Docosahexaenoic acid (DHA) in stroke, Alzheimer's disease, and blinding retinal degenerations: coping with neuroinflammation and sustaining cell survival

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Abstract: *The significance of the selective enrichment in omega-3 essential fatty acids in the nervous system has remained, until recently, incompletely understood. While studying mechanisms of cell survival in neurodegenerations, a new docosanoid synthesized from docosahexaenoic acid [DHA] by 15-lipoxygenase-1 [15-LOX-1] was discovered. This mediator, called neuroprotectin D1 [NPD1], is a docosanoid because it is derived from a 22C precursor (DHA), unlike eicosanoids, which are derived from the 20 C arachidonic acid family member of essential fatty acids not enriched in the nervous system. NPD1 is promptly made in response to oxidative stress and brain ischemia-reperfusion and in the presence of neurotrophins. NPD1 is neuroprotective in experimental brain damage, oxidative-stressed retinal pigment epithelial [RPE] cells, and in human brain cells exposed to amyloid-β peptide. Thus NPD1 is a protective sentinel, one of the very first defenses activated when cell homeostasis is threatened by neurodegenerations. This review highlights the specificity and potency of NPD1 spanning beneficial bioactivity in experimental models of stroke, in retinal cells relevant to early events in age-related macular degenerations, and studies addressing fundamental issues during initiation and early progression of neurodegenerations.*

Key words: *ischemia-reperfusion, neuroprotectin D1, docosanoids, retinal pigment epithelial cells, photoreceptors*

The significance of omega-3 essential fatty acids, in cell function and diseases involving cell injury, immune and inflammatory components, is rapidly being unraveled due to the identification of bioactive docosanoids (Bazan *et al.*, 2010; Marcheselli *et al.*, 2003; Mukherjee *et al.*, 2004; Serhan, 2010). The omega-3 essential fatty acid member docosahexaenoic acid [DHA] is avidly retained and accumulates in the nervous system. In fact, the nervous system (brain, retina and nerves) is mainly where DHA is concentrated in the human body. Docosahexaenoyl chains of membrane phospholipids (22C and 6 double bonds) are richly endowed in photoreceptors, synaptic and other membranes. The study of cell survival mechanisms in brain injury and neurodegenerations led to the discovery of a DHA-derived docosanoid called neuroprotectin D1 [NPD1,10*R*, 17*S*-dihydroxy-docosa-4*Z*, 7*Z*, 11*E*, 13*E*, 15*E*,19*Z* hexaenoic acid]. As a docosanoid, NPD1 is derived from a 22C precursor of the essential fatty acids that are not enriched in the nervous system (see *figure 1* for an illustration of NPD1 biosynthesis). NPD1 is made in response to oxidative stress and brain ischemia-reperfusion and is neuroprotective in experimental brain damage, oxidative-stressed retinal pigment epithelial [RPE] cells, and in human brain cells exposed to amyloid-β peptide. Essentially, NPD1 is a protective sentinel, one of the very first defenses activated when cell homeostasis is threatened by injury or neurodegenerations. We highlight here the knowledge gained from basic research approaches regarding the specificity and potency of the lipid mediator NPD1, spanning beneficial bioactivity during initiation and early progression of retinal degenerations, ischemic stroke, Alzheimer's disease, and other neurodegenerations.

Retinal degenerations

Photoreceptors renew membrane disks, which contain the phototransduction apparatus and phospholipids rich in DHA, intermittently via shedding of their tips and phagocytosis by RPE cells. At the same time, new membrane disks are made at the base of the outer segments; their length remains constant and cell integrity is maintained remarkably

