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Review

Innate Immune and Fungal Model of Alzheimer's Disease

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Abstract. Various fungi and bacteria can colonize in the brain and produce physical alterations seen in Alzheimer's disease (AD). Environmental and genetic factors affect the occurrence of fungal colonization, and how fungi can grow, enter the brain, and interact with the innate immune system. The essence of AD development is the defeat of the innate immune system, whether through vulnerable patient health status or treatment that suppresses inflammation by suppressing the innate immune system. External and mechanical factors that lead to inflammation are a door for pathogenic opportunity. Current research associates the presence of fungi in the etiology of AD and is shown in cerebral tissue at autopsy. From the time of the discovery of AD, much speculation exists for an infective cause. Identifying any AD disease organism is obscured by processes that can take place over years. Amyloid protein deposits are generally considered to be evidence of an intrinsic response to stress or imbalance, but instead amyloid may be evidence of the innate immune response which exists to destroy fungal colonization through structural interference and cytotoxicity. Fungi can remain ensconced for a long time in niches or inside cells, and it is the harboring of fungi that leads to repeated reinfection and slow wider colonization that eventually leads to a grave outcome. Although many fungi and bacteria are associated with AD affected tissues, discussion here focuses on *Candida albicans* as the archetype of human fungal pathology because of its wide proliferation as a commensal fungus, extensive published research, numerous fungal morphologies, and majority proliferation in AD tissues.

Keywords: Alzheimer's disease, APOE, *Candida albicans*, fungi, innate immune system, LCAT

INTRODUCTION

Alois Alzheimer described the first case of Alzheimer's disease (AD) in 1906 in the eponymous female Auguste D. [1, 2], and found abnormal deposits of amyloid protein plaques (amyloid beta, or Aβ) and fibrous protein tangles (neurofibrillary tau) which were considered the cause of neural deterioration. A 1939 review speculated on various causes of AD [3], including constitution, aging related atrophy, and an association with inflammatory conditions, noting the development of plaques near the site of previous trauma mentioning "intercurrent infection", hinting that frequent infection is a component of AD. Dementia can directly result from diffuse axonal injury, identified as a sequela of traumatic brain injury in the 1950s [4], and AD is a known sequela of brain injury [5]. Diffuse axonal injury can manifest punctate hyaline masses known as corpora amylacea, a polyglucosan disease [6]. Corpora amylacea develop independently in the brain tissue of AD patients [7–9], and because corpora amylacea stain antifungal antibodies, fungi are implicated [10]. A 1955 study of identical twins with one of a pair that develops AD emerging after development of rosacea, suggests an infectious etiology [11]. The association of AD

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with infectious processes is now a current topic [12]. There are genetic associations of frequency and age of onset of AD, which is associated with physical, gradual damage to the brain leading to memory loss and slower thought processes, and ultimately death [13]. AD incidence increases exponentially with age with the highest rates in North America and Europe and increases most for patients in their 60s and 70s [14].

The fungal model refers to the 2014 Carrasco et al. fungal etiology based on AD autopsies which exhibit fungi only in affected neural tissue [10, 15–18] and evidence that fungal infection is etiological for AD was updated by Carrasco et al. [19]. Fungal genera found in AD associated tissues identified by modern sequencing methods include yeasts, filamentous fungi, and saprophytes appropriate to infections and allergic reactions in humans [20]: Alternaria, Botrytis, Candida, Cladosporium, Fusarium, and Malassezia. Candida (the most widespread) antibodies tested positive in 89.6% of AD patient serum compared to 8.8% for controls [17]. Recently many bacteria have been found in AD brain tissue [21, 22], of which some are associated with mucosal *C. albicans* biofilms: Burkholderia and Pseudomonas [23]; Firmicutes (dentures [24]); *Staphylococcus epidermidis* [25]; *Stenotrophomonas maltophilia* [26].

Aβ hypothesis for Alzheimer's disease

Amyloid peptide accumulation is associated with a number of diseases, affecting various organs. George Glenner postulated that Aβ, with $A\beta_{42}$ associated with AD, is a cause of AD [27]. AD causation is controversial, and Selkoe and Hardy [28] offer the hypothesis that genetic mutations near the Aβ section of amyloid-β protein precursor (AβPP) are associated with rapid onset of AD and increasing Aβ deposits in memory and cognitive centers. Conversely, a mutation that reduces AβPP is viewed as protective of neural decline [29].

