage is strongly implicated in the pathogenesis of neurodegenerative and cardiovascular diseases including Alzheimer's disease and atherosclerosis (Squier 2001).

Atherosclerosis, a chronic inflammatory disease which is characterized by the accumulation of plasma lipoproteins that carry cholesterol and triglycerides in the arteries, is one of the major causes of morbidity and mortality worldwide. This accumulation results in the proliferation of certain cell types within the arterial wall (Stocker and Keaney 2004). In the atherosclerotic process, macrophage foam cells are formed with the rapid transformation of phagocytic monocytes penetrated into the subendothelial space and atherogenic lipoproteins like modified low-density lipoprotein (LDL) are uptaken by receptor-mediated endocytosis mechanism (Osterud and Bjorklid 2003; Schmitz and Grandl 2007). Following the endocytosis, these cells have an appearance loaded with lipid droplets rich in cholesteryl esters. These foam cells also known as "fatty streaks" and adaptive thickening of the intima are accepted as the main visible lesions at the early stage of the pathogenesis (Steinberg 2009). Cellular uptake of the atherogenic lipids and lipoproteins are mediated by several receptors, and CD36 takes the most important place in the

scavenger receptors playing role in atherosclerotic process (Stocker and Keaney 2004; Schmitz and Grandl 2007).

Alzheimer is another important age-related disease, most common form of adult onset dementia. Neuropathology of AD arises from numerous biochemical changes such as cholinergic deficits (Francis et al. 1999); neuronal metabolic insult (glutamate induced excitotoxicity) (Masliah et al. 1996); and oxidative stress or damage such as lipid peroxidation and protein oxidation (Nunomura et al. 2006). AD progression and memory loss involves various cellular anomalies such as: (1) accumulation of extracellular neuritic plaques of amyloid-β peptide (Aβ) (Butterfield et al. 1996); (2) intracellular neurofibrillary tangles (NFTs); (3) proliferation of astrocytes, synaptic loss; and (4) progressive loss of neurons and microglial activation (Markesbery and Lovell 2007; Sultana et al. 2006).

Basic mechanisms in the cholesterol-induced age-related diseases

Denham Harman introduced the free radical theory of aging in 1956 and proposed that aging results from random deleterious damage to tissues by free reactive species (RS) damage cellular components such as proteins, lipids, carbohydrates, and nucleic acids and several products are known to be produced(Nordberg and Arnér 2001). The main investigated products are malondialdehyde (MDA) and 4-hydroxynonenal (HNE) for lipid peroxidation, 8-hydroxydeoxyguanosine for DNA oxidation and protein carbonyls, nitrotyrosines for protein oxidation (Griffiths et al. 2002; Catalgol and Grune 2009).

Lipid peroxidation and LDL oxidation induced by RS are the early events in atherosclerotic lesion formation (Stocker and Keaney 2004; Vogiatzi et al. 2009; Salvayre et al. 2002) Mostly macrophages are thought to be the source of reactive oxygen species (ROS) formation in the vessel wall but also other cells like endothelial, smooth muscle, and adventitial cells produce ROS in the vessel wall (Fortuno et al. 2005). In this direction, ox-LDL modulates atherosclerosis biology by cell damage induction, proliferation of smooth muscle cells, foam cell formation, chemotaxis of leukocytes, and secretion of inflammatory mediators. Since oxidation of LDL is the main oxidative modification, high plasma levels of native LDL is a risk factor for the progression (Stocker and Keaney 2004; Vogiatzi et al. 2009).

A growing body of evidence supports the notion that lipid rafts play a crucial role in the redox signaling that regulates the pathophysiology of many degenerative diseases. It is also known that distinct cholesterol- and sphingolipid-rich membrane rafts are importantly involved in transmembrane signaling in a variety of mammalian cells (Catalgol and Özer 2010; Das 2010).