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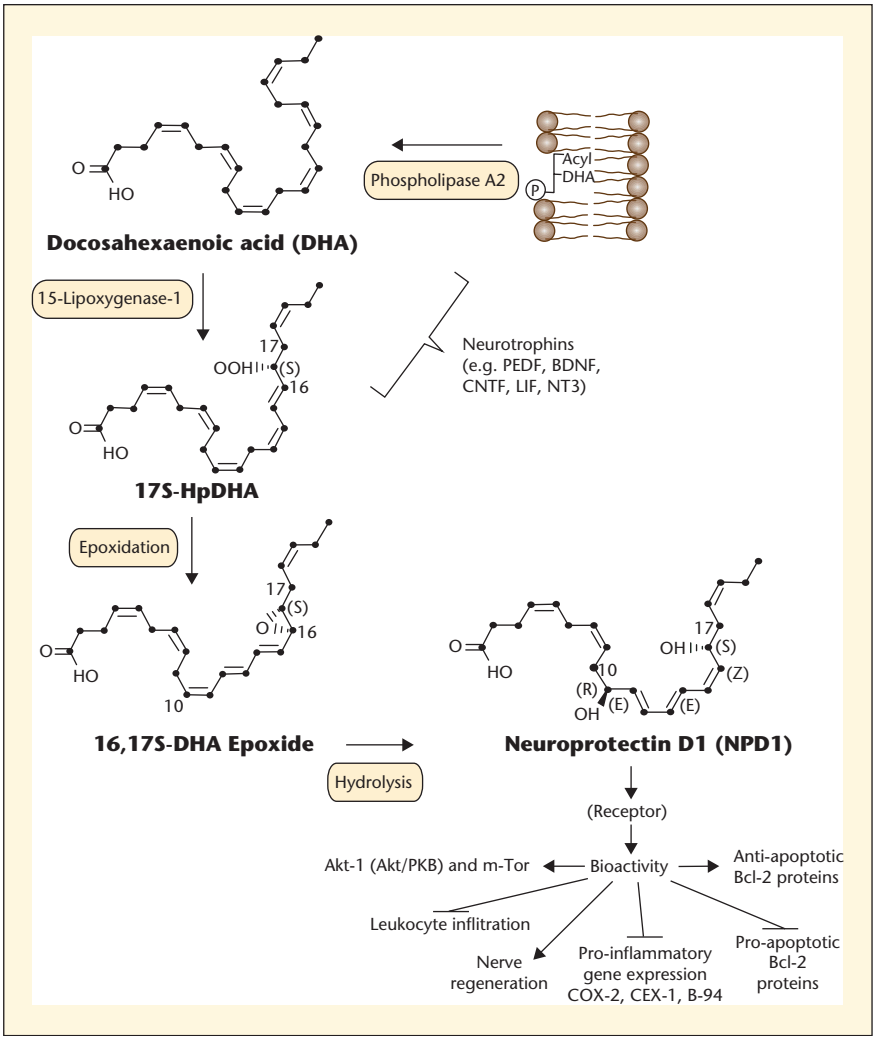

Figure 1. *Biosynthesis of neuroprotectin D1 [NPD1]. A membrane phospholipid containing a docosahexaenoyl chain at sn-2 is hydrolyzed by phospholipase A2, generating free (unesterified) docosahexaenoic acid [DHA] (22:6). Lipoxygenation (Calandria* et al., *2009) is then followed by epoxidation and hydrolysis to generate NPD1. Thus far, a binding site for NPD1 has been identified in retinal pigment epithelial cells and polymorphonuclear cells. Modified, with permission, from the* Annual Review of Nutrition, *Volume 31© 2011 by Annual Reviews www.annualreviews.org*

unchanged throughout many decades. This outcome occurs in spite of the fact that the photoreceptors are in an oxidative stress-prone environment (light, high O_2 consumption, high polyunsaturated fatty acid fluxes, etc.). Phagocytosis of photoreceptor disks promotes, via NPD1 synthesis, specific refractoriness to oxidative stress-induced apoptosis in RPE cells, which in turn fosters homeostatic photoreceptor cell integrity (Mukherjee *et al.*, 2007a,b). Disruptions of the sentinel role of NPD1 during photoreceptor renewal may participate in macular degeneration and other retinal degenerations leading to blindness. A key event takes in RPE cells by either their decreased ability to synthesize NPD1 or by perturbations in its action site/s. As a result, RPE cell damage and apoptosis increases in retinal degenerations. RPE cell apoptosis is involved, and disruptions in NPD1 homeostatic bioactivity are also an early event (Bazan, 2007). *Figure 2* outlines the intercellular routes of DHA arrival from the liver, its retention, and its utilization for membrane phospholipids and NPD1 synthesis. Similar routes likely occur in neurons/astrocytes, which are currently being studied. Overall, this depicts aspects of the DHA signalolipidome, which includes the cellular organization of DHA uptake, its distribution among cellular compartments, the organization and function of membrane domains rich in DHA-containing phospholipids, and the signaling pathways regulated by DHA and NPD1 (Bazan *et al.*, 2011). Neurotrophins are active NPD1 synthesis agonists (Mukherjee *et al.*, 2007a) (*figure 1*).

