Commentary

Candida and Long Covid

Patrick Chambers[1]

1. Torrance Memorial Medical Center, Torrance, United States

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 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 that are analogous to gliadin/gluten (celiac disease antibodies) or that are GPCRs, e.g., Crohn's disease antibodies present only in eukaryotes, that may trigger antigliadin and anti-GPCR autoantibodies respectively. These latter include the Saccharomyces/Candida hyphal GPCR seen in CrD and the Candida hyphal Rrp9 muscarinic GPCR seen in POTS. These two autoantibody producing pathways both activate zonulin and may encompass the broad spectrum of autoimmune diseases seen in LC. IFN-γ, a marker for LC, can activate not only IDO but also zonulin.

The spike protein S on SARS CoV2 can attach to both the ACE2 receptor (required for tryptophan absorption) and Toll-like receptor4 (TLR4) bearing cells (endothelial cells and enterocytes). Spike protein S is persistent in LC and, as a ligand for TLR4, can also activate zonulin. S can also activate the nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing protein 3 (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.

Correspondence: papers@team.qeios.com — Qeios will forward to the authors

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1. Introduction

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

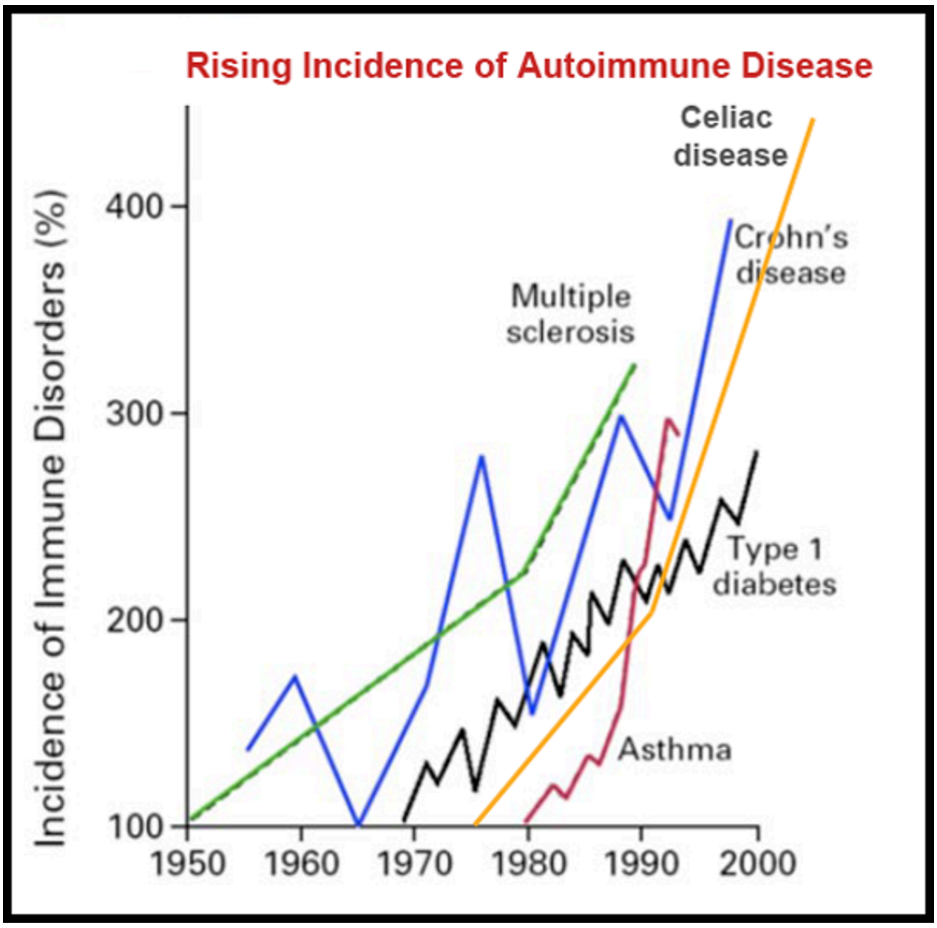

Figure 1. The incidence of autoimmune disease has exploded since the mid 1900s for both Crohn's disease (anti-GPCR antibody) and celiac disease (anti-gluten antibody). Source: Alessio Fasano, MD, Center for Celiac Research, Massachusetts General Hospital.

