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Interrelationship Between the 5-Lipoxygenase Pathway and Microbial Dysbiosis in the Progression of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is an age-related neurodegenerative disorder involving neurofibrillary tangles and amyloid plaques. The tau phosphorylation responsible for neurofibrillary tangles and amyloid deposition which causes plaques are both accelerated through the activity of 5-lipoxygenase (5-LO). In addition to these pathological pathways, 5-LO has also been linked to the neuro-inflammation associated with disease progression as well as to dysbiosis in the gut. Interestingly, gut dysbiosis itself has been correlated to AD development. Not only do gut metabolites have direct effects on the brain, but pro-inflammatory mediators such as LPS, BMAA and bacterial amyloids produced in the gut due to dysbiosis reach the brain causing increased neuro-inflammation. While microbial dysbiosis and 5-LO exert detrimental effects in the brain, the cause/effect relationship between these factors remain unknown. These issues may be addressed using mouse models of AD in the context of different knockout mice in the 5-LO pathway in specific pathogen-free, germ-free as well as gnotobiotic conditions.

Alzheimer's disease (AD) is the most common form of dementia found in the elderly and associated with the loss of neurons mostly found in the hippocampus and cerebral cortex (1). Two pathological features found in AD are misfolded tau protein aggregates and amyloid beta (Aβ) plaque formation. Tauopathies are a group of neurodegenerative diseases characterized by abnormal metabolism and misfolding of tau proteins leading to the formation of neurofibrillary tangles. Hyperphosphorylation of tau proteins causes tau to dissociate from microtubules and form aggregates (2). Diseases in this group include Pick's disease, progressive supranuclear palsy, corticobasal degeneration, chronic traumatic encephalopathy and AD (3, 4). Aβ plaque formation results from the preferential cleavage of APP protein by the β-secretase followed by γ-secretase cleavage which is presumed to initiate the deposition of amyloid seen in AD (5). Number of factors involved in the accumulation of Aβ include an imbalance between β and α-secretase activity, dysregulated production and clearance and decreased degradation by peptidases (reviewed in (6). As majority of cases are not directly linked to any gene mutations, other environmental factors

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individuals encounter over a lifetime are likely responsible for determining progression towards AD. Here, we focus our attention on the role of 5-lipoxygenase (5-LO) pathway and the microbiota as potential mediators of such environmental factors in promoting AD. We propose that age and diet related microbial dysbiosis promotes 5-LO mediated systemic as well as neuroinflammation that perpetuates the dysbiosis and a feed-forward loop during AD development (Figure 1). Numerous early studies have linked the inducible Cyclooxygenase pathway in AD development in human subjects (7) as well as in AD experimental models (8–11). Although COX-2-derived mediators may be important in AD, limited recent studies on COX-2 led us to focus this review on the pathways induced through 5-LO.

5-Lipoxygenase Pathway in AD Pathogenesis

An important aspect of neurodegenerative disorders is the involvement of neuro-inflammation (12). Studies have demonstrated activation of microglia and astrocytes surrounding senile plaques and inflammatory mediators are elevated in AD brains compared to healthy controls (13). A key enzyme involved in the production of eicosanoid lipid mediators, 5-lipoxygenase (5-LO), occupies a pivotal role in the inflammation associated with diseases such as arthritis (14), atherosclerosis (15) and allergy (16). Products of the 5-LO pathway have been demonstrated to alter the progression of AD in multiple studies. Early studies on aged mice given the 5-LO inhibitor, AKBA, showed increased cognitive function setting the stage for examining the other 5-LO inhibitors in neurodegeneration-prone mouse models (17). Reduced 5-LO product, LXA_4, has been associated with AD when compared to healthy controls (18). The 5-LO enzyme itself has been noted as elevated in post-mortem AD brain sections, other neurodegenerative conditions and in small animal models (19–24). Particularly elevated expression of 5-LO has been noted in the hippocampus (25) which further increased with aging (19, 21, 22). Promoter polymorphisms in the 5-LO gene have been associated with early and late onset of AD in two independent small studies (26, 27). The condition of Hyperhomocysteinemia (HHCY) has been noted as a risk factor for AD. The effects of HHCY on AD-like disease have been demonstrated to depend on the 5-LO pathway (28) where accelerated memory decline, amyloidosis, tau pathology, synaptic function and neuro-inflammation are found to require 5-LO activity (29, 30). Increases in amyloid-beta and tau pathology are seen in response to 5-LO activation through γ-secretase and CDK5 pathways (31, 32). Neuronal cells treated with LTB_4, a key product of 5-LO, resulted in increased Aβ formation via up-regulation of γ-secretase proteins positioning LTB_4 as a key component in 5-LO modulation of the amyloidotic phenotype (33).

