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Commentary

Candida and Long Covid: Mannan Not from Heaven

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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 can synthesize its own IDO, altering tryptophan metabolism (ATM). Zonulin, a circulating protein that increases intestinal and endothelial permeability, has emerged as a central player. 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 anti-Gq coupled GPCR auto-antibodies linked to their lectin binding domain respectively. Hyphal mannan may induce auto-antibodies to AT1Rs, α1-ARs, mAChRs, and β2-ARs, prominent in LC, and regulate T cell receptors (TCRs) and regulatory B cell function, compromised in not only LC (vitiligo, psoriasis, alopecia) but also SLE, RA, and many other autoimmune diseases. All are Gq coupled GPCRs. 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. Candidalysin causes hypercitrullination, instrumental in creating ACPAs (anti-citrullinated peptide antibodies) linked to LC, MCAS (mast cell activation syndrome), HSD (hypermobility spectrum disorder), and APS (antiphospholipid syndrome). 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.

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1. Introduction

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

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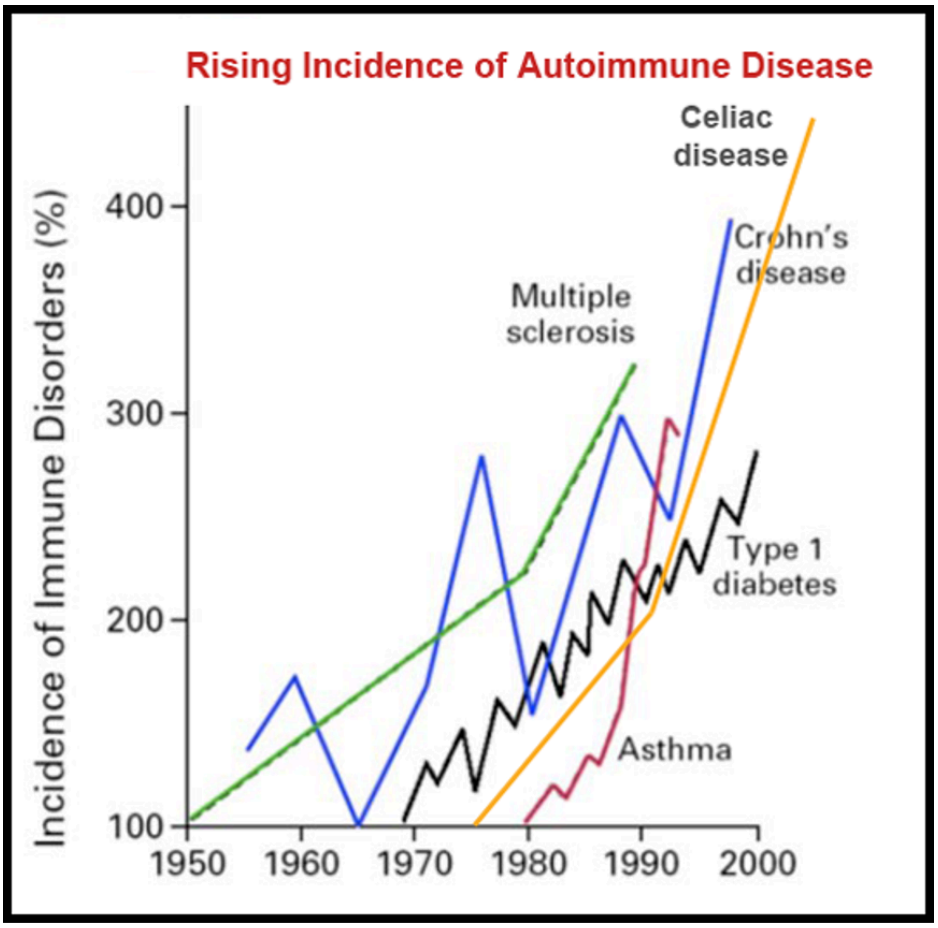

Figure 1. The incidence of autoimmune disease has exploded since the mid 1900s for both CrD (anti-mannan antibody) and CeD (anti-gluten antibody). Source: Alessio Fasano, MD, Center for Celiac Research, Massachusetts General Hospital.

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-Gq coupled 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-Gq coupled GPCRs.