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 closer 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-CXCR3[4], anti-AT1Rs, anti-β2 adrenergic, 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 via ACE2
3. Most long haulers have persistent spike protein S (NIH says 65%)
4. Zonulin is a protease that targets PAR2, a GPCR that enhances intestinal and endothelial permeability, enabling hyphal invasion
5. Candida hyphae secrete a protease that activates the zonulin GPCR on enterocytes and endothelial cells[7]
6. PAR2 induced BBB permeability facilitates neuroinflammation[8]
7. Candida hyphae contain two highly immunogenic epitopes, gluten-like Hwp1 (hyphal wall protein) and the S. cerevisiae GPCR (GPCR epitopes are present only on eukaryotes).
8. These epitopes are linked to both anti-gluten/gliadin (CeD) and anti-S. cerevisiae (CrD) antibodies.
9. Rrp9 (GPCR) on hyphae may trigger anti-muscarinic Ab's reported in POTS
10. Antibodies to host AT1Rs, β2 adrenergic receptors[5], CXCR3[4], and muscarinic receptors characterize LC and some may be due to these hyphal GPCR and other epitopes.
11. Anti-CXCR3 antibodies (LC) compromise T-cell function, mediating autoimmunity and cancer[9] and dementia.
12. The NLRP3 inflammasome links Candida and LC to dementia, cancer, autoimmunity, and obesity via candidalysin and the spike protein S respectively (see figures 2,3)

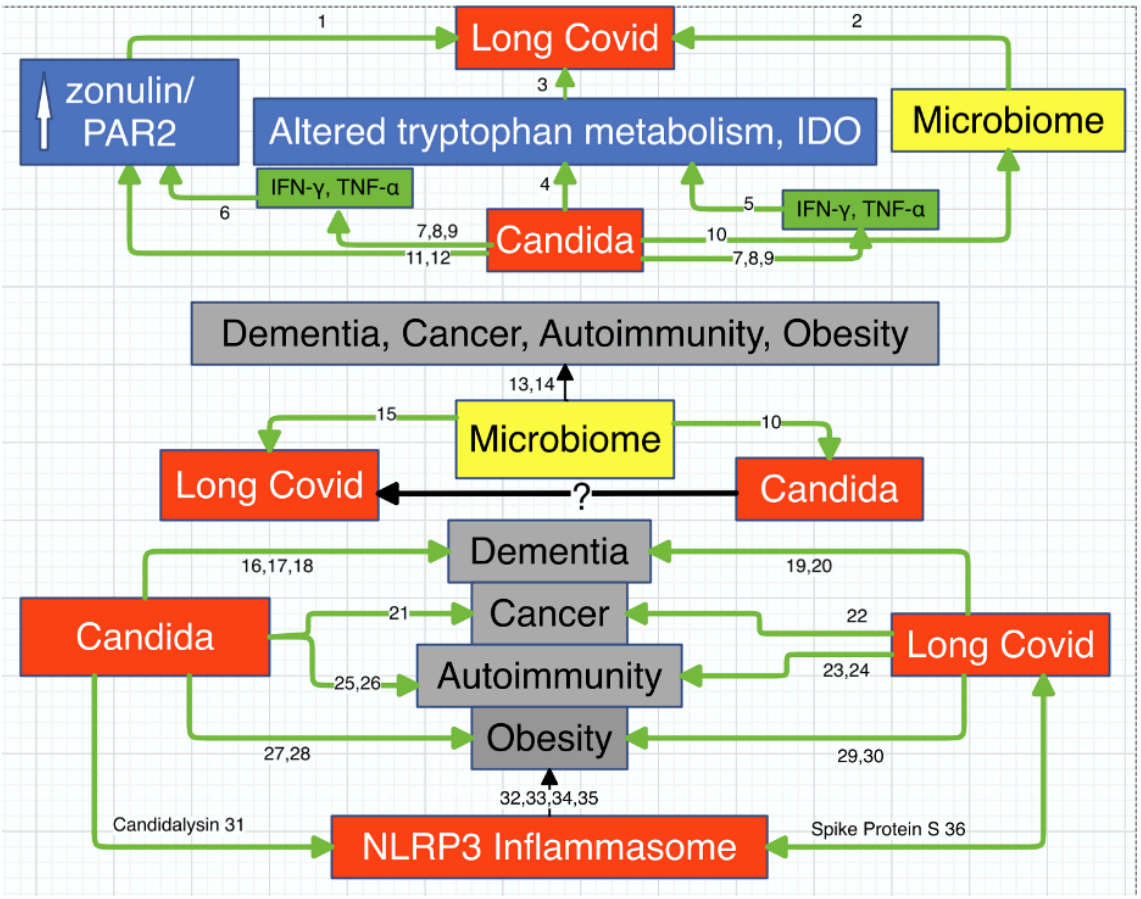

Figure 2. Shown are three related diagrams. PAR2 is protease activated receptor. IDO is indoleamine dioxygenase. Numbers are references (for figure 2). The role of Candida in these four disease may be anti-GPCR antibody mediated and/or candidalysin related thru activation of the NLRP3 inflammasome.