Mouse models of AD have been useful in delineating the linkage of 5-LO to disease pathology. These models either exclusively express either tau pathology or amyloidosis or both. The mouse models of AD take advantage of the genes associated with familial AD in humans expressed in mice. Two models which exhibit tau pathology are the P301S and htau. The P301S mice express the P301S mutant form of human tau protein under the direction of the mouse prion protein promoter (Jax Stock No. 008169). Tau phosphorylation, synaptic integrity, memory and learning were all improved when P301S mice were treated with Zileuton, a 5-LO inhibitor (34). Deletion of 5-LO in P301S mice was found to increase memory, reduce tau phosphorylation and decrease neuro-inflammation (35). Viral over-

expression of 5-LO led to increased tau phosphorylation, motor and behavioral deficits (36). The htau mice express a tau transgene from human driven by the tau promoter. Treatment of htau mice with Zileuton led to significant memory improvement and a reduction in tau pathology (37). Viral overexpression of 5-LO in brain led to higher phosphorylation of tau and higher deficits in memory and learning ability (38).

Two mouse models that focus on the amyloid deposition phenotype are Tg2576 and APP/PS1. The Tg2576 mice express a mutant form of APP, APPK670/671L (Charles River). Zileuton treatment of Tg2576 mice reduced Aβ formation and deposition and was found to inhibit the four components of the γ-secretase complex (39). Interestingly, Zileuton treatment of Tg2576 mice was found to decrease tau phosphorylation in this model (32), while viral overexpression of 5-LO in neurons significantly increased phosphorylation of tau at key loci (40) and increased memory deficits (41). 5-LO deficiency in the Tg2576 model was found to reduce Aβ deposition by 64 to 80% (20). 5-lipoxygenase activating protein (FLAP) which is required for 5-LO activity was linked to AD disease progression in the Tg2576 model where both inhibition of FLAP (42) and knockouts of FLAP (31) were found to decrease amyloidosis. The APP/PS1 mice are double transgenic for a chimeric mouse/human APP (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1-ed9) which are expressed in CNS neurons (MMRRC Stock No. 34832). This model was used to test the effects of CNB-001, a pyrazole derivative of curcumin that inhibits both 5-LO and 15-LO. Improvements in behavioral testing and soluble Aβ were seen when APP/PS1 mice were treated with CNB-001 (43).

The 3xTg model utilizes mice with the Psen1 mutation as well as the APPSwe and tauP301L transgenes (MMRRC Stock No. 34830-JAX). Treatment of 3xTg mice with Zileuton led to a reduction in Aβ levels and phosphorylated tau (44). Treatment of aged 3xTg mice where disease was already established with Zileuton was able to rescue classical AD hallmarks such as amyloidosis and tau pathology as well as neuro-inflammation (45). These results are similar to those seen when 3xTg mice were treated with flavocoxid, which is a mixture of baicalin and catechin that inhibits cyclooxygenase enzymes, cytoplasmic phospholipase A_2 and 5-LO (46). 5-LO knockouts on the 3xTg background have less Aβ and tau pathology confirming the results seen with 5-LO inhibition (47). Even stress-induced acceleration of the AD phenotype was absent in 3xTg mice lacking 5-LO (48). Viral overexpression, in comparison, of 5-LO in neurons in 3xTg mice led to increased memory deficits, plaques and tangle pathology (49). FLAP deficiency or pharmacological inhibition in 3xTg improved memory and decreased Aβ deposition and tau phosphorylation (50).