Stroke

Focal cerebral ischemia injures the brain core and damages the penumbra. The penumbra can be rescued potentially (Fisher, 2006), but it undergoes damage after a few hours unless reperfusion is initiated (Lo, 2008).

In brain ischemia-reperfusion, DHA (i.v.) one hour after two hours of middle cerebral artery occlusion [MCAO] leads to penumbra protection with an extended time window of protection (up to five hours) and with concomitant NPD1 synthesis (Belayev *et al.*, 2011). Anti-apoptotic, BCL-2 protein family availability is positively modulated by NPD1, whereas pro-apoptotic BCL-2 proteins are negatively regulated, as is the arrival of leukocytes due to neurovascular unit breakdown.

Recently low- and medium-dose DHA therapy has been shown to improve neurological and histological outcomes after focal cerebral ischemia (Belayev *et al.*, 2009). Non-invasive magnetic resonance imaging [MRI] and mass spectrometry, in conjunction with behavioral, histological and immunostaining methods, were used to provide evidence for DHA protection of the ischemic penumbra (Belayev *et al.*, 2011).

Neuroprotection is thought to defend neurons from the ischemia-induced neurotoxic environment, however the complex processes that occur after stroke require targeting of multiple factors and cells, including glia, vascular and inflammatory cells. The distribution of molecular markers in the infarcted regions of the DHA-treated brain indicate that treatment with DHA protects not only the neurons, but also astrocytes, which are critical for neuronal maintenance and protection via secretion of growth factors and other neurotrophic mediators. Furthermore, DHA attenuates microglia activation resulting from cellular damage and reduces the inflammatory response that normally