Hypothetical Model (see figures 2,3)

1. Commensal Candida overgrowth (CO) with transition to pathogenic hyphae can invade and link their mannan to lectin receptors associated with Gq coupled GPCRs
2. Antibodies to host Gq coupled GPCRs, including AT1Rs, α1-ARs, β2 ARs[5], and mAChRs (muscarinic cholinergic receptors) characterize LC

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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[6]
6. Zonulin induced BBB permeability facilitates neuroinflammation[7]
7. Persistent spike protein S binds to TLR4[8] on intestinal and endothelial cells, activating zonulin[1] and the NLRP3 inflammasome
8. Candida hyphae contain two highly immunogenic epitopes, gluten-like Hwp1 (hyphal wall protein) and mannan (glyan shield)
9. These epitopes are linked to both anti-gluten/gliadin (CeD) and anti-mannan (CrD) antibodies.
10. The NLRP3 inflammasome[9] links Candida and LC to dementia, cancer, autoimmunity, and obesity via candidalysin and the spike protein S respectively (see figure 2)

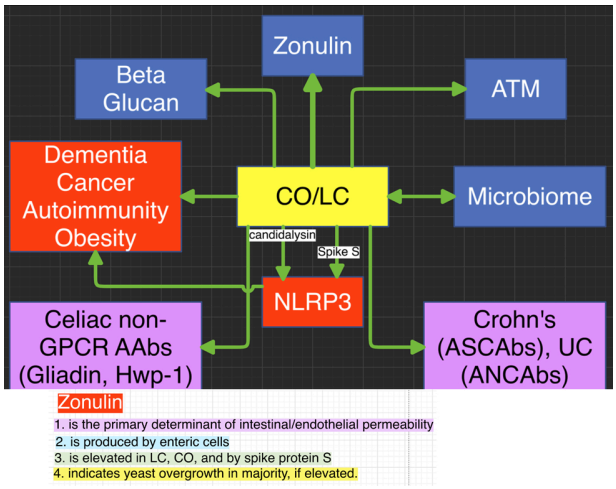

Figure 2. Candida and Spike S are co-conspirators in not only LC but also activation of the NLRP3 inflammasome and increased risk for dementia, cancer, autoimmunity, and obesity. Long Covid is more than just an autoimmune disease.

2. Zonulin and Increased Permeability

Zonulin is the only known physiologic modulator of intercellular TJs[10]. Activated 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., CeD and ankylosing spondylitis[12] and those associated with anti-Saccharomyces cerevisiae antibodies (ASCAs, anti-mannans)[13], e.g., CrD and probably IgA vasculitis/IgA nephropathy (anti-endothelins, Gq coupled GPCRs)[11][14]. All are reported in LC. ASCAs are elevated in inflammatory bowel disease (IBD), especially CrD[15]. ASCAbs are anti-mannan. Hyphal mannan is very immunogenic and mannan binding lectin receptors are potentiated by Gq coupled GPCRs, which include mAChRs (M1,2,3,5), vasopressin receptors, endothelin receptors, thyrotropin-releasing hormone receptors, gonadotropin-releasing hormone receptors, membrane estrogen receptors, chemotactic cytokine receptors (CCRs), α1ARs, β2-ARs, and AT1Rs[16].

B. Dementia, Cancer, Other Diseases

Brain endothelial cells express zonulin receptors and exposure of BBB to zonulin leads to increased permeability[7]. 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]. Elevated zonulin has been linked to numerous cancers, including colon[22][23], breast, lung, ovary, pancreas, brain (gliomas)[12], and liver cancers[24]. Zonulin is directly linked to other diseases, e.g., overweight and obesity[24], multiple sclerosis (MS), schizophrenia[24][25], autism[24][26] and arthritis[27].

3. CeD and CrD

A. Celiac Disease

Zonulin is a biomarker for CeD[28]. Covid-19 may, via CO induced zonulin and hyphal gliadin epitopes, increase the risk of CeD[29]. 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. 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]. Gq coupled GPCR autoantibodies to CCRs are reported in alopecia[44], vitiligo[45], and psoriasis[46]. All are encountered in CO.

B. Crohn's Disease and Ulcerative Colitis

ASCAs and ANCAs (anti-neutrophil cytoplasmic antibodies) are biomarkers for IBD. Both require Gq coupled GPCRs and can be generated by Candida albicans[47]. 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 ANCA aka myeloperoxidase (MPO) ANCA) are usually positive in UC but negative in CrD. A recent (2024) report favored Candida in the pathogenesis of UC[48]. Signaling by all CCRs on T cells is mediated by Gq coupled GPCRs[49]. Many CCR autoantibodies, especially ANCA associated vasculitis, are reported in LC[50]. Might the multitude of CCR 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.