A few specific products of 5-LO have been directly linked to aspects of AD. LTB_4 was demonstrated to increase Aβ formation due to increased steady state levels of 3 of the 4 γ-secretase proteins in N2aAPPswe neuronal cells (33). LTD_4-treated neuronal cells were stimulated to produce more Aβ through enhancement of β and γ-secretase activity (51). These two mediators are inflammatory in nature, but 5-LO is also involved in the production of anti-inflammatory mediators. LXA_4 and RvE1 are two 5-LO products which are recognized as important mediators of resolution of inflammation. LXA_4 was shown to increase cognitive levels, decrease Aβ levels and tau phosphorylation in the 3xTg mouse model (52). When 5xFAD mice were treated with LXA_4 or RvE1, the mice

showed improvements in inflammatory cytokines and chemokines, and decreased levels of Aβ proteins. Both given together decreased AD pathology (53). Neuro-inflammation, neurogenesis, gliosis and sclerosis, and the blood-brain barrier (BBB) are new areas of interest for targeting treatment of AD (54). Neuronal cell death contributes to AD and cysteinyl leukotrienes have been implicated in this pathology (55, 56). Of note, the Aβ and tau protein levels appear unchanged but rather their activity is modified by the activation/inhibition of the 5-LO pathway. It is the phosphorylation of tau and the γ-secretase proteins that consistently become altered when the 5-LO pathway is modified. A summary of studies on the 5-LO pathway in AD mouse models is presented in table-1 and the potential cellular and molecular targets of the 5-LO pathway in AD are outlined in Figure-2.

Role of Microbiota in AD pathogenesis

Bacterial infections and fecal microbiota have both been demonstrated to contribute to AD development. The microbiota does tend to change as individuals near old age leading to the theory of “age-related dysbiosis” which postulates that as the immune system ages and becomes less robust, detrimental changes occur in the microbiota. With aging, increased proteobacteria, decreased probiotics and neuroprotective molecules such as short chain fatty acids (SCFAs) are seen in the gut (57). SCFAs have been shown to play important roles within the brain including cognition, emotion, and psychological function (58). SCFAs are a major product of the gut microbiota with 500-600 mmol being produced daily depending of the amount of consumed fiber in the diet (59). Many of the pathological changes found in AD such as inflammation, immune abnormalities and cognitive impairment have been associated with microbial infections (60–62). LPS, which is released in large amounts by the human microbiota, may also play a major role in the pro-inflammatory cytokines associated with the pathological features of AD (63). In fact, LPS has been reported to be 3 times higher in AD plasma than healthy controls (64). The release of LPS into the periphery is not the only impact microbiota has on brain. In fact, removing the microbiota completely in the germ free (GF) context is deleterious to the brain function. Specific pathogen free (SPF) mice perform better in spatial memory and working memory tasks than their GF counterparts (65) and behavior, brain physiology and neural biochemical pathways are altered (66). In fact, the importance of the fecal microbiota in the gut-brain axis has recently been demonstrated where the term “brain-gut-microbiota axis” has been coined to define these components in neural, immune, endocrine, and metabolic signaling (67, 68).

This sets up a paradigm where some bacteria must have negative effects on the brain while other bacteria and their products are beneficial in cognitive function. Therefore, studies deciphering good vs. bad microbial content are vital to the understanding of how AD develops. This is especially important when considering that the microbiota itself appears to participate in early brain development and neurogenesis in adults (69, 70). Members of the *Lactobacillus* genus are capable of metabolizing glutamate to produce gamma-amino butyric acid (GABA), which is a major inhibitory neurotransmitter in the central nervous system (CNS). GF mice display a decrease in brain-derived neurotrophic factor (BDNF) which is associated with cognitive decline in these mice (reviewed in (60). One area of importance when considering the relationship of the gut microbiota and the intestinal epithelium is the formation of an appropriate barrier to microbial infiltration. Tight junction proteins maintain

part of the barrier to microbial invasion through the epithelium. *Lactobacillus plantarum*, *Escherichia coli Nissle* and *Bifidobacterium infantis* enhance this barrier by increasing the expression of tight junction proteins (71). Enteropathogenic *E. coli*, enterohemorrhagic *E. coli*, *Salmonella typhimurium, Helicobacter pylori*, *Shigella flexneri* and others disrupt tight junctions (72). Therefore, the presence of these microbes may give key hints about the health of the fecal microbiota. Though some microbes have shown positive results in repairing dysbiosis, communities containing several microbes are likely responsible for the establishment of a healthy fecal microbiota.

