Commentary

Candida and Long Covid

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The pandemic has supercharged growing awareness of the gut microbiome as a critical determinant of human health. Long haulers share microbiomes similar to those seen in myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia, all frequently associated with Candida overgrowth (CO). Candida has a unique relationship with indoleamine dioxygenase (IDO) and altered tryptophan metabolism (ATM), mediated by IFN-γ. Zonulin, a circulating protein that increases intestinal and endothelial permeability, has emerged as a central player. This protein can be activated by proteases secreted by Candida and mast cells, enabling myriad autoimmune and other chronic diseases. Many of these are seen in long Covid (LC).

Candida hyphal walls express proteins analogous to gliadin/gluten, e.g., celiac disease (CeD), and mannans, e.g., Crohn's disease (CrD), that may trigger antigliadin and possibly anti-GPCR auto-antibodies linked to their lectin binding domain respectively. These latter may include the GPCR auto-antibodies seen in LC and POTS. Both autoantibody producing pathways activate zonulin. IFN-γ, a marker for LC, can activate not only IDO but also zonulin. Candida can synthesize IDO and the mannan immune epitopes on its hyphae reveal remarkable spatial and phylogenetic diversity.

The spike protein S on SARS CoV2 can attach to both the ACE2 receptor (required for tryptophan absorption) and Toll-like receptor4 (TLR4) bearing endothelial cells and enterocytes. Spike protein S is persistent in most with LC and, as a ligand for TLR4, can also activate zonulin. S can also activate the NLRP3 inflammasome, as can candidalysin. This inflammasome is directly connected to dementia, cancer, autoimmunity and obesity. A hypothetical pathophysiologic model is proposed implicating pre-existing CO, aggravated by Covid-19, in not only the genesis of LC but also that of autoimmune disease, dementia, cancer, many chronic diseases, and aging. Candida may accomplish this directly or through IFN-γ induced upregulation of both IDO and zonulin. Candida can even synthesize IDO.

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1. Introduction

There has been an explosion of autoimmune diseases (see figure 1) over the last half century.

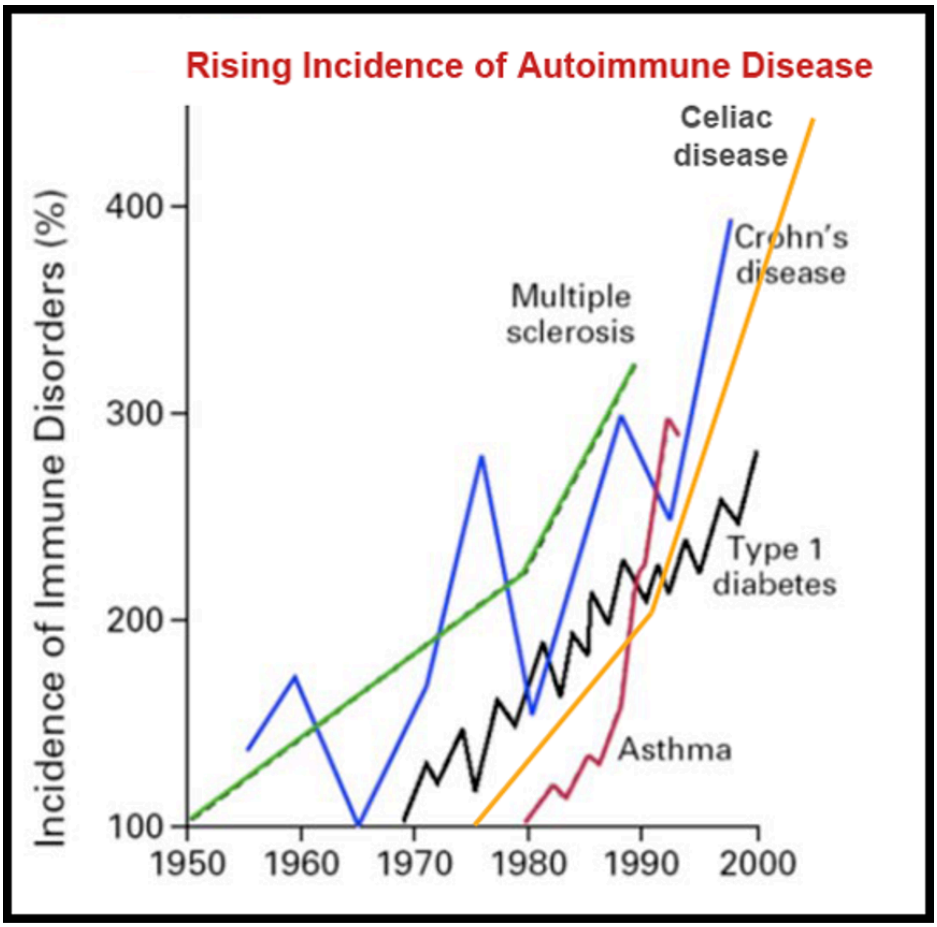

Figure 1. The incidence of autoimmune disease has exploded since the mid 1900s for both CrD (anti-mannan antibody) and CeD (anti-gluten antibody). Source: Alessio Fasano, MD, Center for Celiac Research, Massachusetts General Hospital.