The pathological changes in AD are associated with neurofibrillary tangles, neuropil threads, and hyperphosphorylated tau [30]. The developing view is that the histological evidence of Aβ and hyperphosphorylated tau deposits may not represent a cause but may be the effect of developing AD [31]. There is a poor relationship between the manifest progression of AD which do not correspond to the histological evidence of lesion formation of amyloid plaques [32].

Amyloid deposition is associated with fungal disease and can begin with the deposition of serum amyloid P (SAP) onto *C. albicans* cells [33, 34], or other Candida species [35]. Peptide binding characteristic of *C. albicans* produces adhesive affinity colonization [36, 37] and is characteristic of all invasive morphologies of *C. albicans*: yeasts, hyphae, and pseudohyphae [33]. Surface amyloids expressed by *C. albicans* during infection induce binding by SAP which blocks the inflammatory response and adhere to SAP with fungal colony expansion stretching human cell surface proteins which copiously extrude amyloids [33]. No evidence exists that the presence of SAP increases the risk and development of AD, but as AD develops, SAP levels drop in the cerebrospinal fluid (CSF), perhaps because SAP adherence to fungal cells removes SAP from the CSF and plasma [38].

That the upregulation of AβPP following traumatic brain injury is protective indicates that the processes associated with Aβ are not entirely pathogenic [32]. The pathological deposition of Aβ after administration of sevoflurane anesthetic [39] offers a window into pathogenesis. Sevoflurane is associated with intestinal reperfusion injury and loss of intestinal mucosal barrier function [40]. Loss of intestinal barrier function leads to the opportunity for persorption of bacteria and fungi into the circulatory system [41] and thus ability to colonize in the neural cells of the brain. The innate immune response in the brain generates Aβ which inhibits the growth of *C. albicans* [42, 43]. Animal models in mice and worms along with cell cultures validate that Aβ inhibits the growth bacteria and fungi [44]. Conversely, treatments for AD are often aimed at reducing the deposits of Aβ in the brain [45, 46]. Interfering with the innate immune response to reduce the inflammatory response often aggravates the infection producing inflammation (e.g., use of corticosteroids to relieve inflammation in infections [47, 48]), and reduction of Aβ (an inflammatory agent) in clinical trials has resulted in aggravation of AD [49, 50].

Tau phosphorylation

Tau phosphorylation (hyperphosphorylation) of proteins and the resultant degeneration (tauopathy) through the formation of tangles was early historical physical evidence of AD [51]. Tyrosine phosphorylation corresponds to tau aggregation or tangling [52]. Although hyperphosphorylated tau tangles have a pathological appearance, neuronal cells can survive more than 20 years with extensive tangles [53], and tau filamentation is neuroprotective [54].

Cholinergic model of memory dysfunction

Loss of cognition is due to loss of central nervous system function where the hypothetical key is the disruption of the cholinergic neurotransmitter system, the "cholinergic hypothesis" [55]. In animal studies, changes in choline and acetylcholine are associated with behavior. The growth of *C. albicans* varies with the availability of choline, because choline reduces the need to synthesize PC which is energetically favorable over synthesis via the salvage pathway [56, 57]. Because the brain intracellular space has about 6 times the concentration of choline than blood plasma and 10 times that of the CSF [58], invagination into brain cells becomes the preferred environment for *C. albicans*.

FUNGI AND RELATION TO ALZHEIMER'S DISEASE

C. albicans, the most prolific and morphologically diverse fungal species in humans, was described by Hippocrates as thrush, a formation of white plaques inside the mouth [59] and was isolated by Bennett in 1844 in the sputum of tuberculosis patients, and by Zenker in 1861 from a brain infection in a debilitated patient having spread from thrush lesions [60]. Zenker's report was interpreted as referring to *Cryptococcus neoformans* [61] often confused with *C. albicans*. When carried in the bloodstream as yeasts from the intestines, *C. albicans* the most common commensal fungus can readily infect various organs, and can colonize inside both resident cells and immune cells (macrophages) as endomycosomes or phagosomes [15]. Other pathogenic fungi can affect hosts similarly, including *Cryptococcus gattii* [62], *Aspergillus spp.* [63], and molds [64]. Carrasco et al. first published postmortem evidence that fungi cause AD in 2014 [15].