Several studies have identified microbiota changes in AD patients and mouse models of AD. Studies in humans are complicated since sex, race, age and diet all significantly impact composition of gut microbiota (73, 74). Some differences were noted in 43 AD patients when compared to cognitively normal controls demonstrating the feasibility of teasing out key players in AD initiation and progression, but larger groups would be required to make causative connections (75). The presence of *Helicobacter pylori* has been linked to AD development which matches data seen in PD (76) and the APP/PS1 model (77). AD samples exhibit lower richness and diversity as measured by Chao1, Faiths and Shannon index (78). Subsequent studies have found similar perturbations in microbiota compared to healthy controls (79, 80). Many connections have been made between individual gut microbes and important drivers of AD disease such as inflammatory cytokines and *P. gingivalis* (81), SCFA production and *Acetobacter* and *Lactobacillus* (82) and several other microbes have been linked to neuroinflammation (75). Not only can some bacteria produce neuroprotective compounds such as SCFAs, but some can make outright neurotoxins such as b-N-methylamino-L-alanine (BMAA) which is made by Cyanobacteria sometimes found in gut microbiota and is potentially a contributor to AD (83, 84). A number of microbes have been identified in AD patients or animal models which have the potential to form amyloid-like proteins (85) and their contribution to Aβ accumulation is a risk factor for AD development (86). Interestingly, it is postulated that Aβ is an anti-microbial defense mounted against certain bacteria to rid the body of the invaders (87, 88).

Models of AD allow for the comparison of gut microbiota in a more controlled system when compared to humans. In APP/PS1 mice, there is a noticeable shift in microbiota when compared to non-transgenic mice (77, 89–91). Increases in Rikenellaceae and decreases in *Allobacillum* and *Akkermansia* were noted (89). Another study found the genus *Sutterella* and Erysipelotrichaceae more abundant in APP/PS1 at 6 and 24 months, respectively (90). GF APP/PS1 mice demonstrate reduced Aβ pathology. Changes in composition and diversity were associated with a decrease in SCFAs (91). FMT transfer from WT donors into APP/PS1 mice was able to reverse dysbiosis and increase SCFAs as well as reduce Aβ and tau phosphorylation (92). When FMT was performed with feces from either non-transgenic or APP/PS1 donors and APP-transplanted recipients developed more cerebral Aβ pathology than wild-type transplanted recipients demonstrating the presence of both disease protective (WT) and disease accelerating (APP/PS1) constituents (89). Some sex-related differences in disease promoting microbiota have been observed utilizing this model as well (93). In addition to the use of GF mice in this model, the addition of antibiotics to APP/PS1 mice alters the amyloid pathology whether given postnatally (94) or continuously (95). Prebiotic treatment with *Morinda officinalis* oligosaccharides in APP/PS1 helped maintain

diversity while decreasing Aβ (96) and probiotic treatment with a novel formulation of lactic acid bacteria and bifidobacteria in 3xTg mice has led to improvements in cytokines, brain damage and Aβ aggregates (97). In the ADLP^{APT} model, transfer of WT fecal microbiota slowed the deposition of Aβ and neurofibrillary tangles and improved cognitive functions (98). These data together demonstrate the presence of negative and positive regulators of AD pathology, while underscoring the need for a consensus profile to be defined in animal models which can be applied to humans suffering with AD or, better yet, help us understand those microbes which predispose individuals to develop AD. A summary of studies on microbiota contributions to the AD pathology in humans and mouse models is listed in table 2.