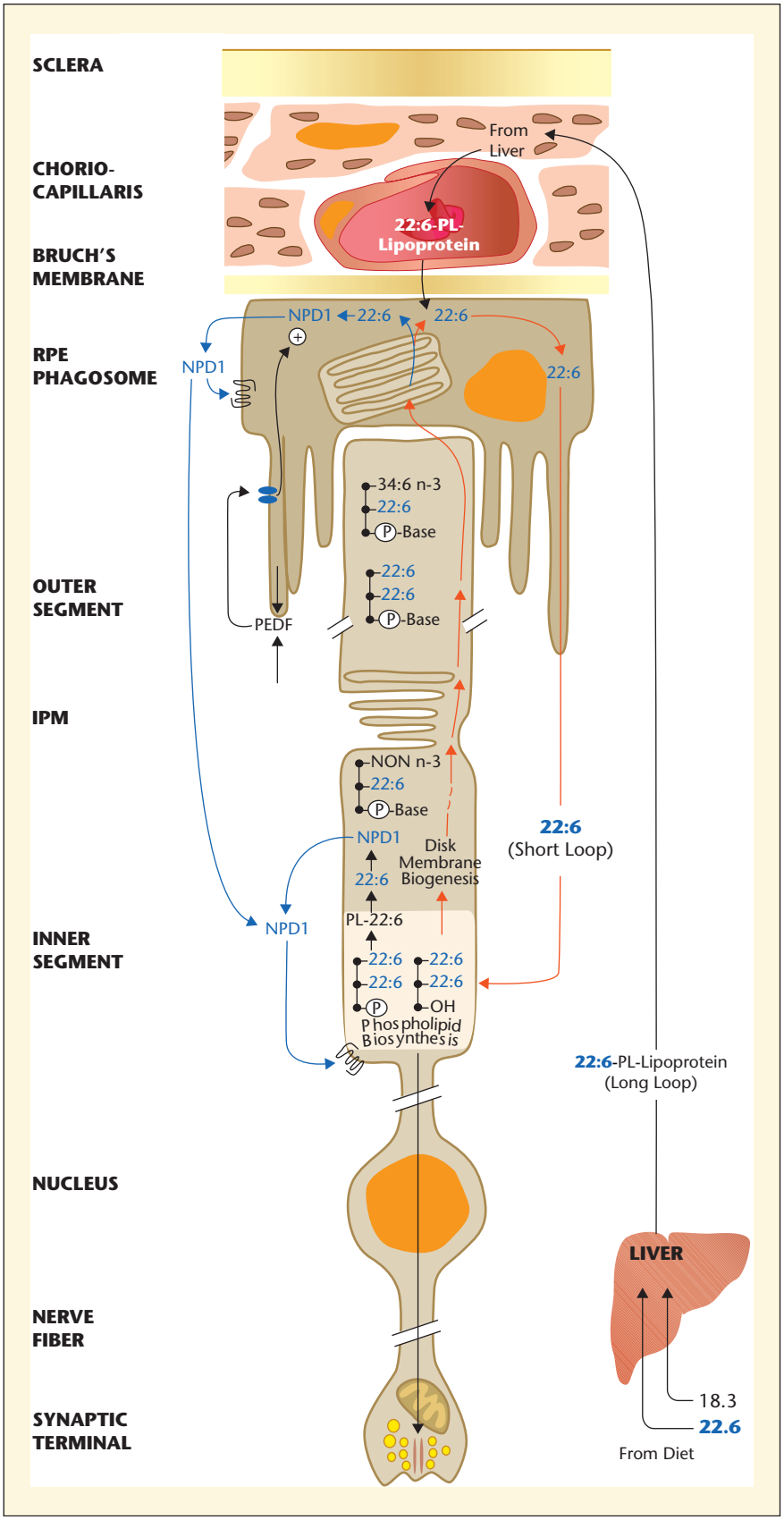

Figure 2. *Docosahexaenoic acid [DHA] (22:6) delivery to photoreceptors from the liver.*

leads to apoptosis and debris removal. This demonstrates the anti-inflammatory properties of DHA during cellular stress (Belayev *et al.*, 2011).

DHA treatment activates NPD1 synthesis in the salvageable penumbral region. NPD1 is a potent lipid mediator that evokes counteracting cell-protective, anti-inflammatory, pro-survival repair signaling, including the induction of anti-apoptotic proteins and inhibition of pro-apoptotic proteins (Belayev *et al.*, 2011). NPD1 triggers activation of signaling pathway/s that modulate/s pro-apoptotic signals, enhancing cell survival in the ischemic stroke-damaged penumbra (Bazan *et al.*, 2010).

Alzheimer's disease

Alzheimer's disease [AD] is a multifactorial, complex neurodegeneration characterized by progressive cognitive impairment. It involves a beta amyloid precursor protein [βAPP] processing dysfunction that leads to increased 42 amino acid Aβ42 peptide oligomer, which in turn impairs synaptic function and, progressively, synaptic circuits. Also, intracellular neurofibrillary tangles are formed, and neuroinflammation is enhanced, leading to apoptosis.

NPD1 is drastically reduced in hippocampal cornu ammonis 1 [CA1] areas of Alzheimer's patients. Thus, NPD1 recapitulates part of the Alzheimer's pathology in cellular models. Human neurons and astrocytes challenged by amyloid-β [Aβ] or by overexpressing APPsw (double Swedish mutation) show that NPD1 downregulates amyloidogenic processing of amyloid-β precursor protein, switches off pro-inflammatory gene expression (cyclooxygenase-2, tumor necrosis factor alpha, and B-94-TNF-α inducible pro-inflammatory element), and promotes neural cell survival. Moreover, anti-amyloidogenic processing by NPD1 targets α- and β-secretases and peroxisome proliferator-activated receptor gamma [PPARγ] receptor activation. The apoptotic cascade involves multiple checkpoints and signaling networks. NPD1 regulation targets upstream events of apoptosis as well as neuroinflammatory signaling, in turn promoting homeostatic regulation of cell integrity.