A dysbiotic gut microbiome appears to be the culprit, mediated by loss of intestinal and endothelial barrier integrity. Zonulin, discovered in 2000 by Alessio Fasano and his research team, is the primary regulator of this barrier integrity. Initially bacterial toxins in the gut microbiome were proposed as the source of the zonulin induced increase in intestinal permeability. But recently the mycobiome has come under close scrutiny in this regard. Although a genetic predisposition to upregulation of zonulin is undeniable, focus has shifted to more controllable inputs. The zonulin hypothesis has been proposed[1]. It reports that SARS CoV2, which can bind TLR4s on enterocytes and endothelial cells, activates zonulin, as

can IL-6 and gliadin[2]. Zonulin in turn activates complement. But does the virus act alone in the devolution of Covid-19 to LC? How are the gender disparities reconciled? Why is the range of LC symptoms so vast and why are explanatory linkages so elusive? Might LC, classified as an autoimmune disease by the Autoimmune Registry, be the consequence of an upsurge in anti-GPCR autoantibodies. Multiple international symposia have targeted this phenomenon[3]. Anti-AT1Rs, anti-α1 and anti- β2 adrenergic receptors[4], and anti-muscarinic cholinergic receptors, frequently encountered in long haulers[5], are all anti-GPCRs.

Hypothetical Model (see figures 2,3)

1. Commensal Candida overgrowth (CO) with transition to pathogenic hyphae can be both cause and effect of gut dysbiosis
2. Persistent spike protein S binds to TLR4[6] on intestinal and endothelial cells, activating zonulin[1] and the NLRP3 inflammasome
3. Most long haulers have persistent spike protein S (NIH says 65%)
4. Zonulin is a protease that enhances intestinal and endothelial permeability, enabling hyphal invasion
5. Candida hyphae secrete a protease that also activates zonulin[7]
6. Zonulin induced BBB permeability facilitates neuroinflammation[8]
7. Candida hyphae contain two highly immunogenic epitopes, gluten-like Hwp1 (hyphal wall protein) and mannan (glyan shield)
8. These epitopes are linked to both anti-gluten/gliadin (CeD) and anti-mannan (CrD) antibodies.
9. Antibodies to host AT1Rs, α1-adrenergic, β2 adrenergic receptors[5], and muscarinic cholinergic receptors characterize LC and may be due to invasive hyphal mannans.
10. The NLRP3 inflammasome links Candida and LC to dementia, cancer, autoimmunity, and obesity via candidalysin and the spike protein S respectively (see figure 2)

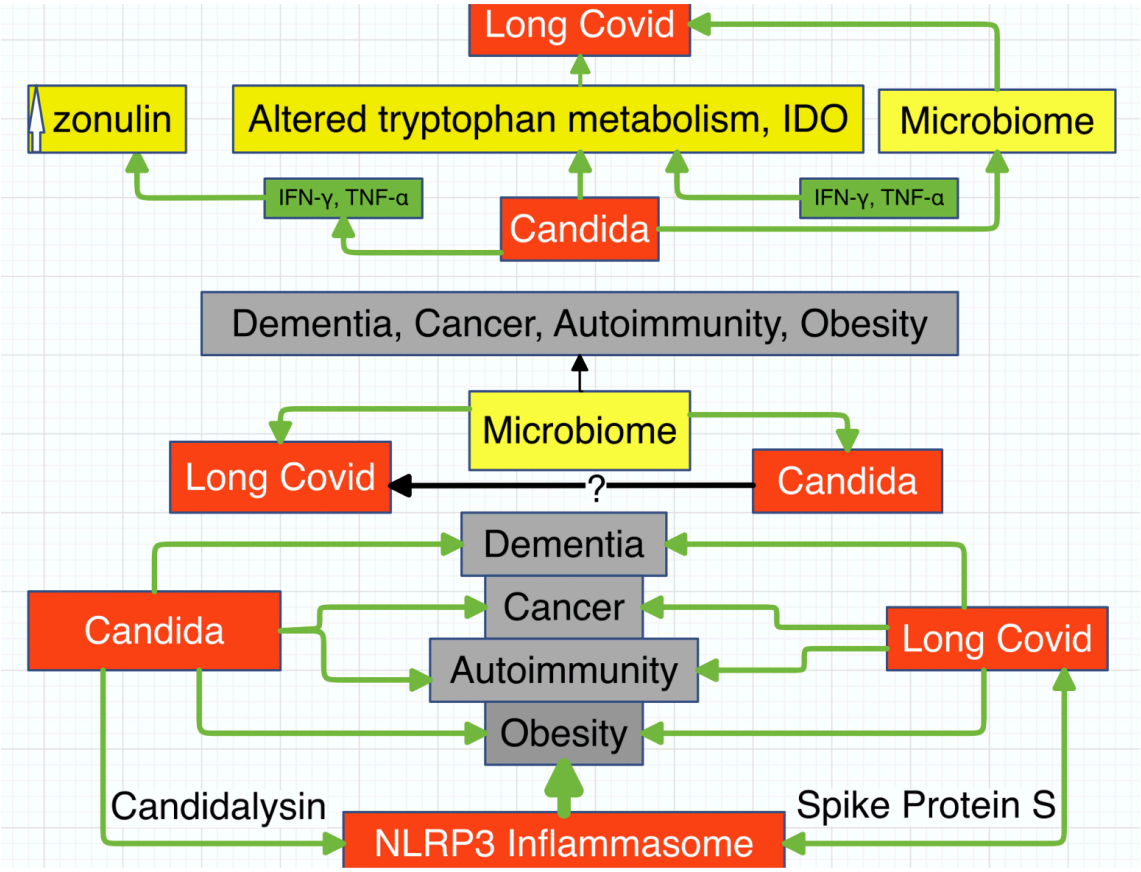

Figure 2. Shown are three related diagrams. The role of Candida in these four diseases may be anti-GPCR antibody mediated and/or candidalysin related thru activation of the NLRP3 inflammasome.