Interrelationship of the 5-LO pathway to Microbial Dysbiosis during AD Progression

As the 5-LO pathway and gut microbiota both play important roles in the development of AD, is there any evidence for the role of 5-LO or its products in making changes in microbiota or *vice versa*? Patients with IBD have a marked increase in LTB_4 production (99) and cysteinyl leukotriene production (100). When rodent models of IBD are treated with 5-LO antagonists, colitis resolves at a faster pace (101, 102). Administration of intracolonic LTB_4 exacerbated experimental colitis (103). These observations are important since gut dysbiosis plays a crucial role in the pathogenesis of ulcerative colitis and other IBDs (104–107). Increased severity of colitis found in BLT1$^{-/-}$ (receptor for LTB_4) mice in a DSS colitis mouse model (108) is associated with a shift in Bacteriodetes vs. Firmicutes content, increased Verrucomicrobia and *Akkermansia mucinophila* in BLT1. Thus, reciprocal regulation of microbiota and the inflammatory pathways appears common under diverse conditions and may be applicable to AD pathogenesis.

The anti-inflammatory or resolution phase mediators derived from the action of 5-LO have also been demonstrated to impact the microbiota in both the intestine and oral cavity. LXA_4 dampens intestinal inflammation (109) and LXA_4 analogues are anti-inflammatory in models of colitis (110). Preventative or therapeutic use of ZK-192, an analogue of aspirin-triggered lipoxin, markedly reduced the severity of colitis in rodents (111). Resolvin E1 (RvE1) treatment of periodontitis was able to reduce damage, reduce osteoclast activity and decrease markers of disease in an animal model (112). Periodontal microbiota reach dysbiosis during periodontitis that was partially restored by treatment with RvE1 where altered levels of *Rothia*, *Granulicatella* and *Enterococcus* were returned to more basal state (113).

As outlined, the microbiota and inflammation are intimately linked and shifts in the microbiota due to diet change (114), antibiotic exposure (115), aging (116) or other factors could trigger changes in gut inflammation. Gut inflammation in turn can modify the microbiota setting up a positive feedforward loop resulting in dysbiosis and chronic inflammation (Figure 1).Given that inhibitors of 5-LO and mice deficient in 5-LO are uniformly protected from AD pathology, the pro-inflammatory mediators resulting from 5-LO pathways are the most important group to consider here. A direct comparison between

5-LO and BLT1 deficient animals or inhibitors in models of AD might help to discern whether it is LTB_4 or another 5-LO derived product which results in the pathologies seen in AD. Performing these experiments in GF and well defined gnotobiotic mice would remove the compounding factor of microbiota in AD pathology. The comparison of these SPF, GF and gnotobiotic mice results would potentially untangle the contribution of inflammation and gut-derived products on the development of these key aspects of neurodegeneration.