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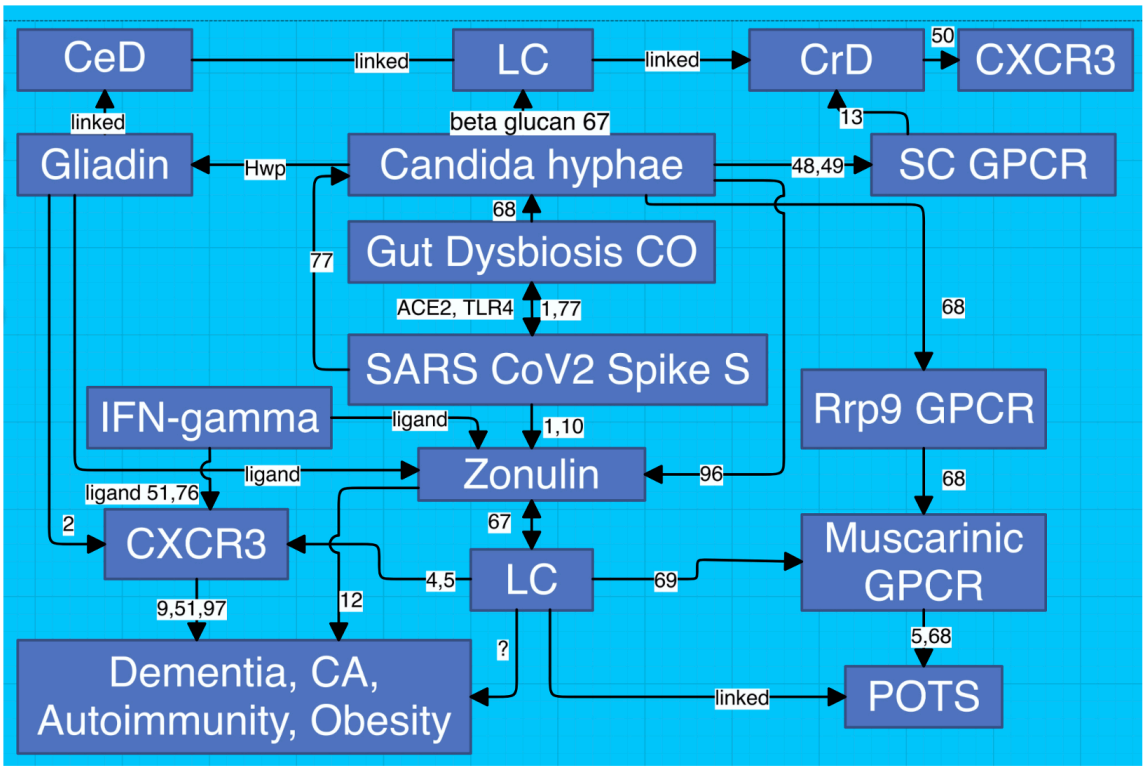

Figure 3. TLR is toll-like receptor on enterocytes and endothelial cells. CXCR3 is a chemokine receptor on T cells. SC is Saccharomyces cerevisiae. Numbers are references.

2. Zonulin and Increased Permeability

Zonulin is the only known physiologic modulator of intercellular TJs[10]. Activated PAR2 and zonulin receptors increase intestinal and endothelial permeability[11]

A. Autoimmune Disease

Zonulin release is linked to autoimmune diseases, both those associated with gluten sensitivity (anti-gliadin antibodies), e.g., celiac disease and ankylosing spondylitis[12] and those associated with anti-Saccharomyces cerevisiae antibodies (ASCAs)[13], e.g., Crohn's disease and probably IgA vasculitis/IgA nephropathy (anti-endothelins, GPCRs)[11][14]. All are reported in LC. ASCAs are anti-GPCRs[15] and are elevated in inflammatory bowel disease (IBD), especially Crohn's disease, but not in celiac disease[13]. Celiac patients have higher IgA anti-gliadin antibodies than controls or IBD patients[16]. Both autoantibody types trigger an increase in zonulin

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B. Dementia

Brain endothelial cells express zonulin receptors and exposure of BBB to zonulin leads to increased permeability[8]. IL-17, biomarker for autoimmune disease[17] and IFN-γ, biomarker for LC[18], also elevate zonulin. Zonulin is elevated in AD[19] and PD[20][21]

C. Cancer

Elevated zonulin has been linked to numerous cancers, including colon[22][23], breast, lung, ovary, pancreas, brain (gliomas)[12], and liver cancers[24].