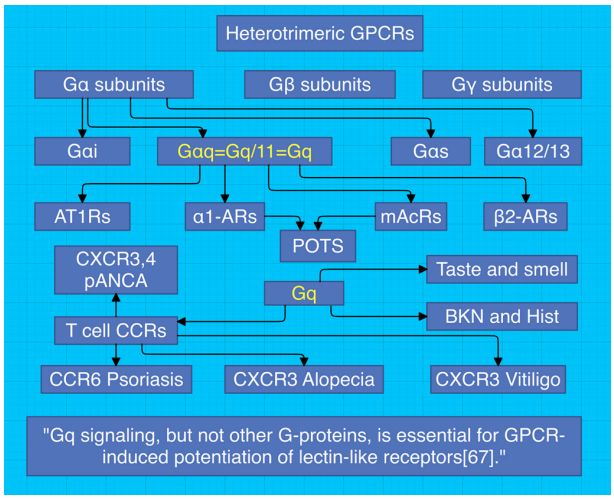

Figure 3. Gq coupled GPCRs mediate all CCR signals from T cells. Antibodies to Gq coupled GPCRs, induced by lectin bound hyphal mannans, may represent the pathway to LC, as the lectin receptor domain may be part of the Gq coupled GPCR platform. ASCAbs are anti-Saccharomyces cerevisiae antibodies, linked 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

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[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 Gq coupled 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

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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 some autoimmune vasculitides. ANCA associated vasculitis is linked with CCR autoantibodies (CXCR3,4), 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 fibrosis and cancer (see figure 4).

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[61][62]. This links Candida and CeD and suggests that CO compromises the efficacy of a gluten free diet. Candida hyphae also secrete aspartyl protease[63] that activates surface PAR2, aka thrombin[6], 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[64]. 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-ARs (both Gq coupled GPCRs). Subsequent exposure to their endogenous ligands (angiotensin II and catecholamines),[65] was ineffective. Gq is the major G protein activated by the AT1 receptor[66]. Gq signaling, but not other G-proteins, is essential for GPCR-induced potentiation of lectin-like receptors[67]. Gq is also the major G protein activated by the α1-adrenergic receptor[68]. Although β2-AR activity is generally tightly linked to Gs-coupled receptors, in the lungs β2-AR activity is linked to Gq-coupled receptors[69]. mAChRs, which are almost exclusively parasympathetic in function, interact with Gq-type G proteins[70]. Autoantibodies to either mAChRs or β2-ARs are seen in 75% of those with significant orthostatic hypotension[71], 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. CCR signaling also involves Gq coupled GPCRs. Antibodies to CXCR3, a CCR/TCR, have also been reported in LC (see figure 3).

Once endothelial cells are exposed to Candida hyphal mannans, Gq type GPCRs, e.g., 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 autoimmune and may also sterically hinder the receptor. 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 (AT1Rs) and for function of some ACTH receptors (MC4R)[72]. However, a causative Candida connection to the autoantibodies in LC/autoimmune disease remains theoretical.

5. Candidalysin and MCAS, POTS, HSD, APS

Hyphal mannan isn't the only contribution to autoimmunity that Candida projects. In addition to its pro-inflammatory role candidalysin also induces hypercitrullination and NETosis[73], a prominent feature of Covid-19 and LC[74]. A certain amount of citrullination is tolerated, but hypercitrullination may exceed the threshold and initiate an ACPA response[75]. ACPAs are tightly linked to RA, exacerbated by Covid-19 and LC[76]. ACPAs are linked to LC[77] and to zonulin levels[78]. Hypercitrullination and ACPAs are linked to periodontitis[79], as is Candida[80]. ACPAs are increased in HSD[81]. POTS and HSD are linked[82]. Interestingly

POTS typically is associated with anxiety induced elevated cortisol. Elevated cortisol is also reported in vasovagal syncope and presumed to be anxiety induced[83]. HSD typically manifests higher baseline cortisol with elevated catecholamines and histamine[84], while cortisol in LC is usually low. Might those with HSD and LC/POTS explain this discrepant elevation of cortisol in those "long haulers" with POTS?