C. albicans may be partially symbiotic because of the genes for the glyoxylate cycle and gluconeogenesis which are suppressed by glucose concentrations found *in vivo* [65], but when *C. albicans* is phagocytosed by macrophages and neutrophils, these paths become expressed. The glyoxylate cycle produces glucose from fatty acids and glucose is needed in large quantities to enable *C. albicans* growth [66]. These fatty acids can be cytotoxic or suppressive to microbes; a mechanism in *C. albicans* that converts fatty acids to glucose, which is key to the virulence of *C. albicans* [67], could also be of biological advantage in human starvation, taking stored fats and converting them to glucose.

Candida albicans morphologies

The virulence of *C. albicans* is aided by its interchange between four morphologies [68]. *C. albicans* can appear as a 2 to 8 micron unicellular yeast (blastoconidia) that can grow in a colony, and when they bud can lengthen into chains with constrictions (pseudohyphae). Germ tubes appear from single cells and extend to the first constriction, perhaps form hyphae which are important for invasion and pathogenesis. *C. albicans* blastoconidia are less hydrophobic than germ tubes [69] making germ tubes resistant to phagocytosis by macrophages and monocytes, and makes *C. albicans* more virulent [70].

Giant blastoconidia, an unusual form of *C. albicans*, called chlamydoconidia (8 to 12 microns in diameter), result from inflammatory responses and are found in cardiac, kidney, cartilage, or bronchial vegetations [71]; application of antifungals may induce their formation. Chlamydoconidia are important because they have been confused with *Cryptococcus neoformans* [72, 73].

Virulence

Primary virulence factors of *C. albicans* are: conversion of yeast-like cells to hyphae [74], lytic secretions (aspartyl proteases [75], lipases, and phosphatases) and cell surface proteins [76] which enable adhesive penetration, persorption, or phagocytosis [77]. To enable the commensal *C. albicans* to invade requires overwhelming either impaired or normal innate immunity or the means to block innate immunity [78] such as aspartyl proteases which block the complement system increasing virulence [79]. In oral thrush, *C. albicans* invades endothelial epithelial cells by both endocytosis and penetration [80]. Virulence in the intestines is by proteolytic penetration which aspartyl protease inhibitor pepstatin blocks [81]. *C. albicans* prevents removal by the immune system by maintaining low levels of colonization (commensal) which avoids activating the MAPK alarm pathway [82]. As the fungal burden increases, the ensuing hyphal development activates cytokines that recruit macrophages and neutrophils. As the immune response clears the fungal burden, the colony falls below the virulent state returning to the commensal state [83].

Yeast to hyphal transition

The yeast to hyphal transition is associated with the virulence of *C. albicans* because of the invasion of epithelial cells by hyphae and pseudohyphae. A *C. albicans* cytolytic protein, "Candidalysin", invades the epithelium, kills cells, and blunts the immune response [84]. *C. albicans* adapts to the environment inside macrophages by making the yeast to hyphal transition, a defense against pyroptosis: The macrophage cell death mechanism that attacks pathogens with immune responses to block replication [85]. Macrophages phagocytose *C. albicans* as part of the immune response, inducing *C. albicans* to alter its metabolism in response the environment, and to develop hyphae, which in turn induces macrophage pyroptosis thereby enabling *C. albicans* to escape [86, 87] and to induce massive killing of macrophages after this first phase, a non-pyroptotic macrophage death.

In AD, the hazard is the immune evasion of *Candida spp.* (*C. spp.*) by hiding inside endothelial cells [88] whereby a victim cell is induced to extend a pseudopod to endocytose the fungal cell. Binding to the endothelium was demonstrated for germ tubes and buds inside the cells, forming pseudohyphae without any changes to the morphology of the endothelial cells [89]. In acidic conditions, *C. albicans* can raise pH from 4 to over 7 within 12 hours, which results in self-induction of the yeast to hyphal transition [90]. In the case of glucose deprivation, the pathway to raise pH is the general degradation and proteolysis of proteins to produce ammonia [91], a base for which *C. albicans* has a more powerful reaction to acidity than other fungi. Excessive ammonia is found in the CSF and blood of AD patients [92] which produces pathologies during glucose deprivation such as metabolic dementia [93].