Oxidative stress is closely associated with the neuropathology of AD, a major neurodegenerative disorder characterized by multiple neurological events, gradual decline in cognitive functions, and rapid aging of the brain tissue. The major alterations in this disease are senile plaques (SP) and neurofibrillary tangles (NFT) represent an accumulation of intraneuronal and extracellular filamentous protein aggregates. Major proteins in these formations are hyperphosphorylated tau in NFT and amyloid beta (Aβ) peptide derived from amyloid precursor protein for SP (Markesbery and Lovell 2007). These protein aggregate formations in Alzheimer's disease cause the researchers to focus on the role of oxidative stress mainly protein oxidation in the process. The oxidative damage found in Alzheimer's disease includes advanced glycation end products (Smith et al. 1994; Ledesma et al. 1994), nitration (Good et al. 1996), lipid peroxidation adduction products (Salvayre et al. 2002; Montine et al. 1996), carbonyl modified neurofilament protein, and free carbonyls (Smith et al. 1991; Smith et al. 1995). Oxidized proteins (protein carbonyls) were found to be increased in frontal pole and occipital pole in Alzheimer's disease patients compared with controls (Sayre et al. 1997). Mishto et al. (Mishto et al. 2006) found a decrease in trypsin-like activity of proteasome emerged in hippocampus and cerebullum of Alzheimer's disease patients. In a study of Alzheimer's disease subjects compared with control groups, there was a significant increase in mitochondrial DNA oxidation in parietal cortex (Mecocci et al. 1994). Lovell et al. (Lovell et al. 1997) found elevated levels of free and protein-bound HNE in ventricular fluids of Alzheimer's disease patients. Iron in a redox-active state, thought to play an important role in free radical production in Alzheimer's disease, was shown to be increased in NFT as well as Aβ deposits (Good et al. 1992). Iron catalyzes the formation of hydroxyl radical from H_2O_2 and also the formation of advanced glycation end products. Aβ itself has been directly implicated in ROS formation through peptidyl radicals (Hensley et al. 1994). Additionally, advanced glycation end products and Aβ, activate-specific receptors, such as the receptor for advanced glycation end products (RAGE) and the class A scavenger-receptor, to increase reactive oxygen production (Yan et al. 1996).

Genetic factors (apolipoprotein E ε4 allele), germline mutations (amyloid-β protein precursor gene, presenilin-1 gene, and presenilin-2 gene), environmental causes, lifestyle-related factors (smoking), and certain health conditions such as diabetes, brain injury, and hypercholesterolemia cause oxidative stress in AD patients (Nunomura et al. 2006). Oxidative stress affects proteins (Hensley et al. 1998), nucleic acids (Smith et al. 1991), lipids (Sayre et al. 1997;

Pratico et al. 2001; Schuessel et al. 2005), and enzymes (Premkumar et al. 1995) in AD patients. Increased nitrative stress in human AD brains has been reported in the form of increased levels of protein oxidation (Hensley et al. 1995), protein nitration (Keller et al. 2005), 3-nitrotyrosine, 3,3′-dityrosine in hippocampus, and major regions of the brain including inferior parietal lobule, neocortical regions, and ventricular cerebrospinal fluid (Hensley et al. 1998). Both nuclear and mitochondrial DNA has been modified by oxidative stress to increased levels of 8-hydroxy-2-deoxyguanosine and oxidized bases in cerebral cortex and cerebellum of AD patients as compared with age-matched control subjects (Mishto et al. 2006; Wang et al. 2005). Increased levels of malondialdehyde, a measure of lipid peroxidation, are found in human AD brains (Balazs and Leon 1994). Numerous cellular and animal models of AD have been developed and considerable efforts have been taken to identify mechanisms of redox state-mediated gene regulation in relation to AD pathology.