2. Zonulin and Increased Permeability

Zonulin is the only known physiologic modulator of intercellular TJs[9]. Activated zonulin receptors and PAR2 increase intestinal and endothelial permeability[10]

2.1. A. Autoimmune Disease

Zonulin release is linked to autoimmune diseases, both those associated with gluten sensitivity (anti-gliadin antibodies), e.g., CeD and ankylosing spondylitis[11] and those associated with anti-Saccharomyces cerevisiae antibodies (ASCAs)[12], e.g., CrD and probably IgA vasculitis/IgA nephropathy (anti-endothelins, GPCRs)[10][13]. All are reported in LC. ASCAs are elevated in inflammatory bowel disease (IBD), especially CrD[14]. CeD patients have higher IgA anti-gliadin antibodies than controls or IBD patients[15]. Both autoantibody types trigger an increase in zonulin

2.2. B. Dementia, Cancer, Other Diseases

Brain endothelial cells express zonulin receptors and exposure of BBB to zonulin leads to increased permeability[8]. IL-17, biomarker for autoimmune disease[16] and IFN-γ, biomarker for LC[17], also elevate zonulin. Zonulin is elevated in AD[18] and PD[19][20]. Elevated zonulin has been linked to numerous cancers, including colon[21][22], breast, lung, ovary, pancreas, brain (gliomas)[11], and liver cancers[23]. Zonulin is directly linked to other diseases, e.g., overweight and obesity, at least in the young[24][25], multiple sclerosis (MS), schizophrenia[23][26], autism[23][27] and arthritis[28].

3. CeD and CrD

3.1. A. Celiac Disease

Zonulin is a biomarker for CeD[29], a well described autoimmune disease encountered in LC and linked to antigliadin antibodies. These have high sensitivity and specificity for CeD[30]. Anti-gliadin antibodies are present in 5-12% of the general population. They are also encountered in rheumatoid arthritis (RA)[31], SLE, Sjögren's syndrome[32], sarcoidosis[33][34], T1DM[35], MS[36], psoriasis, Grave's disease[37], and Hashimoto's thyroiditis[38]. Others include systemic sclerosis[39] and autoimmune hepatitis[40]. However, there is considerable overlap, as GPCR autoantibodies and anti-gliadin antibodies can be concomitant, e.g., RA, SLE, and Graves' disease[36][37][38]. All are seen in LC. Many skin diseases expressing anti-GPCR antibodies are linked to CrD and reported in LC. These include psoriasis[41], alopecia areata[42], and vitiligo[43]. GPCR autoantibodies suppress hair follicle stem cells[44] and growth of melanocytes[45] and a GPCR is vital in the regulation of skin proliferation[46]. CO is associated with alopecia, vitiligo and psoriasis.

3.2. B. Crohn's Disease

ASCAs are biomarkers for IBD, especially CrD, and can also be generated by Candida albicans[47]. These fungal mannan antibodies are seen in both CrD disease and LC[4]. CrD, increased in LC and linked to ASCAs, is associated with greater risks for colon cancer, liver cancer, lymphoma, melanoma, squamous cell skin cancer, and cancers of lung and bladder. ASCAbs are usually positive in CrD and negative in ulcerative colitis (UC) while pANCAbs (perinuclear anti-neutrophil cytoplasmic antibody aka myeloperoxidase (MPO) ANCA) are usually positive in UC but negative in CrD. Recently (2024) Candida

has been implicated in the pathogenesis of UC[48]. Signaling by all chemokine receptors on T cells is mediated by Gq coupled GPCRs[49]. Many chemokine autoantibodies, especially ANCA associated vasculitis, are reported in LC[50]. Might the multitude of chemokine and GPCR autoantibodies reported in LC be due to anti-mannan antibodies induced by Candida hyphae that bind to lectin receptors on Gq coupled GPCR platforms? (see figure 3). This would be in addition to candidalysin released by hyphae that upregulates NLRP3 inflammasome[51] and that is known to play a key role in many autoimmune diseases, dementia, cancer, and obesity.