Ten to 25% of Americans have hypermobile joints[85]. Joint Hypermobility Syndromes are present in > 50% of POTS patients[86]. Might hyperadrenergic POTS, characterized by elevated catecholamines and mast cells, be due to candidalysin, while neuropathic POTS, characterized by alpha1-AR and AT1R antibodies, be due to mannan[87]?

GI problems are prominent in HSD[88]. Fibromyalgia is commonly found in people with joint hypermobility, with prevalence estimates ranging from 24% to 86%. Hypermobility was first noted to be associated with anxiety in 1988, with ADHD by 2000, and with ASD (autism spectrum disorder) and autonomic dysfunction by 2014[89]. Candida overgrowth has been implicated in the pathogenesis of FM, ADHD, and ASD.

ACPAs activate mast cells, which are associated with RA, spondyloarthritis, psoriatic arthritis, and HSD, all seen in LC[90][91]. Candida hyphae can also activate mast cells[92]. MCAS and HSD are also linked[93]. MCAS is prevalent in LC[94][95]. MCAS is a frequent finding in POTS and HSD[96]. Almost 80% of those with LC have POTS[97]. Candida overgrowth is an emerging suspect in the pathogenesis of Covid-19 and LC[98]. This indirectly links CO and POTS. POTS and APS are also linked[99]. Citrullination may play a role in the pathogenesis of APS[100]. Might candidalysin induced ACPAs be involved? These linkages are provocative but do not constitute cause and effect.

6. LC and Autoimmune diseases

A. The Candida Connection

Zonulin and β-glucan, a marker for translocation of fungal products from intestinal lumen to vascular lumen, are elevated in individuals with long Covid. Fungal but not bacterial translocation was observed during LC[101]. Candidalysin, a toxin secreted by hyphae, damages intestinal mucosa and inhibits intestinal bacterial competition[102]. 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.

B. Spike S and TLR4

The spike protein (viral or vaccine) of SARS CoV2 activates TLR4. Activation of TLR4 on enteric and endothelial cells releases zonulin, enhancing their permeability[1]. 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)[103] via antibodies induced by translocated Candida hyphae. The CNS is rich in EGFRs, which are predominantly Gq coupled GPCR dependent. 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/TLR4 related or Candida hyphal invasion/Gq coupled GPCR related[104].

7. IFN-γ and Tryptophan

Females are robust producers of interferon, especially IFN-γ. Candida elicits robust production of this cytokine, a ligand for zonulin receptors, according to a recent study[105]. Upregulated IFN-γ increases intestinal and endothelial permeability[7].

But Candida and IFN-γ do much more than this. Altered tryptophan metabolism is a characteristic feature of LC. IFN-γ drives IDO and the pivot of tryptophan metabolism from its 5% allocation for the serotonin/melatonin pathway to nearly 100% for the kynurenine pathway. This pivot also shunts tryptophan from the indole pathway to the kynurenine pathway, elevateing several neurotoxic metabolites (see figure 4).

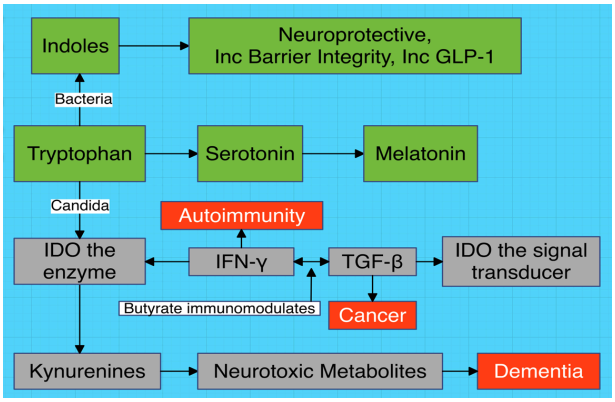

Figure 4. ATM characterizes LC (autoimmunity), cancer, dementia, obesity, and many other diseases. IFN-γ and TGF-β counterbalance each other. TGF-β oversees tolerogenesis - too much and cancer antigens are tolerated, too little and host antigens are not. Candida can release its own IDO.