The oligomer Aβ42 accumulates as an aggregate and becomes a component

of senile plaques (Bertram *et al.*, 2010; Goedert *et al.*, 2010; Golde *et al.*, 2006; Haass, 2010; Haass and Selkoe, 2007; Haass and Mandelkow, 2010). Aβ42 peptides are generated from βAPP via tandem cleavage by β- and γ-secretases. Alternatively, a second pathway may be activated through α-secretase distintegrin and metalloproteinase 10 [ADAM10] that cleaves βAPP to yield soluble amyloid precursor protein alpha (sAPPα) (neurotrophic or nonamyloidogenic pathway).

The central nervous system [CNS] response to injury, and to the onset and progression of neurodegeneration, involves the release of free DHA and arachidonic acid [AA] along with the synthesis of stereospecific docosanoid derivatives. Human neural [HN] progenitor cells in primary culture during eight weeks display an eightfold-enhanced synthesis and release of Aβ40 and Aβ42 peptides that resembles Aβ deposition during brain aging and in AD. In HN cells, Aβ42 triggers damaging signals (accompanied by the early onset of apoptosis) and changes in gene expression that emulate neurodegenerative events characteristic of AD. DHA partially counteracts cognitive decline in the elderly (Fotuhi *et al.*, 2009). Moreover, omega-3 essential fatty acid-rich diets are associated with a trend in reduced risk for mild cognitive impairment [MCI] and with MCI conversion to AD, whereas DHA has been shown to be beneficial in transgenic AD models (Akbar *et al.*, 2005; Fotuhi *et al.*, 2009; Green *et al.*, 2007; Lim *et al.*, 2005a; Salem *et al.*, 2001). The DHA-derived NPD1 displays neuroprotective bioactivity in brain and retinal cells against various insults, including oxidative injury, ischemia-reperfusion, and inflammation (Antony *et al.*, 2010; Li *et al.*, 2001; Lim *et al.*, 2005b; Moore, 2001; Salem *et al.*, 2001). The AD brain (Lukiw *et al.*, 2005) exhibits reductions in DHA and NPD1. We further characterized the anti-inflammatory and anti-apoptotic activity of NPD1 in cocultures of HN cells stressed with the Aβ42 oligomer, and studied the NPD1-mediated modulation of α- and β-secretase activity that resulted in reduced shedding of Aβ42 (Zhao *et al.*, 2011).

The hippocampal CA1 region, the area of cortex most heavily damaged by AD, displays one-twentieth of the NPD1 of age-matched controls, even though the difference in free DHA was only two-fold lower; these changes were not present in other brain regions (Lukiw *et al.*, 2005). Potent protective bioactivity of NPD1 was shown in various models of neuroinflammatory pathology, including age-related macular degeneration [AMD] (Bazan, 2006, Bazan, 2007; Mukherjee *et al.*, 2004), stroke (Bazan, 2003; d'Abramo *et al.*, 2005; Lim *et al.*, 2005b), epilepsy (Bazan, 2007), AD (Bazan, 2009; DeMar *et al.*, 2006; Lukiw *et al.*, 2005), and oxidative stress (Lukiw *et al.*, 2005; Marcheselli *et al.*, 2003; Mukherjee *et al.*, 2004). These observations implicate NPD1 as an integral homeostatic modulator of long-term function and highlight the needs of DHA accretion in the CNS.

Neuroinflammatory signaling

Neuroinflammatory signaling associated with Aβ42 is an important contributor to the pathology of neurodegenerations (Amor *et al.*, 2010; Walsh and Selkoe, 2007). While glial cells provide some neuroprotective ''shielding'' when exposed to Aβ42, both neuronal and glial cells release cytokines that activate more microglia and astrocytes and reinforce pathogenic signaling. In HN cell models of Aβ42 toxicity, microarray and Western blot analysis revealed down-regulation of proinflammatory genes (cyclooxygenase-2, tumor necrosis factor alpha, and B94), suggesting that the anti-inflammatory bioactivity of the neuroprotective lipid mediator NPD1 partially targets this gene family (Lukiw *et al.*, 2005) and that these effects are persistent up to 12 hours after treatment by Aβ42 and NPD1 (Zhao *et al.*, 2011).