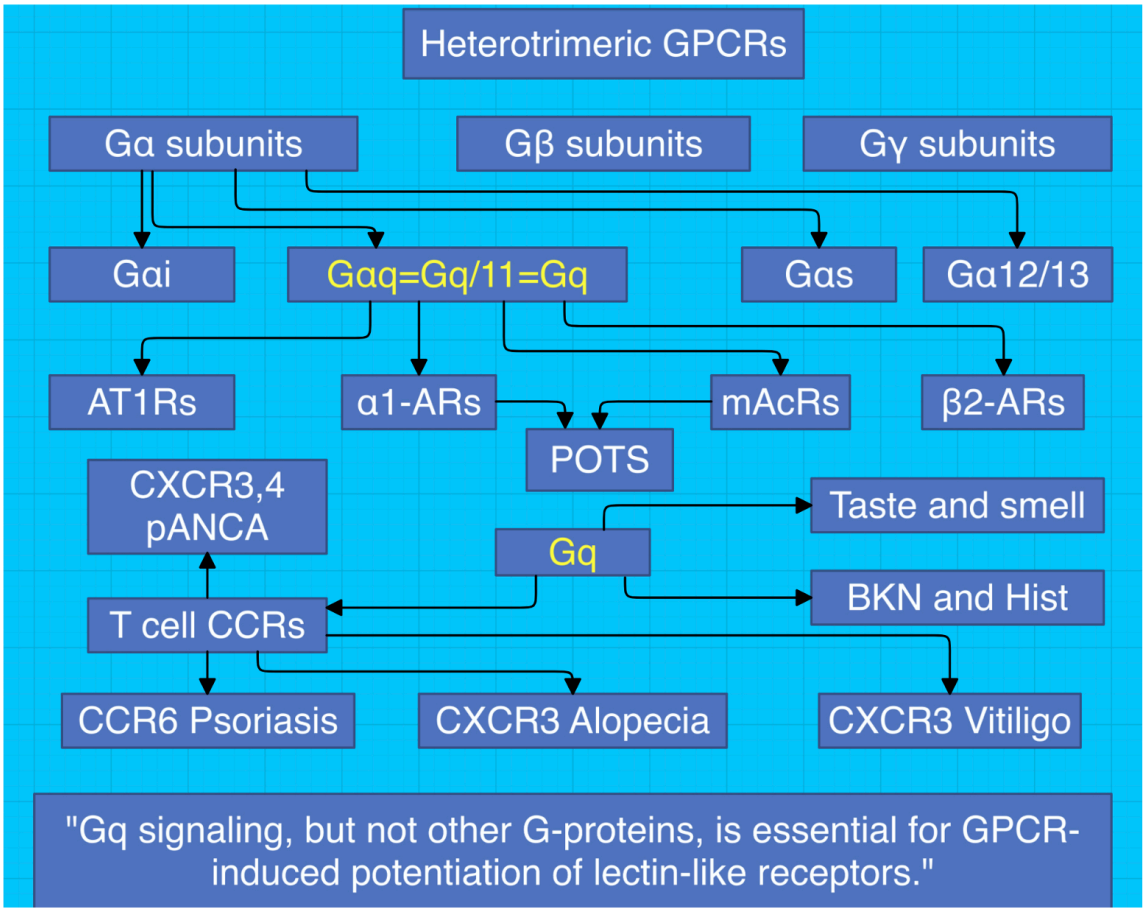

Figure 3. Gq coupled GPCRs mediate all chemokine signals from T cells. Antibodies to Gq coupled GPCRs, induced by lectin bound hyphal mannans, may represent the pathway to LC, as the lectin receptor domain may be part of the Gq coupled GPCR platform. ASCAbs are anti-Saccharomyces cerevisiae antibodies, linked to CrD, that are anti-mannan antibodies. CCRs are chemotactic cytokine receptors. mACR is muscarinic cholinergic receptor. AR is adrenergic receptor. BKN is bradykinin, Hist is histamine.

4. Candida

4.1. A. Gender

Females with autoimmune disease outnumber males (4:1). This may be due to their robust production of interferons, especially IFN-γ, which is an especially proficient antifungal. One study[51] of 600,000+ vaccine-naive, PCR-confirmed Covid-19 individuals demonstrated a significant increase in autoimmune disease within 3-15 months. But surprisingly the highest rates for recent onset were found for vasculitides, which are somewhat rare. Furthermore, although females are more susceptible to autoimmune disease, including LC, the incidence of autoimmune vasculitides in those with LC was higher in males. For example, IgA nephropathy (IgAN) has been reported post Covid-19 and post Covid-19 vaccine[52] and IgA vasculitis has been reported in LC[53] and possibly in Covid toes[54]. IgAN and IgA vasculitis are mediated by IgA antibodies to endothelin receptors. Endothelin receptors are GPCRs. These two autoimmune diseases predominate in males, 4:1 for IgAN[55] and 2:1 for IgA vasculitis[56]. MIS-C and MIS-A, systemic vasculitides, are more common in males, and also involve endothelin receptors. Although the LC autoimmune response is more prominent in women following asymptomatic infection, the range and extent of expression in males correlates more with severity of Covid-19[57]. Autoantibodies targeting GPCRs and RAS-related molecules associated with Covid-19 severity, seen primarily in males[4], is directly related to TGF-β[58], which increases endothelin. Estrogen depresses endothelin synthesis[59], which may provide protection against some autoimmune vasculitides. ANCA associated vasculitis is linked with chemokine autoantibodies, unrelated to endothelin (see figure 3). SARS CoV2 in females (asymptomatic) may be more autoimmune and IFN-γ related, while in males (severe), it may be more vascular/connective tissue and TGF-β related (thrombosis and fibrosis). This may hypothetically put female long haulers at slightly greater relative risk for dementia/autoimmunity and male long haulers at slightly greater relative risk for cancer.

4.2. B. Epitopes and GPCRs

An epitope or antigenic determinant is the locus on an antigen that is particularly immunogenic. Expression of surface amino acid sequences on Candida hyphae (Hwp-1) analogous to the gluten protein gliadin (CeD) was first reported in 2015[60][61]. This links Candida and CeD. Candida hyphae also secrete aspartyl protease[62] that activates surface PAR2, aka thrombin[7], an ubiquitous receptor on host cells.