Hypercholesterolemia is a major risk for coronary artery diseases. In the development of atherosclerosis, ROS are produced by endothelial cells, smooth muscle cells, and macrophages oxidize LDL in the subendothelial space, at the sites of endothelial damage, initiating events that culminate in the formation of a fibrous plaque. Rupture of fibrous plaque leads to thrombus formation and occlusion of the vessel (Stokes et al. 2002; Madamanchi et al. 2005). Prasad et al. (Prasad et al. 1997) showed that cholesterol feeding of rabbits caused an increase in MDA levels and glutathione peroxidase activities and a decrease in superoxide dismutase activity in the myocardium. Patients with elevated cholesterol may have increased susceptibility to AD in addition to coronary artery disease and hypertension (Pappolla et al. 2003). Cholesterol may initiate Aβ formation, which mentioned as a potent source of oxidative stress and irreversible protein aggregation. In one of our studies, to show the possible role of high cholesterol in AD, rabbits were fed with high cholesterol and following the increase in the serum cholesterol levels, MDA levels were shown to be increased consistent with the previous results (Aytan et al. 2008; Ozer et al. 2006; Ozer et al. 1998). Additionally, slight increase in HNE-proteins, 3-nitrotyrosinated proteins, and protein carbonyls was observed in hippocampus area of the rabbits. Proliferation of smooth muscle cells that migrate from arterial media into the subendothelial space is a central event in the onset of atherosclerosis both in humans and in animals. Ex vivo smooth muscle cells obtained from the aorta of cholesterol-fed rabbits exhibited a twofold increase in protein kinase C (PKC) expression and activity (Sirikci et al. 1996).

Key components in atherogenesis including signaling molecules such as redox sensitive transcription factor NFκB activation and adhesion molecules such as selectins, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) and chemokines such as monocyte chemoattractant protein-1 (MCP-1) expressions in the vascular endothelium are known to be increased by RS. Expression of adhesion molecules and MCP-1 are also key steps for the monocyte adhesion and emigration to form macrophages and foam cells. Macrophage colony-stimulating factor (M-CSF) is an important factor regulating the survival, proliferation, differentiation, and chemotaxis of macrophages (Harizi and Gualde 2006; Pixley and Stanley 2004; Chitu and Stanley 2006; Fan and Watanabe 2003). The effects of ox-LDL on NFκB may be biphasic as concentration dependent. Normally, it activates NFκB and upregulates the expressions of adhesion molecules, tissue factor, and LOX-1. In high concentration, ox-LDL inhibits NFκB activation triggered by inflammatory agents such as lipoxygenases and therefore exert immunosupressive effect (Robbesyn et al. 2004). HNEs were shown to activate MAPK in endothelial cells either by directly interacting with PKC or through activation of the EGF receptor (Uchida et al. 1999).

The presence of foam cells in the atherosclerosis process confirms the importance of CD36 scavenger receptors. CD36 has an important role in the intake of ox-LDL by macrophages in the arteria walls and long-chain fatty acids into the cells. Following binding of ox-LDL to CD36 receptor, lyn kinase, a src protein tyrosine kinase, is activated. This activation induces mitogen ERK kinase kinase 2 (MEKK2) and c-jun N-terminal kinase (JNK) activation and phagocytosis of proatherogenic ox-LDL (Rahaman et al. 2006). CD36 was shown to be upregulated by PKC and PPARγ pathway which are common signaling mechanisms for IL4 and ox-LDL (Feng et al. 2000). CD36 scavenger receptor expression was shown to be increased in ox-LDL treated aortic smooth muscle cells in culture (Ricciarelli et al. 2000). It has been shown as in vivo that hypercholesterolemia increases foam cell formation and atherosclerosis by increasing CD36 mRNA expression and PKC activity in rabbits (Ozer et al. 2006; Ozer et al. 1998; Sirikci et al. 1996).