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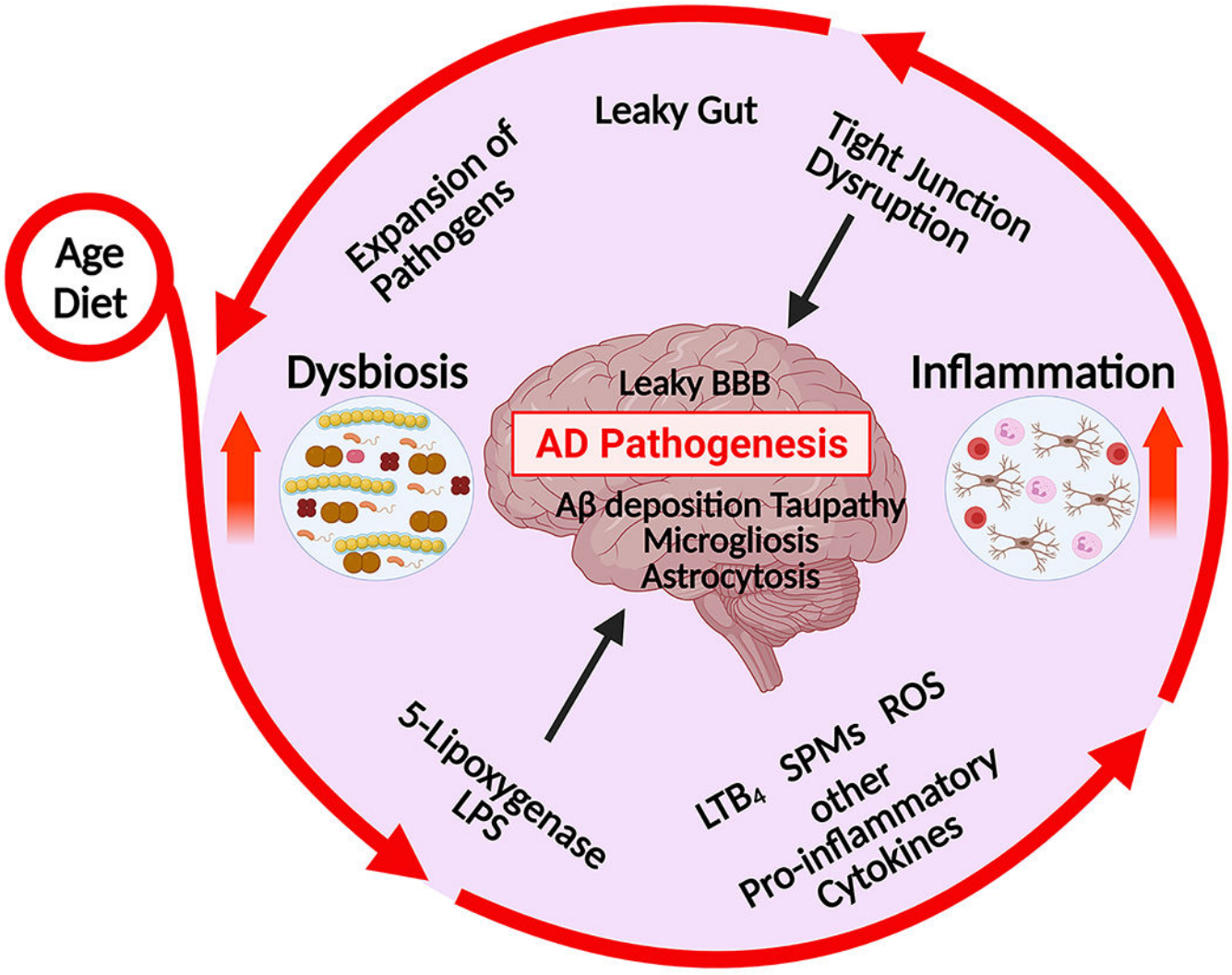

Figure 1: Potential links between microbial dysbiosis and 5-LO pathway mediated inflammation in AD pathology:

Changes in diet and aging leads to dysbiosis within the gut. Increases in LPS, 5-lipoxygenase and cyclooxygenase-2 lead to increased production of inflammatory molecules such as LTB_4, ROS and other pro-inflammatory cytokines, while decreases in anti-inflammatory SPMs are correlated with dysbiosis. These same pathways are directly responsible for Aβ deposition, tauopathy, microgliosis and astrocytosis associated with AD pathology. Increased inflammatory conditions found locally in the gut causes leaky gut and the expansion of pathogens which exacerbates dysbiosis refueling a feed-forward loop of dysbiosis and inflammation. These increased inflammatory conditions have detrimental effects at distal sites including the brain, where tight junction disruption occurs resulting in leaky BBB which contributes to neuroinflammation associated with AD.