Growth in saliva and glucose

Low submandibular saliva flow is associated with moderate to advanced AD [94] and may be the result of deterioration of the nerves serving the submandibular salivary glands, possibly associated with *C. albicans* infection. Conversely, dementia's effect on executive function results in poor hygiene [95] may increase *C. albicans* growth. *C. albicans* does not normally grow in saliva, but its growth can be stimulated by higher levels of dietary glucose or serum glucose as found in diabetes patients [96]. Normally bacteria break down glucose in saliva, but antibiotics that kill the bacteria, or glucocorticosteroids, can stimulate the growth of *C. albicans* [97].

C. albicans lipases

The lipolytic enzymes of *C. albicans* provide fatty acids and glycerol as a food and energy source [98] and create an advantage for maintaining growth in the intestine and skin, and enabling acidification which contributes to virulence and tissue damage. The action of *C. albicans* lipases [99] produce lipid droplets in macrophages becoming foam cells hepatocytes becoming, and thereby induce cytotoxicity [100]. The effect of *C. albicans* lipase on the liver (the initial defensive organ against invasion from the gut and circulation by taking up the fungal cells) can induce nonalcoholic steatohepatitis, and under stress, causes liver damage [101]. The development of hepatic encephalitis associated dementia and the onset of AD should be examined as parallel, not separate, disorders.

Calcineurin

Calcineurin is a Ca2+ serine/threonine protein phosphatase activated by calmodulin that regulates processes in eukaryotes ranging from yeasts to humans [102]. *C. albicans* expresses calcineurin which is essential to virulence [103] and, in yeasts, it regulates cell cycle progress, the action of polarization in growth, and Na+ and Cl- ions and pH. Calcineurin in the human brain has a regulatory function similar to that of yeasts and is associated with the pathologies of dementia [104]. Levels of calcineurin increase greatly as one ages or suffers from injury or infection, and high levels of calcineurin are found in the astrocytes of the hippocampus in a mouse model for AD, and in human AD patients [105].

Application of calcineurin inhibitors (cyclosporine and tacrolimus) to a murine model of AD was protective, perhaps even slowing or reversing the progression of AD [106]. A study of kidney transplants with fungal involvement showed a decreased probability of AD, likely due to the chronic administration of calcineurin inhibitors (tacrolimus and cyclosporine) used to limit and control tissue rejection [107]. Tacrolimus is recognized as an antifungal [108] suggesting a connection because kidneys and brains are receptacles of fungi [109].

Tyrosine phosphorylation

In the bloodstream, *C. albicans* induces endocytosis by stimulating tyrosine phosphorylation endothelial proteins of 80 and 82 kDa [110], and thus hyperphosphorylation may be evidence of invasion and induction by *C. albicans,* and is independent of Aβ deposition which has been suggested as dependent on introduction and formation of Aβ [111]. Belanger et al. show that the tyrosine kinase inhibitors genistein and tyrophostin 47 reduced phosphorylation as *C. albicans* endocytoses.

Fungal markers associated with AD

Chitins, chitinase, fungal proteins, and fungal antibodies may be excellent biomarkers of AD if fungi are etiological. Chitinase appears in humans in response to allergens (many of which contain fungi) and fungal pathogens. Since there are no external sources for chitinase in the CSF, the presence of chitinase signals fungal infection [112]. Chitin-like polysaccharides are an integral component of the amyloid plaques and amyloid angiopathy of AD [113], as demonstrated by colocalized calcofluor staining of AD plaques, chitinase treatment, and subsequent fluorescence decrease indicating that plaques contain fungal cells or detritus. Subsequently, more accurate immuno-staining was used to identify chitins, and two fungal proteins, enolase and β-tubulin in the brain tissue of AD patients [18].

Chitotriosidase

Elevated levels of chitotriosidase, a human chitinase enzyme, are a marker for AD and cerebrovascular dementia [114] and are associated with the deposition of Aβ without observation of fungal infection. Chitotriosidase is produced by activated macrophages associated with ischemic cardiovascular disease (CVD) and AD. Detection of chitinase activity in the CSF with an accuracy of 86% is a superior AD marker than Aβ or tau both at 78% [112], where Aβ is likely an immune response to a *C. albicans* infection [115]. YKL-40 (chitinase-3-like protein 1) is a superior marker for AD [116]. Radiolabeled detection of chitin using ^{123}I-chitinase functioned well as a radioligand for detection of fungal infections in mice [117]. In a neonate study of chitotriosidase produced by phagocytes in response to bacterial and fungal infections, there is a population of 6% that cannot express chitotriosidase for which one would expect a lowered ability to fight chitin containing pathogens [118], and note the high 50% level of false negative fungal cultures.