Vitamin E: from an antioxidant to a signaling molecule

Vitamin E was discovered in 1922 in green leafy vegetables by University of California researchers, Herbert Evans, and Katherine Bishop. Two decades after the "biological antioxidant theory" (Green and Bunyan 1969) was reported, and Burton and Ingold presented the first comprehensive review article discussing that α-tocopherol has near optimal activity as a chain-breaking antioxidant and that both the phenolic head and phytyl tails contributed to the biological properties of the vitamin E molecule

(Burton and Ingold 1989). In recent studies, vitamin E term includes eight naturally occurring components including the respective α, β, γ, and δ derivatives of tocopherol and tocotrienol. Among them, RRR-α-tocopherol is by far the most abundant lipid-soluble antioxidant in humans and it is present in cellular and sub-cellular membranes (Cordero et al. 2010). Besides this, tocotrienols were shown to possess powerful neuroprotective, anti-cancer, and cholesterol lowering properties (Sen et al. 2006).

Vitamin E emerged as an essential, fat soluble nutrient that functions as an antioxidant in the human body. It is essential, because the body cannot manufacture its own vitamin E and foods and supplements must provide it. Vitamin E represents one of the most fascinating natural resources that have the potential to influence a broad range of mechanisms underlying human health and disease. There are many studies carried out to gain insight into the effects of Vitamin E components, especially tocotrienol, on the several age-related diseases. In hypercholesterolemic human subjects tocotrienol lowered serum cholesterol (Qureshi et al. 1991), lowered both serum total cholesterol, and low-density-lipoprotein cholesterol (Tan et al. 1991), regulated cholesterol production in mammalian cells by post-transcriptional suppression of 3-hydroxy-3-methylglutarylcoenzyme A reductase (Parker et al. 1993), lowered plasma cholesterol level in hypercholesterolemic subjects (Qureshi et al. 1995), tocotrienol-rich fraction of rice bran suppressed serum cholesterol dose-dependently (Qureshi et al. 2002). Qureshi et al. (2001) claimed that in hypercholesterolemic humans, tocotrienol is converted to tocopherol in vivo. In another human study, dietary tocotrienols were shown to be incorporated into circulating human lipoproteins where they react with peroxyl radicals as efficiently as the corresponding tocopherol isomers (Suarna et al. 1993). Palm tocotrienols was shown to protect ApoE± mice from diet-induced atheroma formation (Black et al. 2000) and tocotrienols was shown to inhibit atherosclerotic lesions in ApoE-deficient mice (Qureshi et al. 2001). It is thought that the unsaturated side chain of tocotrienol allows for more efficient penetration into tissues that have saturated fatty layers such as the brain and liver (Suzuki et al. 1993). Also tocotrienol administration reduced oxidative protein damage and extended the mean life span of C. elegans (Adachi and Ishii 2000).

α-Tocopherol was identified as the major antioxidant present in human lipoproteins, it received much attention as a suppressor of LDL lipid oxidation and as an epidemiological marker for ischemic heart disease. At the post-translational level, α-tocopherol was shown to inhibit protein kinase C, 5-lipoxygenase and phospholipase A2 and activate protein phosphatase 2A and diacylglycerol kinase (Sen et al. 2006). The mechanism of PKC regulation by α-tocopherol has been investigated in smooth muscle cells. Treatment of rat aortic A7r5 smooth muscle cells with α-tocopherol resulted in a time- and dose-dependent inhibition of PKC. Autophosphorylation and kinase activities of the different isoforms have shown that only PKCα was inhibited by α-tocopherol. The inhibitory effects were not mimicked by β-tocopherol, an analog of α-tocopherol with similar antioxidant properties (Ricciarelli et al. 1998). The role of d-α-tocopherol in the proliferation and protein kinase C activity of smooth muscle cells promoted by native and malondialdehyde-modified LDL was also investigated. The data showed that d-α-tocopherol inhibits vascular smooth muscle cell proliferation and protein kinase C activation produced by both types of LDL (Ozer et al. 1993).