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[106]. The essential, neutral amino acid methionine also requires $B^{\{m/0/\}}AT$. This suggests that those with at least one MTHFR (methylenetetrahydrofolate reductase) variant allele may be especially adversely affected by LC. Caucasians are more likely than not to have at least one variant allele.

IDO is more than an enzyme. It can function as an intracellular signal transducer[107][108][109], which TGF-beta can up regulate (see figure 4). 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 drives IDO and any increase, e.g., SARS CoV2, may initiate such damage, as IFN-γ upregulates IDO the enzyme[110]. Covid-19 severity is directly related to TGF-β[59]. TGF-β suppresses IFN-γ[111][112]. Low IFN-γ translates to low IDO activity and elevated tryptophan. Since tryptophan inhibits Candida hyphal formation and Candida synthesis of IDO[113], 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[59].

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. 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[114] and TGF-β (transforming growth factor), which are reciprocals and counterbalance each other[111][112]. 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 5).

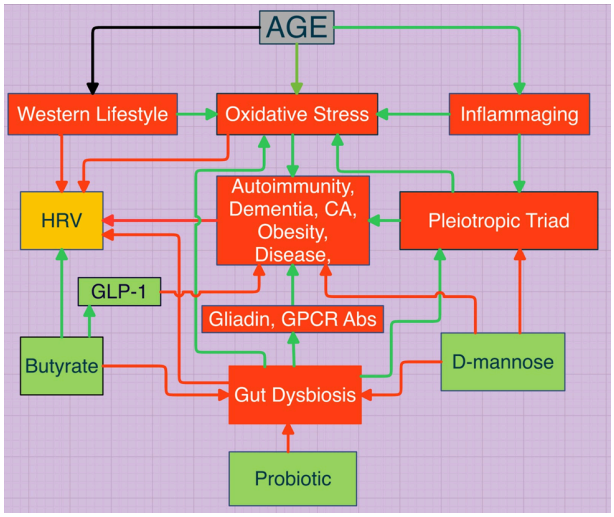

Figure 5. A prebiotic, probiotic, postbiotic approach may slow the inevitable age related decline in lifespan and healthspan, as reflected by decreasing heart rate variability (HRV). The pleiotropic triad is IL1-β, TNF-α, and IL-6.

8. 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. Candida hyphal mannan epitopes 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 GPCRs[67] and induce autoantibodies to many Gq coupled GPCRs, including AT1Rs, α1-ARs, mAChRs, β2-ARs. Gq coupled GPCRs mediate TCR[49],[115] (including CCRs) as well.

CCR abnormalities are reported in SLE (CXCR3,4,5) and RA (CXCR3,4,7). T cell surveillance normally suppresses viral reactivation, e.g., EBV, via TCRs. But Gq coupled GPCRs regulate TCRs/T cell immune response[115] and anti-Gq coupled GPCRs might compromise surveillance.

Candida yeast forms can synthesize IDO to regulate host tryptophan, which inhibits the yeast to hyphae transition. IFN-γ and TLR4 also upregulate IDO. 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. Candida hyphae can create not only an inflammaging route but also an autoimmune route to dementia, cancer, and obesity. Candidalysin can create another autoimmune route that links HSD, MCAS, APS, and LC via ACPAs.

Mutual associations (see figure 2) - 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 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.”

9. 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.

Such opportunities are not limited to immunosuppression.

Deterioration of the modern diet opens that door of opportunity. The Candida connection to LC and the listed diseases may be anti-Gq coupled GPCR antibody mediated and candidalysin related thru activation of the NLRP3 inflammasome and hypercitrullination. 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[40]. For example, D3[116] (and tryptophan[113]) inhibits 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[117]. Mg^{2+} is a calcium antagonist, glutamate NMDA receptor blocker, vasodilator, antioxidant, and anti-inflammatory agent. It also opposes Candida immune evasion[118]. Elevated Ca^{2+} compromises mitochondrial function[119]. 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[120], as do GPCR antibodies[121] and TLR4 activation[122][123]
3. Alpha lipoic acid is a strong anti-oxidant, immuno-modulates autoimmune disease[124] and can arrest the growth of Candida albicans[125]
4. A triple play of prebiotic, probiotic, and postbiotic regimen addresses many modern maladies[126] (see figure 5). Butyrate (postbiotic) inhibits yeast growth[127]. 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[105].
5. Exercise reversibly improves the gut microbiome[128]. Walking is a man's best medicine (Hippocrates).

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