Beta glucans

Beta glucans are β-D-glucose polysaccharides found in plant, bacteria, and fungi/yeast cell walls, and are a marker for infection which can temper the immune response facilitating fungal survival [119]. Disseminated fungal infections seen in AD patients are associated with the widespread observation of beta glucans which are seen in serum along with antibodies for yeast and fungi species [17, 112, 120]. Finding the fungal (1, 3)-β-glucan becomes evidence for disseminated infection, and when it is found in the CSF, it is a marker for CNS fungal infection [121, 122].

IMMUNE SYSTEM

The primary cells responsible for the removal and destruction of *C. albicans* cells are the neutrophils and macrophages. Neutrophils are found to execute the effect of TNF-α in the course of systemic candidiasis [123], and according to the ARTEMIS survey various *C. spp.* are found [124]. A review of neutrophil and macrophage activity finds that neutrophils kills *C. albicans* intracellularly and extracellularly, and blocks germ tube formation [125]; in fungal carbohydrate starvation, the glyoxylate cycle and the nitric oxide (NO) stress response are upregulated only when neutrophils phagocytose the fungus, while the oxidative stress response (superoxide dismutase or glutathione reductase) is active intracellularly and extracellularly [126].

Nasopharyngeal defense

Nasal mucosal secretions are the first defense against microbial intrusion with various proteins and lipids. The most hydrophobic lipids are generally more anti-microbial, in particular cholesteryl linoleate, and cholesteryl arachidonate [127]. These non-polar lipids are most effective against bacteria, but because *C. albicans* biofilms are combinations with bacteria, often MRSA, inhibition of bacteria effects diminution of biofilms, and thus an indirect reduction in overall *C. albicans* colonization [128–130]. There have been several cases of various fungal infections, mostly mucormycoses associated with diabetes, where hyphae have travelled through the neural cells to the brain [131, 132]. Invagination of

the blood vessel walls are directly involved in mycotic aneurysms [133].

Dose related cerebral mycosis

A 1978 survey showed *C. albicans* to be the predominant cerebral mycosis [134] and corrected the mistaken diagnosis of *Cryptococcus spp.* infection reported in previous surveys. The authors warned that *C. albicans* in large numbers from any site "portends infection of the central nervous system." Systemic *C. albicans* infections are associated with immunocompromised patients, but high doses of *C. albicans* can establish infection in immunocompetent subjects. One experiment administering 10^{12} cfus of *C. albicans* orally (comparable to the intestinal fungal colonization of patients treated with broad-spectrum antibiotics) on a healthy volunteer resulted in systemic fungemia caused by persorption of *C. albicans* cells across the intestinal wall [41].

Role of Aβ as an antifungal

Formation of Aβ is likely a direct innate immune response to *C. albicans* because Aβ is most specifically antimicrobial for *C. albicans* among organisms tested [115], and thus protects against infection in the brain; this action is directly contrary to efforts to reduce Aβ and thereby reduce AD damage. In addition, Aβ reduces *E. coli* growth by 200 times *in vitro*, along with general antibacterial effects [135]. Reduction of Aβ in AD patients appears to have the effect of stimulating pro-inflammatory effects would then marshal a general immune response [115]. Large clinical trials of Aβ immunization in order to reduce Aβ found a significant increase in encephalitis in those immunized [136], and similarly, infection increased in those treated to reduce Aβ [137]. A summary noted that Aβ formed plaques to trap pathogens and block invasion [138]. Membrane destabilization is another anti-pathogenic mechanism for Aβ [139].

C. albicans antigens and arteritis

C. albicans antigens have been shown to induce arteritis [140], and giant cell arteritis is associated with cerebral amyloid deposits in the arteries [141] which suggests a connection between the development of AD and active *C. albicans* inflammation. In a study of candidemia in mice, a *C. albicans* water soluble beta glucan-mannoprotein complex exhibited significant cytotoxicity and injured the vascular endothelium through inflammatory response increasing production of IFN-α, IL-6, and IL-10, and myeloperoxidase [142]. Together this accounts for arteritis and the resulting inflammation which would be aggravated by platelet aggregation and adhesion [143]. Note that glucan-mannoprotein complexes are a significant component in beer and ale [144].