Some genes (e.g., scavenger receptors, α-TTP, α-tropomyosin, matrix metalloproteinase-19, and collagenase) are specifically modulated by α-tocopherol at the transcriptional level. α-Tocopherol also inhibits cell proliferation, platelet aggregation and monocyte adhesion. These effects have been characterized to be unrelated to the antioxidant activity of vitamin E and possibly reflect specific interactions of α-tocopherol with enzymes, structural proteins, lipids, and transcription factors (Zingg and Azzi 2004). The role of Vitamin E on CD36 expression in an in vivo model was tested. Atherosclerosis was induced by a 2% cholesterol containing Vitamin E poor diet. Three groups of six rabbits each were studied. The first group (control) was fed on Vitamin E poor diet. The second group was fed with Vitamin E poor diet containing 2% cholesterol, and the rabbits in the third group were fed with Vitamin E poor diet containing 2% cholesterol and received injections of 50 mg/kg of Vitamin E i.m. After 4 weeks, aortas were removed and analyzed by light microscopy for atherosclerotic lesions. Aortic samples were analyzed for CD36 mRNA expression. The aortas of cholesterol-fed rabbits showed typical atherosclerotic lesions, detected by macroscopic and microscopic examination, and exhibited an increase in CD36 mRNA expression. Vitamin E fully prevented cholesterol-induced atherosclerotic lesions and the induction of CD36 mRNA expression. The effects observed at the level of CD36 scavenger receptor expression in vivo suggest an involvement of reduced foam cell formation in the protective effect of Vitamin E against atherosclerosis (Ozer et al. 2006).

The effect of tocopheryl phosphate on atherosclerosis progression has been studied in rabbits, fed with a 2% cholesterol diet and compared with an equivalent amount of α-tocopheryl acetate. The results show that the atherosclerosis preventing effect of the phosphate derivative was more pronounced than that of the acetate derivative. α-Tocopheryl phosphate was also more potent in diminishing the expression of CD36 than the acetate derivative (Negis et al. 2006).

The possible role of vitamin E on the cardiovascular diseases was initially proposed in the so-called "antioxidant hypothesis of atherosclerosis" (Gey 1995). On the other hand, vitamin E may as well exhibit pro-oxidative activity under specific conditions, possibly leading to tocopherol-mediated lipid peroxidation (Thomas et al. 1995; Upston et al. 1999). Other research investigations have reported evidence on alternative functions of vitamin E on atherosclerosis beyond its antioxidant role such as anti-inflammatory functions, regulation of the expression of genes involved in growth, apoptosis and inflammation, modulation of the immune response, and detoxification of xenobiotics (Azzi et al. 1995; Kaul et al. 2001; Ricciarelli et al. 2001; Traber and Atkinson 2007).

The association between vitamin E intake from food and/or supplements and cardiovascular disease (myocardial infarction and/or stroke) events (fatal and/or non-fatal) has been analyzed by the following nine prospective cohort studies: Health Professionals Follow-up Study (HPFS) (Rimm et al. 1993; Ascherio et al. 1999), Iowa Women's Health Study (IWHS) (Kushi et al. 1996; Yochum et al. 2000), Scottish Heart Health Study (SHHS) (Todd et al. 1999), Cancer Prevention Study II (CPS-II) (Watkins et al. 2000), Physician Health Study (PS) (Muntwyler et al. 2002), Nurses' Health Study (NHS) (Stampfer et al. 1993), Finnish Cohort Study (FS) (Knekt et al. 1994), The Zutphen Study (ZS) (Bocan et al. 1993), and one analyses from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) (Smith 1974). These studies reported a 5% reduction of coronary heart disease risk among men from dietary vitamin E intake (SHHS) (Todd et al. 1999), a 32% reduction of coronary heart disease risk among men from dietary vitamin E intake (FS) (Knekt et al. 1994), a 40% reduction of coronary heart disease risk among men from dietary and supplemental vitamin E intake (HPFS) (Rimm et al. 1993), a 34% reduction of major coronary heart disease risk among women from dietary and supplemental vitamin E intake (NHS) (Stampfer et al. 1993), a 62% reduction of coronary heart disease risk among women from dietary vitamin E intake (IWSS) (Kushi et al. 1996), a 65% reduction of coronary heart disease risk among women from dietary vitamin E intake (FS) (Knekt et al. 1994), a 10–14% reduction of ischemic heart disease risk among women users of vitamin E, vitamin C, and/or vitamin A without multivitamins or plus multivitamins (CPS-II) (Watkins et al. 2000), and a 59% reduction of coronary heart disease mortality among men who took vitamin E supplements for more than 4 years (a secondary analysis within PS) (Muntwyler et al. 2002). A total of four analyses addressed the relationship between the vitamin E intake and stroke events with a 60% reduced stroke mortality associated with higher dietary vitamin E intake within the IWHS (Yochum et al. 2000) and a 15% reduced stroke incidence among women who took vitamin E-containing multivitamins for more than 5 years within the CPS-II (Watkins et al. 2000). In contrast, supplementation with vitamin E had no effect on cardiovascular disease incidence in most of the randomized control trials conducted so far. In our animal studies, the rabbits were made atherosclerotic by using a cholesterol-rich diet, commonly used to produce atherosclerosis (Aytan et al. 2008; Ozer et al. 2006; Ozer et al. 1998; Sirikci et al. 1996). A high cholesterol supplementation was preferred to lower cholesterol containing diets. This decision turned out to have the advantage of maximizing the atherosclerotic result and diminishing the treatment time. Although some studies reported (Bocan et al. 1993; Smith 1974; Guyton et al. 1985), diminution of plasma cholesterol associated with vitamin E supplementation was not visible under these conditions. However, the very high cholesterol supplementation may also be the reason for the lack of a statistically significant effect of vitamin E.