PAR2 is a GPCR targeted by zonulin that, when activated, increases permeability. Furthermore, hyphal mannan may via this same zonulin enabled pathway induce a spectrum of autoimmune diseases. In a study of 33 patients with a variety of inflammatory and autoimmune diseases 60% of those with an elevated zonulin tested positive for yeast overgrowth[63]. Fungi possess GPCRs, but share none in common with humans.

A 2023 study on rodents reported that Candida hyphal mannans (glycan shield of linked mannose molecules) can interact with endothelial AT1Rs and α1-adrenergic receptors (α1-ARs)(both GPCRs). Subsequent exposure to their dedicated ligands (angiotensin II and catecholamines),[64] was ineffective. Gq is the major G protein activated by the AT1 receptor[65]. Gq signaling, but not other G-proteins, is essential for GPCR-induced potentiation of lectin-like receptors[66]. Gq is also the major G protein activated by the α1-adrenergic receptor[67]. Although β2-AR activity is generally tightly linked to Gs-coupled receptors, in the lungs β2-AR activity is linked to Gq-coupled receptors[68]. Muscarinic cholinergic receptors, which are almost exclusively parasympathetic in function, interact with Gq-type G proteins[69]. Autoantibodies to either muscarinic cholinergic or β2-adrenergic receptors are seen in 75% of those with significant orthostatic hypotension[70], suggesting that orthostatic hypotension may be an early indicator of Candida overgrowth. Taste and smell GPCRs involve Gq coupled GPCRs. Bradykinin and histamine utilize Gq coupled GPCRs. Chemokine signaling also involves Gq coupled GPCRs. Antibodies to CXCR3, a chemokine receptor, have also been reported in LC (see figure 2).

Once endothelial cells are exposed to Candida hyphal mannans, Gq type GPCRs (AT1Rs, α1-ARs, β2-ARs, mAcRs) with lectin-like domains may bind these foreign mannans. This induces a conformational change in the GPCR that sterically hinders subsequent response to angiotensin/catecholamines/acetylcholine. The Candida hyphal mannan/GPCR complex may induce a humoral response that is also autoimmune. All four of these autoantibodies (anti-AT1R, anti-α1 AR, anti-β2-AR, anti-mAcR) have been frequently reported in LC and POTS. The conformational change can activate, inactivate, or neither. Although POTS is seen in some long haulers, cortisol is elevated in POTS but depressed in LC. Gq coupled GPCRs are vital to CRH release from the paraventricular nucleus and for function of ACTH receptors. However, a causative Candida connection to the autoantibodies in LC/autoimmune disease remains theoretical.

5. LC and Autoimmune diseases

5.1. A. The Candida Connection

Zonulin and β-glucan, a marker for translocation of fungal products into circulation, are elevated in individuals with long Covid. Fungal but not bacterial translocation was observed during LC[71]. Candidalysin, a toxin secreted by hyphae, damages intestinal mucosa and inhibits intestinal bacterial competition[72]. Furthermore, it is linked to cancer, Alzheimer's disease, and obesity, perhaps in part due to its up regulation of the NLRP3 inflammasome. Although Covid-19 has accelerated cognitive decline, the incidence of AD and PD in long haulers over the long term remains to be seen.

5.2. B. Spike S and TLR4

The spike protein (viral or vaccine) of SARS CoV2 activates TLR4, another GPCR[6]. Activated TLR4 on enteric and endothelial cells activates zonulin, enhancing their permeability[1] (see figure 2). Since TLR4 is present on the spike protein S (viral or vaccine), the risk for zonulin induced autoimmune disease and cancer may be elevated regardless. Neuroinflammation in LC may be mediated by persistent spike protein that directly activates epidermal growth factor receptors (EGFRs)[73] by anti-EGFR antibodies or by translocated Candida hyphae. The CNS is rich in EGFRs, which are GPCRs. In addition cancer, dementia, autoimmunity, and obesity are linked to the NLRP3 inflammasome (see figure 2). The spike protein S drives this inflammasome. These receptors and their ligands support a pathogenic model for LC involving Candida induced autoimmune disease. So, several pathways may be involved, spike protein S and TLR4/GPCR related or Candida hyphal invasion[74].

6. IFN-γ and Tryptophan

Females are robust producers of interferon, especially IFN-γ. Candida elicits robust production of this cytokine, an indirect ligand for zonulin receptors, according to a recent study[75]. Upregulated IFN-γ increases intestinal and endothelial permeability[8].

But Candida and IFN-γ do much more than this. Altered tryptophan metabolism is a characteristic feature of LC. IFN-γ is a required cofactor for indoleamine dioxygenase (IDO) and drives the pivot of tryptophan metabolism from its 5% allocation for the serotonin/melatonin pathway to nearly 100% for the

kynurenine pathway. This pivot elevates several neurotoxic metabolites, facilitated by IFN-γ (see figure 4).