Immune evasion

The ability of *C. albicans* to reside in endomycosomes [15] may be the result of biological selective pressure to survive identification and avoid destruction by the immune system. When host cells engulf *C. albicans* through phagocytosis, *C. albicans* alters its transcription toward starvation response with gluconeogenic growth, fatty acid beta oxidation (which consumes naturally anti-pathogenic short chain FFAs, free fatty acids), and reduction of ribosomal translation [145]. The immune system destroys pathogens by creating reactive oxygen species and free radicals (including $\bullet O2^{-}$, $\bullet OH$, $ClO\bullet$, and $NO\bullet$) inside macrophage phagosomes, where *C. albicans* produces a catalase and six superoxide dismutases to neutralize reactive oxygen species and free radicals [146] and inhibit production of NO [147].

Cholesterol esterification, LCAT

LCAT (lecithin-cholesterol acyltransferase) is a glycoprotein enzyme responsible for esterifying cholesterol and is bound to high-density lipoproteins (HDL) or low-density lipoproteins (LDL). LCAT esterifies free cholesterol in the plasma, removes a fatty acid from the 2 glycerol position in phosphatidylcholine, and combines them. In doing this, LCAT changes the composition and conformation of HDL from compact, dense spheroid, or floppy discoid shapes, known variously as HDL3 and pre-beta, to a larger spheroid alpha shape that is able to contain the large and very hydrophobic cholesteryl ester in its core [148]. HDL slows progression of CVD by inhibiting cytokine induced expression of adhesion molecules that attach leukocytes to the endothelium [149] increasing adhesion to *C. albicans*. ApoE deficient mice producing depleted lipoproteins and increased VLDL show increased susceptibility to candidiasis because of increased virulence and reproduction due to uptake of plasma lipids as a growth medium [150].

LCAT and the immune system

Poorly functioning LCAT is correlated to a compromised immune system because LCAT esterifies cholesterol to antimicrobial fatty acids and transports the hydrophobic resultant into HDL. LCAT deficiency was found to reduce the ability of HDL to remove lipopolysaccharides (LPS) and aggravate LPS induced inflammation [151]. LCAT deficient HDL showed reduced levels of ApoA-I and ApoA-II and was primarily composed of ApoE. Additionally, reducing LCAT levels increased the number of monocytes in circulation after an LPS insult. The combined effect of poor removal of LPS, and the increase in monocytes produced a more severe inflammation. LCAT deficiency led to massive candidiasis in the upper respiratory system and mouth in a transplant patient with familial LCAT deficiency [152]. Inflammatory and anti-inflammatory responses can be contradictory, and one study on cholesteryl arachidonate/linoleate showed that they may induce inflammation [153].

FFAs inhibit microbes, and DHA and EPA kill many different cells [154]. The effect of LCPUFAs (long chain polyunsaturated fatty acids) is to destabilize lipid rafts in the following relative strength: "stearic acid <oleic acid <EPA $\leq$DHA". The toxicity of triglycerides to monocyte-macrophages increases with increasing desaturation [155]:

"Triolean = trilinolein <trilinolenin <triarachidonin <tri-EPA = tri-DHA"

For the cholesterol esters, the order is: **"cholesteryl linolenate $\tilde{\leq}$ cholesteryl oleate <cholesteryl linoleate <cholesteryl arachidonate <cholesteryl EPA = cholesteryl DHA"**

FFAs are toxic both to microbes and macrophages, and both compete to lipolyze triglycerides and cholesterol esters leaving free cholesterol. To survive, the macrophage must efflux the excess cholesterol, i.e., "HDL function" [156], in human macrophages [157].

Transporting lipids, especially LCPUFAs, to the site of inflammation/infection is important in infections, as they are active [158] against numerous pathogens, including *Streptococcus mutans* and *C. albicans* [159]. DHA facilitates lysozyme incorporation into the membrane of *Pseudomonas aeruginosa* bacteria, common in lung infections, which allows influx of more DHA, leading to bacterial cell death [160]. Many medium chain FFAs are antimicrobial against *C. albicans* [161], and more potent are short chain FFAs of which capric acid was applied as an antifungal [162].