The majority of the age-related diseases has increased the preclinical evaluation of putative antioxidant agents ranging from prototypic natural antioxidants such as vitamin E (α-tocopherol) to sophisticated synthetic free radical traps and catalytic oxidants. In spite of scientific evidence supporting oxidative stress as a pathogenic factor in age-related diseases, human clinical trials with antioxidant protectants has been generally negative (Keli et al. 1996; Hirvonen et al. 2000; Kamat et al. 2008) although some vitamin E experiments in AD showed a positive effect on quality-of-life parameters, such as time to enter a nursing facility (Sano et al. 1997).

Vitamin E is an archetype micronutrient which has been able to reach sub-therapeutic levels in brains of AD patients and decrease lipid peroxidation susceptibility by 60% in AD patients as compared with control subjects (Galbusera et al. 2004; Veinbergs et al. 2000). Vitamin E has been frequently tested in epidemiologic and clinical studies for AD and cognitive disorders. The data from these trials are available for symptomatic treatments (Sano et al. 1997; Cash et al. 2002) as well as preventive therapies for AD (Nunomura et al. 2006). Some of the clinical trials for vitamin E, alone or in combination with vitamin C, against cognitive disorders showed positive effects for vitamin E; e.g., Honolulu-Asia Aging study (3,385 men) (Masaki et al. 2000); Chicago Health and Aging Project (815 subjects; 3.9 years follow-up study) and Nurses' Health Study (14,986 women aged 70–79 years) (Grodstein et al. 2003) whereas, some studies showed contrasting effects for vitamin E (Petersen et al. 2005), which include Honolulu-Asia Aging study (2,459 men; Vitamin E alone) (Petersen et al. 2005; Laurin et al. 2004; Luchsinger et al. 2003), Washington Heights Study (980 subjects; 4 year follow-up study), and Cache Country Study (4,740 subjects; 3 years

follow-up study) (Zandi et al. 2004). Many of the above studies focused on vitamin E and C supplements alone or in combination with each other or other supplements. Among the different preventive and therapeutic strategies dietary α-tocopherol supplementation has been shown in some studies to exert positive effects in the brain (Sano et al. 1997; Morris et al. 2002).

Conclusion

There is a large body of evidence connecting the effects of oxidative stress and related signaling mechanisms with hypercholesterolemia-induced age-related diseases. The majority of these diseases in the aging and the role of oxidative stress-related changes in the progress pushed researchers to focus on the investigation of removal and repair mechanisms for the balance of oxidative stress. Vitamin E components took the main place in these investigations and thought to bring hopeful results in the clinical applications.

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