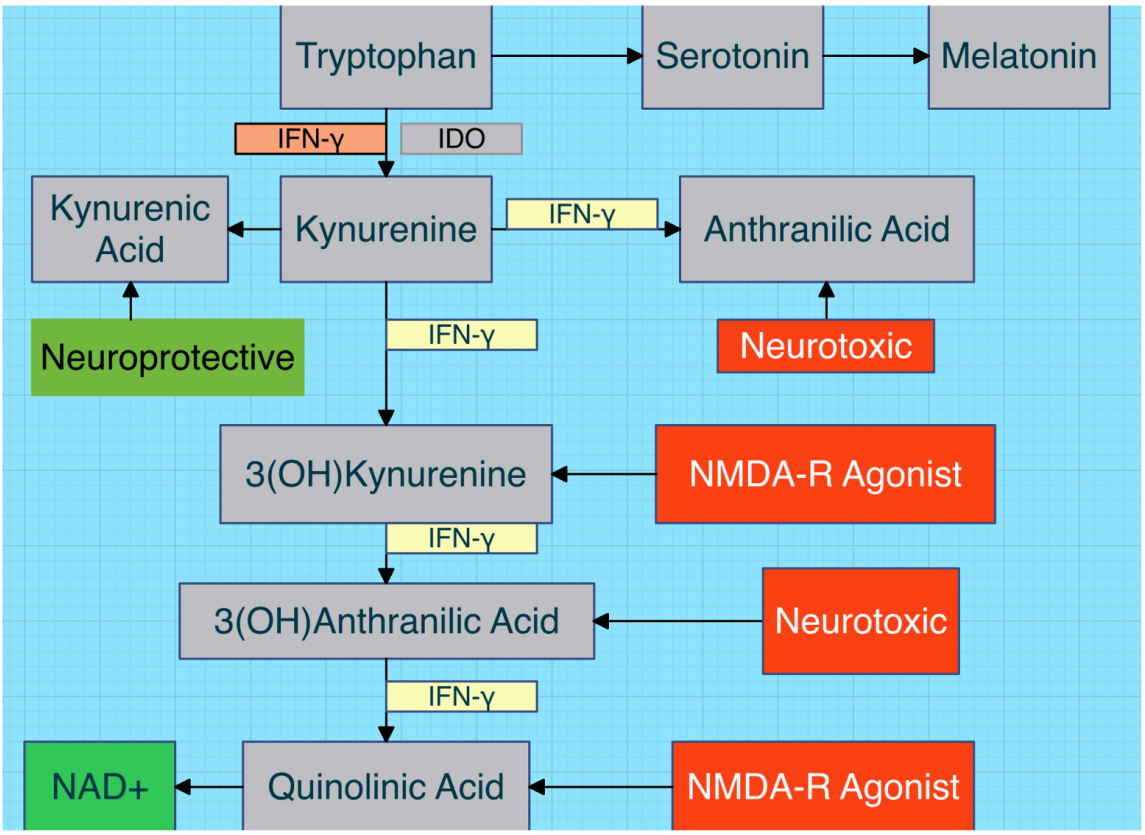

Figure 4. ATM characterizes LC (autoimmunity), cancer, dementia, obesity, and many other diseases. Covid-19 aggravates this, as intestinal ACE2 receptor bearing cells are required for tryptophan absorption.

Furthermore, ACE2 receptors must complex with $B^{\{m/0/\}}AT$, a neutral amino acid transporter required for absorption of dietary tryptophan, a neutral, essential amino acid[76]. Cell death of tryptophan rich cells after SARS-CoV2 invasion might explain the reported increased levels of tryptophan and its metabolites in Covid-19[77]. The decrease in tryptophan in LC suggests exhaustion, as tryptophan is significantly lower and kynurenine higher in severe v. mild LC (high consumption, diminishing supply)[78][79]. The essential, non-polar amino acid methionine also requires $B^{\{m/0/\}}AT$. This suggests that those with at least one MTHFR (methylene tetrahydrofolate reductase) variant allele may be especially adversely affected by LC. Caucasians are more likely than not to have at least one variant allele.

IDO in a healthy individual is highest, when Candida is a colonist. Any further increase in IDO risks mucosal damage by hyphal invasion, as the opposing tryptophan is depressed. IFN-γ is a required cofactor for IDO and any increase, e.g., SARS CoV2, may initiate such damage, as IFN-γ upregulates IDO[80]. Covid-19 severity is directly related to TGF-β[58]. TGF-β suppresses IFN-γ[81][82]. Low IFN-γ translates to low IDO activity and elevated tryptophan. Since tryptophan inhibits Candida hyphal formation and Candida synthesis of IDO[83], CO and autoimmune disease should be suppressed. Since males are less capable of robust interferon production, they are more likely to exhibit a greater TGF-β response to Covid-19. Covid-19 severity in males with more asymptomatic cases in females supports this view. IFN-γ is elevated in LC[17] and the predilection of LC for females also supports this view. There is a slight predilection of autoimmune disease and dementia for females and a slight predilection of cancer for males. TGF-β regulates tolerogenesis; too little (too much IFN-γ) and self antigens targeted, too much (too little IFN-γ) and tumor antigens are not targeted.

Butyrate immuno-modulates IFN-γ[84] and TGF-β (transforming growth factor), which are reciprocals and counterbalance each other[81][82]. Butyrate, a postbiotic, also stimulates the release of glucagon-like peptide (GLP-1). Ozempic, the popular weight loss drug, is a GLP-1 agonist, and obesity is directly linked to zonulin. D-mannose, a prebiotic and fiber substitute, opposes zonulin[28] (see figure 5).