C. albicans may enter into the cranial cavity through the nasopharyngeal nerve complex and then into the olfactory bulb, a region implicated in the early development of AD and dementia [163]. Oropharyngeal mucous contain the antimicrobial cholesteryl arachidonate, transported by HDL with other antipathogenic fatty acids fluids [127]. Arachidonic acid (AA) released by cPLA2α has a demonstrated role in protecting the lung from *C. albicans* infection [164]. Since the brain is one of the largest stores of AA [165, 166], expect its availability to play a role in host defense against invasion by *C. albicans*. In the AD brain, there is an observable decrease in AA, EPA, and 22:4 [167]. Comparing the decrease in AA to the observation that *C. albicans* induces release of AA [54] suggests the conversion of AA to various oxidized metabolites that can affect *C. albicans* viability [168].

LCAT and ApoE

The biochemical relationship between ApoE and AD is significant because of the linked roles of LCAT and ApoE, both in the formation of HDL types and in the transportation of cholesterol, triglycerides, and cholesteryl esters. Coupling *LCAT* knockout mice with LDL receptor (*LDLr*) knockout and *APOE* knockout, there is a notable reduction in HDL, an increase in LDL, and an increase in the saturation of cholesteryl esters in LDL [169] which resulted in significantly more cholesterol deposited in the aorta. A study of disseminated candidiasis in ApoE deficient mice [150] found increased mortality for ApoE deficiency, elevated lipids, and elevated apolipoproteins. Given that omega 3 fatty acids (which are antimicrobial) in the 2 position in phosphatidylcholine are preferentially esterified by LCAT, deficiency results in saturated lipids (and proteins) as food sources for Candida and an impaired immune response due to increasing saturation of FFAs.

The combined effects of LCAT and ApoE deficiency reduce the macrophage cholesterol efflux capacity of HDL and are a predictor of atherosclerotic CVD [170], and for AD the *APOE-ε4* alleles are associated with degraded cholesterol efflux from macrophages. Similar to LCAT knockout, there is an increase in CVD for *APOE-ε4/ε4* macrophages because of impaired efflux capacity [171]. Because excess cholesterol is considered toxic to macrophages and CNS astrocytes, sufficient cholesterol efflux will avoid loss of immune function. ApoE2 HDL exhibits delayed clearance because it interferes with the LDL receptor site and effluxes cholesterol more efficiently,

and ApoE4 has the highest cellular reuptake of cholesterol [172].

LCAT: AD and Down's syndrome

AD and Down's syndrome (DS) share similar characteristics, because after age 40, DS patients can develop aspects of AD [173]: amyloid deposition, deterioration of cognition, and reduction of the cholesterol esterification rate as serum cholesterol increases. Reduction of the fractional LCAT cholesterol esterification rate was the only difference observed in DS subjects [174]. DYRK1A kinase is overexpressed in DS due to trisomy 21 and activates STAT3 which affects LCAT expression and decreases LCAT activity because of activation a tyrosine phosphatase, SHP2 [175]. Similarly, for AD patients with dementia, LCAT esterification is also limited [176], and is perhaps due to the binding of Aβ to HDL which inhibits LCAT [177].

SUMMARY

In the fungal model of AD, defeat of the innate immune system allows colonization of neural cells with fungi. Aβ is a natural antifungal and targeting its inhibition should be questioned, PUFAs and short chain FFAs inhibit infection, ApoE and LCAT function are interrelated, ingesting high levels of soluble beta glucans and chitin can interfere with fungal immunity, and untreated mycoses are problematic. Superior markers for AD are chitins and chitinase. Severe head injuries resulting in diffuse axonal injury, can result in fungal corpora amylacea that increase the risk of AD.

Like a trojan horse, fungi defeat the innate immune system by hiding inside neural cells as endomycosomes. To control fungal and pathogenic infections in the brain, humans likely evolved an immune system that was just sufficient to attain reproductive age. Primitive man survived by sequestering fungi in neural cells instead of letting fungi reproduce and destroy the host. Sequestration was the only means to control fungal growth in a horrible diet that persorbed prodigious pathogens into human circulation and thence to the brain. Only now with improved diet and health these slower long-term debilities such as AD become manifest.

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CONFLICT OF INTEREST

The author has no conflict of interest to report.

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