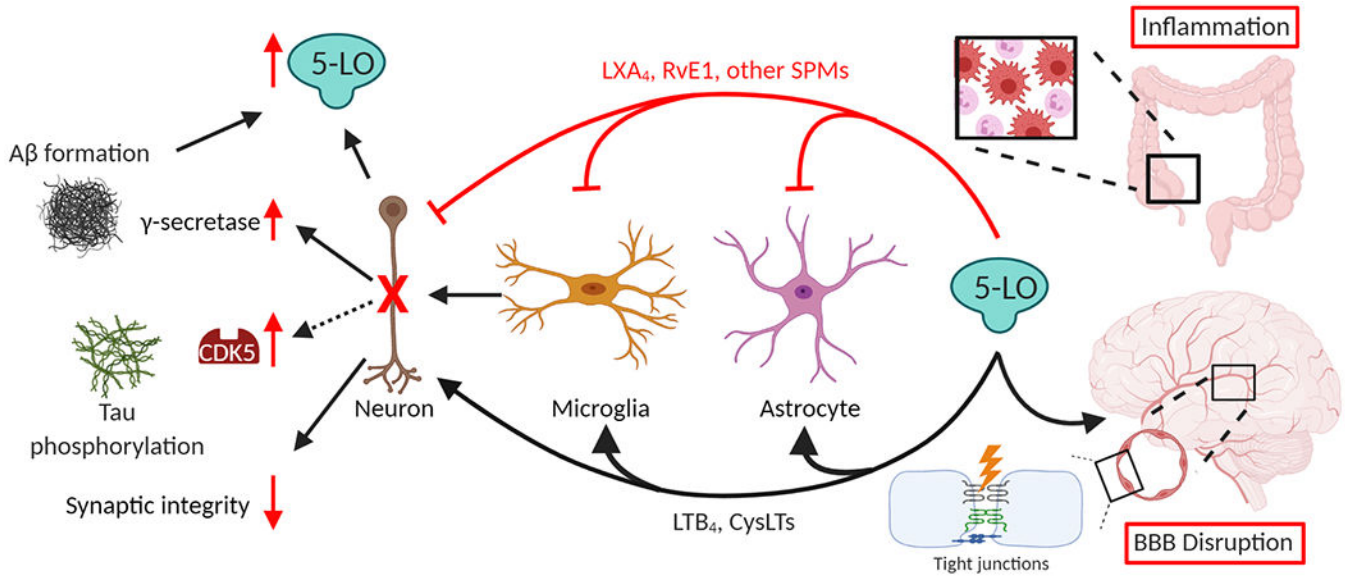

Figure 2: Cellular and molecular targets of 5-lipoxygenase activity in brain.

Dysbiosis and activated immune cells generate increased levels of 5-LO activity locally and in the periphery. Inflammatory products of the 5-LO pathway, LTB_4 and CysLTs, weaken tight junctions in brain vasculature disrupting the Blood Brain Barrier allowing for inflammatory mediators and cells to more freely move into brain. LTB_4 and CysLTs directly activate astrocytes, microglia and neurons within the brain. Activated microglia influence neurons to up-regulate 5-LO increasing overall levels of 5-LO in the brain. Continued activation leads to astrocytosis, microgliosis and neuronal cell death. LTB_4 and CysLTs are both involved in the increased γ-secretase activity found within neurons leading to Aβ accumulation and aggregation associated with amyloid plaques found in AD. 5-LO activity also increases CDK5 function resulting in tau phosphorylation leading to neurofibrillary tangles. These pathological phenotypes as well as other neuroinflammatory processes initiated by 5-LO lead to detrimental changes in synaptic integrity. Specialized pro-resolving mediators such as LXA_4 and RvE1, which are 5-LO-derived anti-inflammatory mediators, have the opposite effect on astrocytes, microglia and neurons where they can return these cells to a more basal non-activated state and protect them from damage and death. Moreover, some resident cells of the brain, such as astrocytes, produce SPMs like the lipoxins promoting neuroprotection following injury.