D. Other Diseases

Zonulin is directly linked to other diseases, e.g., overweight and obesity, at least in the young[25][26], multiple sclerosis (MS), schizophrenia[24][27], autism[24][28] and arthritis[29]

3. Celiac Disease and Crohn's Disease

A. Celiac Disease

Zonulin is a biomarker for celiac disease[30], a well described autoimmune disease encountered in LC and linked to antigliadin antibodies. These have high sensitivity and specificity for celiac disease[31]. Anti-gliadin antibodies are present in 5-12% of the general population. They are also encountered in rheumatoid arthritis (RA)[32], SLE, Sjögren's syndrome[33], sarcoidosis[34][35], T1DM[36], MS[37], psoriasis, Grave's disease[38], and Hashimoto's thyroiditis[39]. Others include systemic sclerosis[40] and autoimmune hepatitis[41]. However, there is considerable overlap, as GPCR autoantibodies and anti-gliadin antibodies can be concomitant, e.g., RA, SLE, and Graves' disease[37][38][39]. All are seen in LC. Many skin diseases expressing anti-GPCR antibodies are linked to Crohn's disease and reported in LC. These include psoriasis[42], alopecia areata[43], and vitiligo[44]. GPCR autoantibodies suppress hair follicle stem cells[45] and growth of melanocytes[46] and a GPCR is vital in the regulation of skin proliferation[47]. CO is associated with alopecia, vitiligo and psoriasis.

B. Crohn's Disease

ASCAs are biomarkers for IBD, especially Crohn's disease. They are anti-GPCR antibodies[13] and can also be generated by Candida albicans[48][49]. CXCR3 is another GPCR with autoantibodies seen in both Crohn's disease[50] and LC[4]. Crohn's disease, increased in LC and linked to ASCAs (anti-GPCRs), is associated with greater risks for colon cancer, liver cancer, lymphoma, melanoma, squamous cell skin cancer, and cancers of lung and bladder. CXCR3s on T cells help suppress cancer[51]. Anti-GPCR antibodies in LC may overshadow disease due to anti-gliadin antibodies (see figure 4). In turn anti-GPCR antibodies in LC may be overshadowed by candidalysin released by hyphae that upregulates NLRP3 inflammasome[52] and that plays a key role in many autoimmune diseases, dementia, cancer, and obesity.