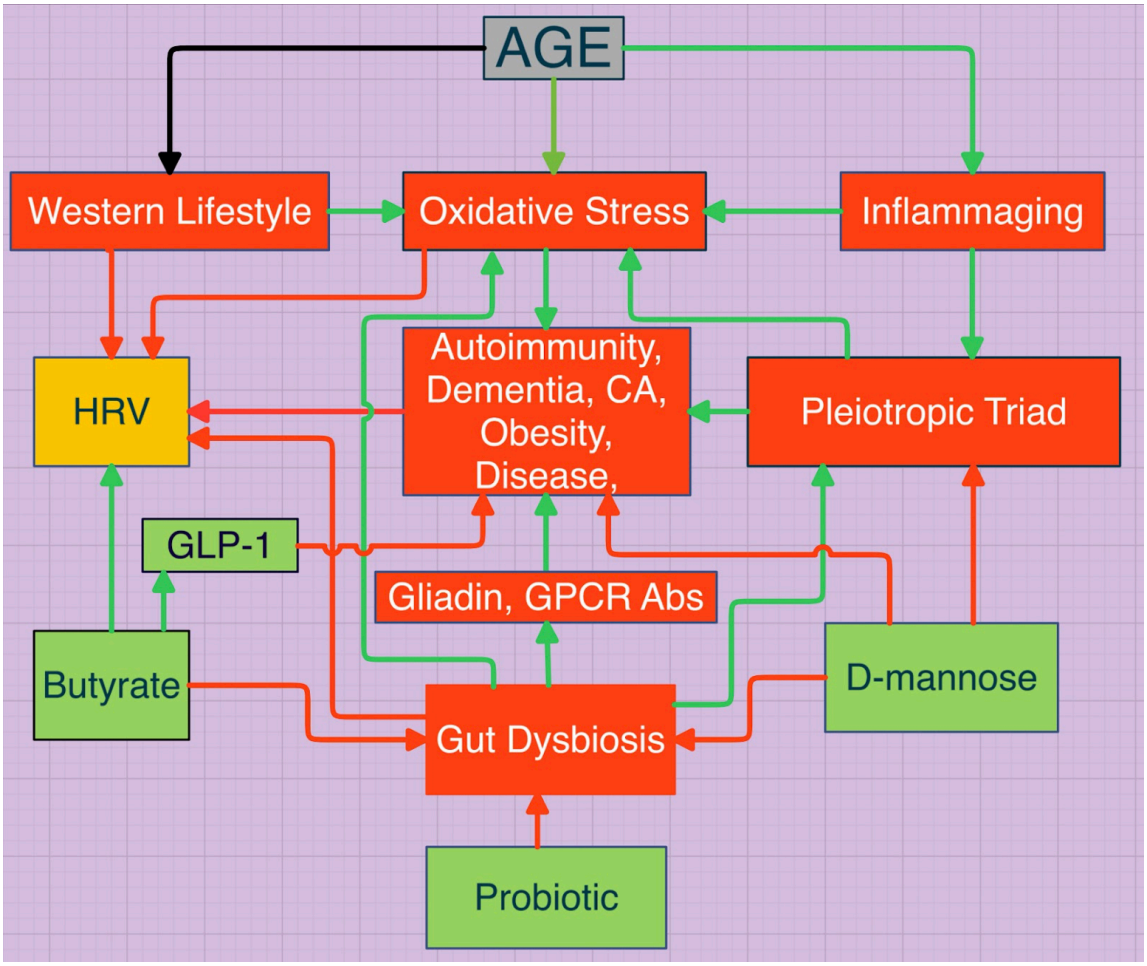

Figure 5. A prebiotic, probiotic, postbiotic approach may slow the inevitable age related decline in lifespan and healthspan, as reflected by decreasing heart rate variability (HRV). The pleiotropic triad is IL1-β, TNF-α, and IL-6.

Summary

Figure 2 demonstrates the links between Long Covid and CO. These associations are well supported by the most recent medical literature. Long Covid may arise in those with at least mild CO, aggravated by Covid-19. Residual spike protein with its TLR4 epitope may conspire with Candida hyphal epitopes to trigger many of the autoantibodies and diseases (gliadin and CeD, Candida mannans and CrD) linked to LC. Candida hyphae may bind lectin-like receptors on Gq coupled GPCR platforms and induce autoantibodies to many Gq coupled GPCRs, including chemokine receptor antibodies. Candida yeast forms can synthesize IDO to regulate host tryptophan, which inhibits the yeast to hyphae transition. The increased K/T (see figure 5) promotes mast cell activation. IFN-γ and TLR4 also upregulate IDO. Candida

hyphae can also activate MCP-II (see figure 3), which will further upregulate mast cell activity. Thus, CO in partnership with SARS CoV2 may be linked with LC via altered tryptophan metabolism in addition to increased intestinal/endothelial permeability (mast cell and hyphal proteases) and suboptimal gut microbiome. β-glucan is also associated with long Covid and Candida. The linkage of NLRP3 inflammasome to both CO and the spike protein S lends additional credence to the Candida-LC coupling.

These mutual associations (see figure 6) - anti-gliadin antibodies, ASCAs, β-glucan, independent association with dementia, cancer, auto immunity, obesity, independent association with NLRP3 inflammasome, altered tryptophan metabolism, zonulin, and poor butyrate production by gut microbiota make the causative roles of CO and/or residual spike protein S in the pathogenesis of LC a distinct possibility. Intersection with the gut microbiome underscores its overarching role in our health, as Hippocrates surmised nearly 2500 year ago, "all disease begins in the gut."