Table-1

Summary of Studies on the 5-LO pathway in AD mouse models

Model	Alteration	Main Findings	Reference
Tg2576	Zileuton	↓Tau phosphorylation, CDK5	(32)
	Zileuton	↓ Aβ deposition, γ-secretase	(39)
	5-LO knockout	↓Brain deposition of Aβ, ↓ γ-secretase	(20)
	AAV over-expressed 5-LO	↓ synaptic integrity ↑ phosphorylated tau, CDK5	(40)
	AAV over-expressed 5-LO	↓ memory ↑ Aβ deposition	(41)
	MK-591	↓ tau phosphorylation ↑ synaptic integrity, GSK-3β activity	(42)
	MK-591	↓ Aβ deposition, γ-secretase	(31)
	Aspirin-triggered LXA_4	↓ Aβ deposits ↑ cognition	(117)
h-tau	Diet deficient in B6, B12 and folate	↓ learning ↑ tau phosphorylation and pathology, 5-LO and LTB_4 levels	(30)
	Zileuton	↓ tau pathology, CDK5 ↑memory, synaptic integrity	(37)
	AAV over-expressed 5-LO	↓ memory and learning ↑ neuroinflammation, synaptic pathology, tau phosphorylation, CDK5	(38)
P301S	Zileuton	↓Tau phosphorylation, CDK5 ↑ memory, learning, synaptic integrity	(34)
	5-LO knockout	↓Tau phosphorylation, neuroinflammation, synaptic pathology ↑ memory	(35)
	AAV over-expressed 5-LO	↓ behavioral and motor functioning ↑ synaptic pathology, tau phosphorylation, CDK5	(36)
3xTg	Zileuton	↓Hcy, Aβ, tau phosphorylation, pathology ↑memory, learning	(29)
	Zileuton	↓ Aβ deposition, γ-secretase, phosphorylated tau, CDK5 ↑ memory, synaptic integrity	(44)
	Zileuton	↓ Aβ deposits, tau phosphorylation, γ-secretase, CDK5 ↑ memory	(45)
	Flavocoxid	↓ tau phosphorylation, Aβ plaques, neuronal loss ↑ memory and learning	(46)
	5-LO knockout/Zileuton	↓ synaptic dysfunction, Aβ, tau pathology ↑ memory	(47)
	5-LO knockout	↓ tau phosphorylation, GSK-3β ↑ memory	(48)
	AAV over-expressed 5-LO	↓ memory ↑ Aβ, tau pathology, γ-secretase, CDK5	(49)
	FLAP knockout/MK-591	↓ synaptic dysfunction, Aβ, tau pathology, γ-secretase, CDK5 ↑ cognition, memory	(50)
	Aspirin-triggered LXA_4	↓ Aβ, phosphorylated tau, GSK-3β ↑ memory	(52)
APP/PS1	CNB-001	↓ intracellular Aβ ↑ memory	(43)
5xFAD	RvE1 and LXA_4	↓ Aβ pathology, neuroinflammation	(53)

Table-2:

Contribution of Microbial dysbiosis to AD pathology.

Organism	Alterations	Main Findings	Reference
Human	AD patients vs. normal controls	*Bacteroides*, *Actinobacteria*, *Ruminococcus*, *Lachnospiraceae*, *Selenomonadales* altered	(75)
	AD patients vs. normal controls	↓ diversity, ↓ Firmicutes, *Bifidobacterium, SMB53, Dialister, Clostridium, Turicibacter, Adlercreutzia, cc115* ↑ Bacteroidetes, *Blautia, Bacteroides, Alistipes, Phascolarctobacterium, Bilophila, Gemella*	(78)
	AD patients vs. MCI patients vs. normal controls	↓ phylogenetic diversity, *Acinetobacter, Dorea, Blautia, Akkermansia, Lactobacillus, Bifidobacterium, Streptococcus* ↑ *Bacteroides, Prevotella, Alistipes, Parabacteroides, Sutterella, Succinivibrio, Paraprevotella, Haemophilus, Alloprevotella, Butyrivimonas, Barnesiella*	(79)
	AD patients vs. MCI patients vs. normal controls	↓ microbial diversity, Firmicutes ↑ Proteobacteria, *Gammaproteobacteria, Enterobacteriales,* Enterobacteriaceae	(80)
Mouse	APP/PS1	↓ diversity, ↑ *Odoribacter*, *Helicobacter*, ↓*Prevotella*	(77)
	APP/PS1	↑ a-diversity at 8 months, Rikenellaceae, *S24-7*↓ *Akkermansia, Allobaculum*	(89)
	APP/PS1	↑ species richness, Proteobacteria, Erysipelotrichaceae, *Sutterella* ↓ Rikenellaceae	(90)
	APP/PS1	↓ SCFA production from perturbed microbiota	(91)
	APP/PS1	FMT ↓ Verrucomicrobia, Proteobacteria, *Akkermansia, Desulfovibrio, Staphylococcus* ↑ SCFA production, *Faecalibaculum, Enterococcus, Erysipelatoclostridium*	(92)
	APP/PS1	↑ *Prevotella, Bacteroides, Odoribacter, Paraprevotella, Ruminococcus*	(93)
	APP/PS1	Antibiotic treatment ↓ in Lachnospiraceae and *S24-7* associated with ↓ pathology	(94)
	APP/PS1	Oligosaccharides ↑ diversity and stability associated with ↓ Proteobacteria ↑ Acidobacteria, Euryarchaeota, TM7, Verrucomicrobia	(96)
	3xTg	Probiotic treatment ↑ SCFAs	(97)