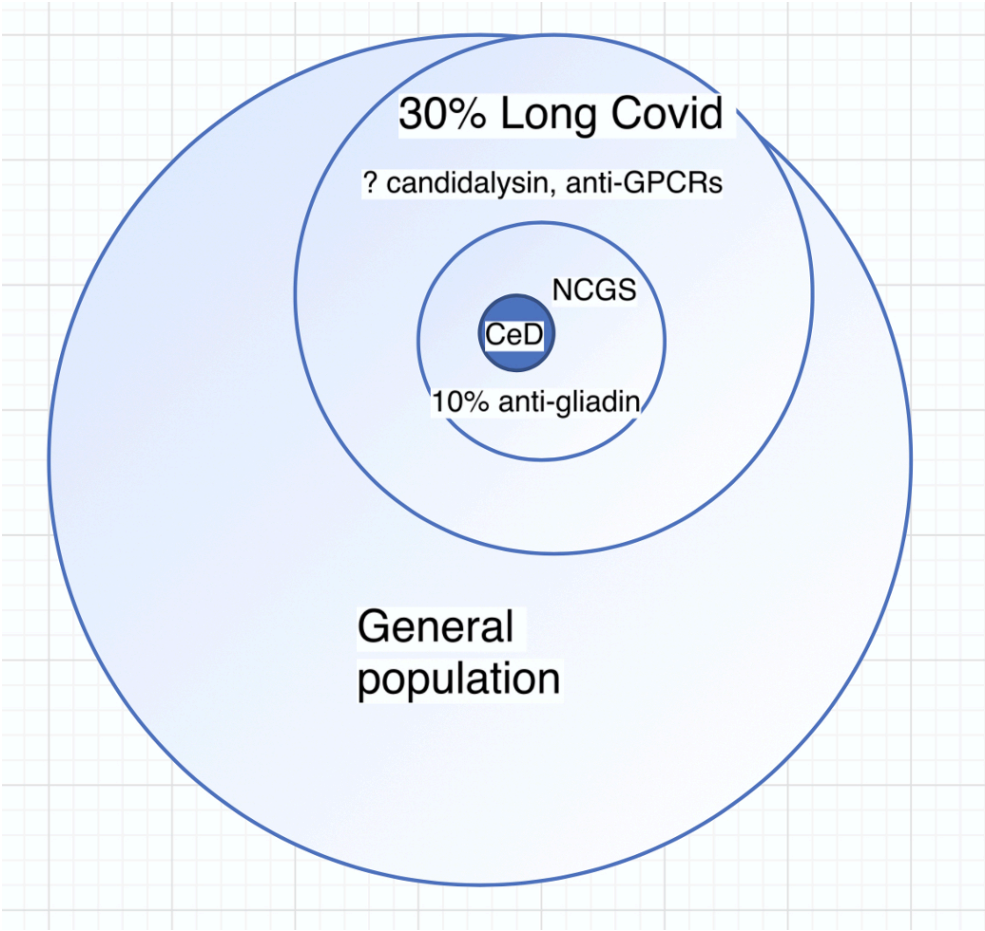

Figure 4. The blue circle represents the 2% incidence of celiac disease. The 10% circle represents the approximate incidence of gluten antibodies in the general population. Thus, non-celiac gluten sensitive (NCGS) disease is about 8%. Although there is significant overlap between NCGS and GPCR mediated autoimmune disease, the majority of LC may be linked to anti-GPCRs and/or candidalysin. Both celiac disease and Crohn's disease are more common in females.

4. Candida

A. Gender

Females with autoimmune disease outnumber males (4:1). This may be due to their robust production of interferons, especially IFN-γ, and the estrogen enabled immune evasion of Candida. One study[52] 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[53] and IgA vasculitis has been reported in LC[54] and possibly in Covid toes[55]. 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[56] and 2:1 for IgA vasculitis[57]. 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[58]. Autoantibodies targeting GPCRs and RAS-related molecules associated with Covid-19 severity, seen primarily in males[4], is directly related to TGF-β[59], which increases endothelin. Estrogen depresses endothelin synthesis[60], which may provide protection against autoimmune vasculitides. SARS CoV2 in females may be more autoimmune and IFN-γ related, while in males it may be more vascular/connective tissue and TGF-β related (thrombosis and fibrosis). This may hypothetically put female long haulers at slightly greater risk for dementia and male long haulers at slightly greater risk for cancer.

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 analogous to the gluten protein gliadin (celiac disease) was first reported in 2015[61][62]

Indeed celiac disease might serve as a partial proxy for CO and invasion. Candida hyphae secrete aspartyl protease[63] that activates surface PAR2, an ubiquitous receptor on host cells. It is also known as coagulation factor II (thrombin) receptor-like 1 (F2RL1)[7]. PAR2 is a GPCR targeted by zonulin that, when activated, increases permeability and may jointly mediate associated autoimmunity by enabling an invasive pathway for exposure to CXCR3 bearing T-cells (see figure 3). Furthermore, GPCR laden hyphae may via this same zonulin enabled pathway induce a spectrum of autoimmune diseases. This interpretation is supported by the concomitant surge in both anti-GPCR mediated autoimmunity[3] (Crohn's disease) and Hwp1 linked celiac disease[64] (see figure 3).

Candidemia can also trigger ASCAs[65], tightly linked to Crohn's disease[13]. Consequently anti-Hwp1 antibodies and ASCAs link Candida to both celiac disease[47] and Crohn's disease. 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[65][66]. Linkage between zonulin and yeast overgrowth[67] provides additional support for an etiologic Candida-LC coupling. Rrp9, a muscarinic cholinergic epitope on Candida hyphae, resembles human M1 muscarinic GPCRs[68]. Hyphae bearing this GPCR upon invasion may elicit an autoimmune response indistinguishable from that seen in 87% of POTS patients[68], specifically the M1 muscarinic receptor autoantibody in LC[69]. This hyphal GPCR reportedly signals yeast to hyphal transition, suggesting that orthostatic hypotension may represent an early symptom of hyphal invasion. However, a causative Candida connection to the autoantibodies in LC/autoimmune disease remains theoretical.