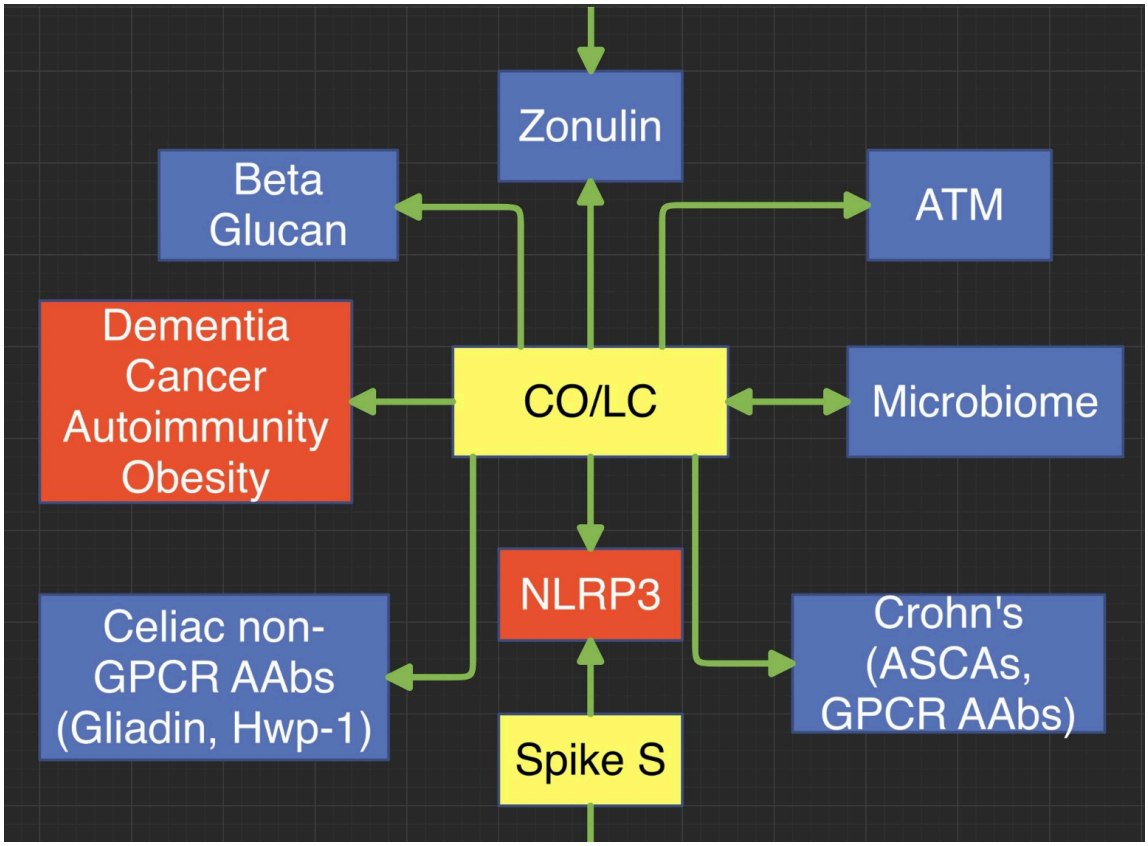

Figure 6. Candida and LC are each independently linked in many ways.

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Conclusion

The commensal Candida has been a quiet member of the human microbial community for many millennia. But a potential Jekyll and Hyde pathogenic hyphal transformation has always lurked in the shadows, arising when opportunity presents. Deterioration of the modern diet must be at the top of that list. The Candida connection to LC and the listed diseases may be anti-GPCR antibody mediated and/or candidalysin related thru activation of the NLRP3 inflammasome. LC is considered an autoimmune disease, but the role of residual spike protein S and the NLRP3 inflammasome in LC suggests something more.

LC is responsible for untold pain and suffering. But a micronutrient approach might alleviate much of this.

1. Vitamin D, so frequently deficient, provides many benefits, especially for autoimmune disease[39]. For example, D3[85] (and tryptophan[83]) inhibit hyphal transition.
2. Ca:Mg is too high in the typical Western diet and too low in the typical Asian diet; Ca^{2+} may upregulate zonulin[86]. Mg^{2+} is a calcium antagonist, glutamate NMDA receptor blocker, vasodilator, antioxidant, and anti-inflammatory agent. It also opposes Candida immune evasion[87]. Elevated Ca^{2+} compromises mitochondrial function[88]. Magnesium impairs Candida albicans immune evasion[82]. Candida subsists on refined sugar and alcohol. Accordingly CO can elevate acetaldehyde (brain fog), which is degraded in mitochondria by an enzyme that requires magnesium as cofactor. Oxidative stress consumes antioxidants and compromises mitochondrial function. Mg^{2+} deficiency mimics symptoms of aging[89], as do GPCR antibodies[90] and TLR4 activation[91][92]
3. Alpha lipoic acid is a strong anti-oxidant, immuno-modulates autoimmune disease[93] and can arrest the growth of Candida albicans[94]
4. A triple play of prebiotic, probiotic, and postbiotic regimen addresses many modern maladies[95] (see figure 5). Butyrate (postbiotic) inhibits yeast growth[96]. D-mannose, a prebiotic and fiber substitute, supports intestinal barrier integrity (see figure 5). Our food should be our medicine and our medicine should be our food (Hippocrates). The “good bacteria,” Bifidobacterium and Lactobacillus (butyrate producers), suppress intestinal release of zonulin levels, whereas other primarily Gram-negative bacteria induce zonulin release[75].

5. Exercise reversibly improves the gut microbiome[97]. Walking is a man's best medicine (Hippocrates).

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