Studies show, however, that NPD1 had no effect on PS1 levels in primary human glial [HG] cells, but rather a significant increase in ADAM10 occurred in conjunction with a decrease in beta-site amyloid precursor protein-cleaving enzyme 1 (β-secretase-1) [BACE1]. NPD1 reduced Aβ42 levels released from HN cells, and examination of other βAPP fragments revealed that after NPD1 addition, levels of βAPP expression remained unchanged. Hence this indicates a shift by NPD1 in βAPP processing from the amyloidogenic to nonamyloidogenic pathway. NPD1 further down-regulated BACE1 and activated ADAM10, a putative α-secretase. ADAM10 siRNA knockdown and BACE1 overexpression-activity experiments confirmed that both are required in NPD1's regulation of βAPP. Therefore, NPD1 appears to function favorably in both of these competing βAPP-processing events.

In addition, PPARγ activation leads to anti-inflammatory, anti-amyloidogenic actions and anti-apoptotic bioactivity, as does NPD1. Some fatty acids are natural ligands for PPARγ, which has a predilection for binding polyunsaturated fatty acids (Camacho *et al.*, 2004; d'Abramo *et al.*, 2005; Henke, 2004). NPD1 is a PPARγ activator, as shown by using both human adipogenesis and cell-based-transactivation assay (Zhao *et al.*, 2011). NPD1 may activate PPARγ via direct binding or other interactive mechanisms (Avramovich *et al.*, 2002; Yamamoto *et al.*, 2005). Analysis of βAPP-derived fragments revealed that PPARγ does play a role in the NPD1-mediated suppression of Aβ production. Activation of PPARγ signaling is further confirmed by the observation that PPARγ activity decreases BACE1 levels, and a PPARγ antagonist overturns this decrease. Thus,

Retention mechanisms and synthesis of neuroprotectin D1 [NPD1]. DHA (22:6) or linolenic acid from the diet are processed in the liver. Hepatocytes incorporate 22:6 into 22:6-phospholipid (22:6-PL)-lipoproteins, which are then transported by the blood stream to the choriocapillaris. 22:6 crosses Bruch's membrane from the subretinal circulation and is taken up by the retinal pigment epithelial [RPE] cells lining the back of the retina to subsequently be sent to the underlying photoreceptors. This targeted delivery from the liver to the retina is referred to as the 22:6 long loop. Then 22:6 passes through the interphotoreceptor matrix [IPM] and into the photoreceptor inner segment, where it is incorporated into phospholipids for cell membrane, organelles, and disk membrane biogenesis. As new 22: 6-rich disks are synthesized at the base of the photoreceptor outer segment, older disks move apically toward the RPE cells. Photoreceptor tips are phagocytized by the RPE cells each day, removing the oldest disks. The resulting phagosomes are degraded within the RPE cells, and 22:6 is recycled back to photoreceptor inner segments for new disk membrane biogenesis. This local recycling is referred to as the 22:6 short loop. Upon inductive signaling, such as pigment-epithelium derived factor [PEDF], 22:6 is cleaved from a phospholipid pool for the synthesis of NPD1.

the antiamyloidogenic bioactivity of NPD1 is associated with activation of the PPARγ and the subsequent BACE1 downregulation. The decreases in BACE1 may be the cause for Aβ reduction (Sastre *et al.*, 2006; Zhao *et al.*, 2011).

There is evidence that DHA initiates a cascade of mediators, where NPD1 is the first identified. NPD1 is endowed with strong anti-inflammatory, antiamyloidogenic, and anti-apoptotic bioactivities. These results suggest that the anti-amyloidogenic effects of NPD1 are mediated in part through activation of the PPARγ receptor, whereas NPD1 stimulation of nonamyloidogenic pathways is PPARγ independent (Zhao *et al.*, 2011). NPD1 stimulation of ADAM10, coupled to suppression of BACE1-mediated Aβ42 secretion, clearly warrants further study since these dual secretase-mediated pathways may provide effective combinatorial or multi-target approaches in the clinical management of the neuroinflammatory process.

Conclusion

The further unraveling of the DHA signalolipidome will contribute to harnessing the endogenous homeostatic signaling that counter-regulates neuroinflammation, and thus sustain cell integrity by downregulating apoptotic cell death.

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