5. LC and Autoimmune diseases

A. The Candida Connection

Zonulin and β-glucan, a marker for translocation of fungal products into circulation, are elevated in individuals with long Covid[70]. Fungal but not bacterial translocation was observed during LC[71]. In mice amyloid beta is a marker for CNS Candida hyphal forms[72]. Hippocampal amyloid beta is tightly linked to Alzheimer's disease. This Candida-LC coupling is further supported by the generation of anti-GPCRs in animals infected with SARS CoV2[73]. GPCRs are expressed only in eukaryotes. Although Covid-19 has accelerated cognitive decline, the incidence of AD and PD in long haulers over the long term remains to be seen.

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)[74] 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[75].

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[76]. 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 5).

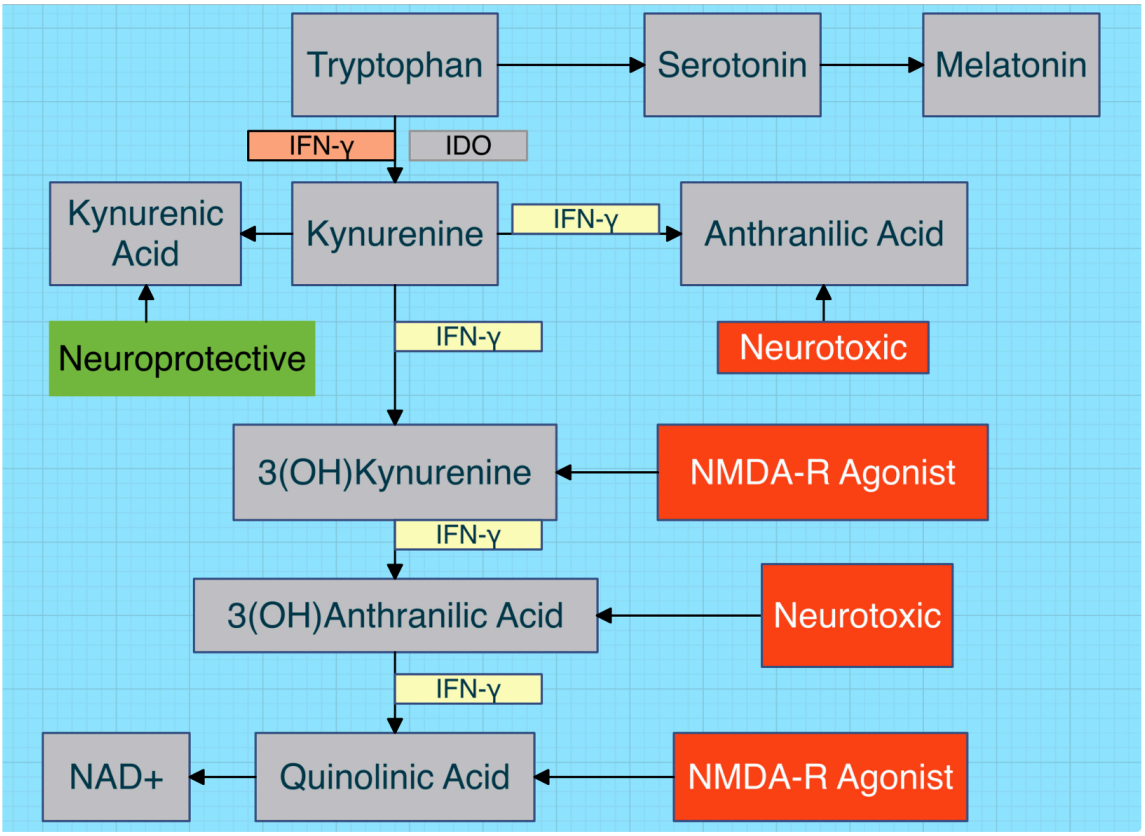

Figure 5. ATM characterizes LC (autoimmunity), cancer, dementia, obesity, and many other diseases. Covid-19 aggravates this, as intestinal ACE2 receptor bearing cells are required for tryptophan absorption.

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[77]. Cell death of tryptophan rich cells after SARS-CoV2 invasion might explain the reported increased levels of tryptophan and its metabolites in Covid-19[78]. 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)[79][80].

IDO in a healthy individual is highest, when Candida is a colonist. Any further increase in IDO risks mucosal damage, as tryptophan (fungicidal) 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[81]. Covid-19 severity is directly related to TGF-β[59]. TGF-β suppresses IFN-γ[82][83]. Low IFN-γ translates to low IDO activity and elevated tryptophan. Since tryptophan inhibits Candida hyphal formation[84], 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[18] and the predilection of LC for females also supports this view. The slight predilection of autoimmune disease and dementia for females and the slight predilection of cancer for males supports this view. 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[85] and TGF-β (transforming growth factor), which are reciprocals and counterbalance each other[82][83]. 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[29] (see figure 6).

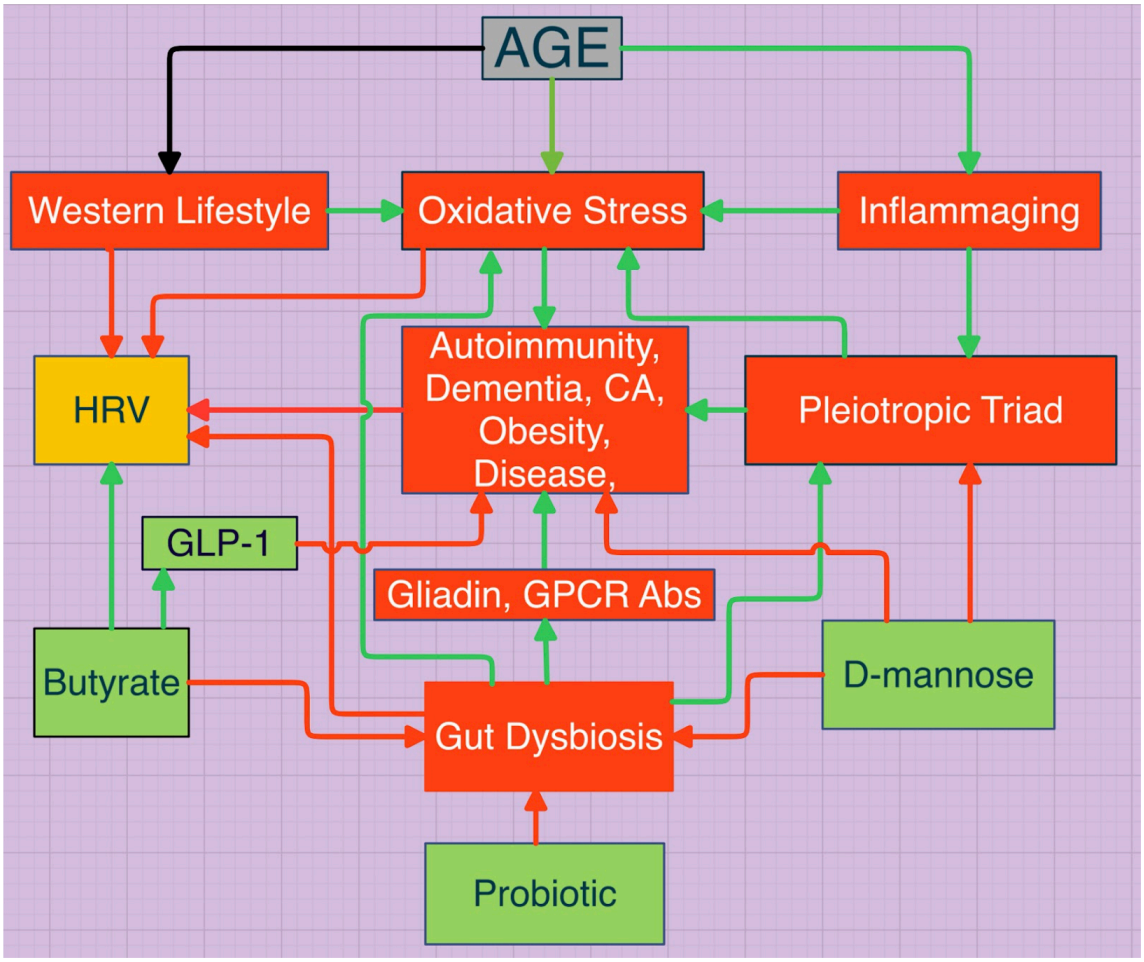

Figure 6. A prebiotic, probiotic, postbiotic approach may slow the inevitable age related decline in lifespan and healthspan, as reflected by decreasing heart rate variability (HRV). The pleiotropic triad is IL1-β, TNF-α, and IL-6.

7. 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, S cerevisiae GPCR epitope and CrD) linked to LC. The hyphal gliadin epitope is also a ligand for the CXCR3 receptor on T cells, linked to cancer, dementia, and autoimmunity.

Candida yeast forms can synthesize IDO to regulate host tryptophan, an anti-fungal. The increased K/T (see figure 5) promotes mast cell activation. IFN-gamma and TLR4 also upregulate IDO. Candida hyphae can also activate MCP-II (see figure 3), which will further upregulate mast cell activity. The Rrp9 hyphal epitope may trigger host muscarinic cholinergic receptor autoantibodies that are present in most with POTS.

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. Beta glucan is also associated with long Covid and Candida. They are also independently associated with dementia, cancer, autoimmunity and obesity. 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 7) - anti-gliadin antibodies, anti-GPCR antibodies (ASCAs, Rrp9/muscarinic cholinergic antibodies), beta-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 difficult to dismiss. Intersection with the gut microbiome underscore its overarching role in our health, as Hippocrates surmised nearly 2500 year ago, “all disease begins in the gut.”

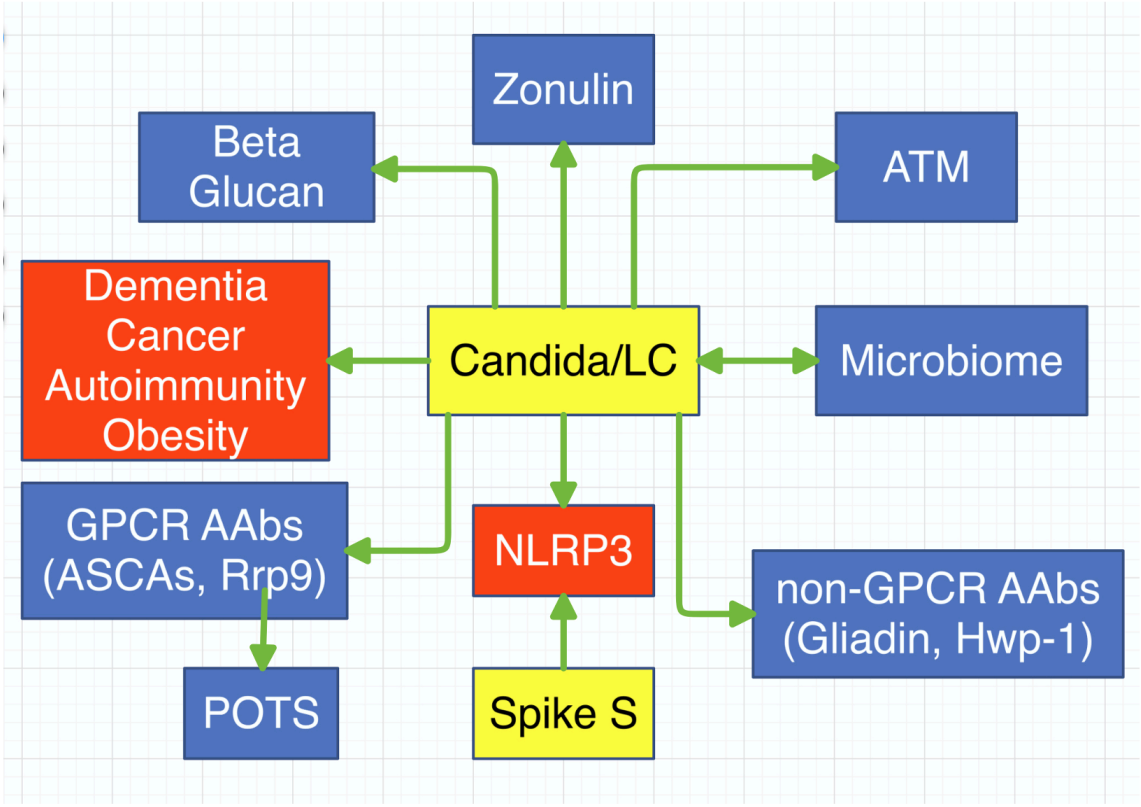

Figure 7. Candida and LC are each independently linked in many ways.

8. 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 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[40]. For example, D3[86] (and tryptophan[84]) 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[87]. Mg^{2+} is a calcium antagonist, glutamate NMDA receptor blocker, vasodilator, antioxidant, and anti-inflammatory agent. It also opposes Candida immune evasion[88]. Elevated Ca^{2+} compromises mitochondrial function[89]. Magnesium impairs Candida albicans immune evasion[83]. 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[90], as do GPCR antibodies[91] and TLR4 activation[92][93]
3. Alpha lipoic acid is a strong anti-oxidant, immuno-modulates autoimmune disease[94] and can arrest the growth of Candida albicans[95]
4. A triple play of prebiotic, probiotic, and postbiotic regimen addresses many modern maladies[96] (see figure 5). Butyrate (postbiotic) inhibits yeast growth[97]. 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[76].
5. Exercise reversibly improves the gut microbiome[98]. Walking is a man's best medicine (Hippocrates).

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