Open Peer Review on Qeios

Candida and Long Covid: Mannan Not from Heaven

Patrick Chambers[1]

1 Torrance Memorial Medical Center

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

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.

Keywords: zonulin, hyphae, G-protein coupled receptor (GPCR), chemokine, mannan.

1. Introduction

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

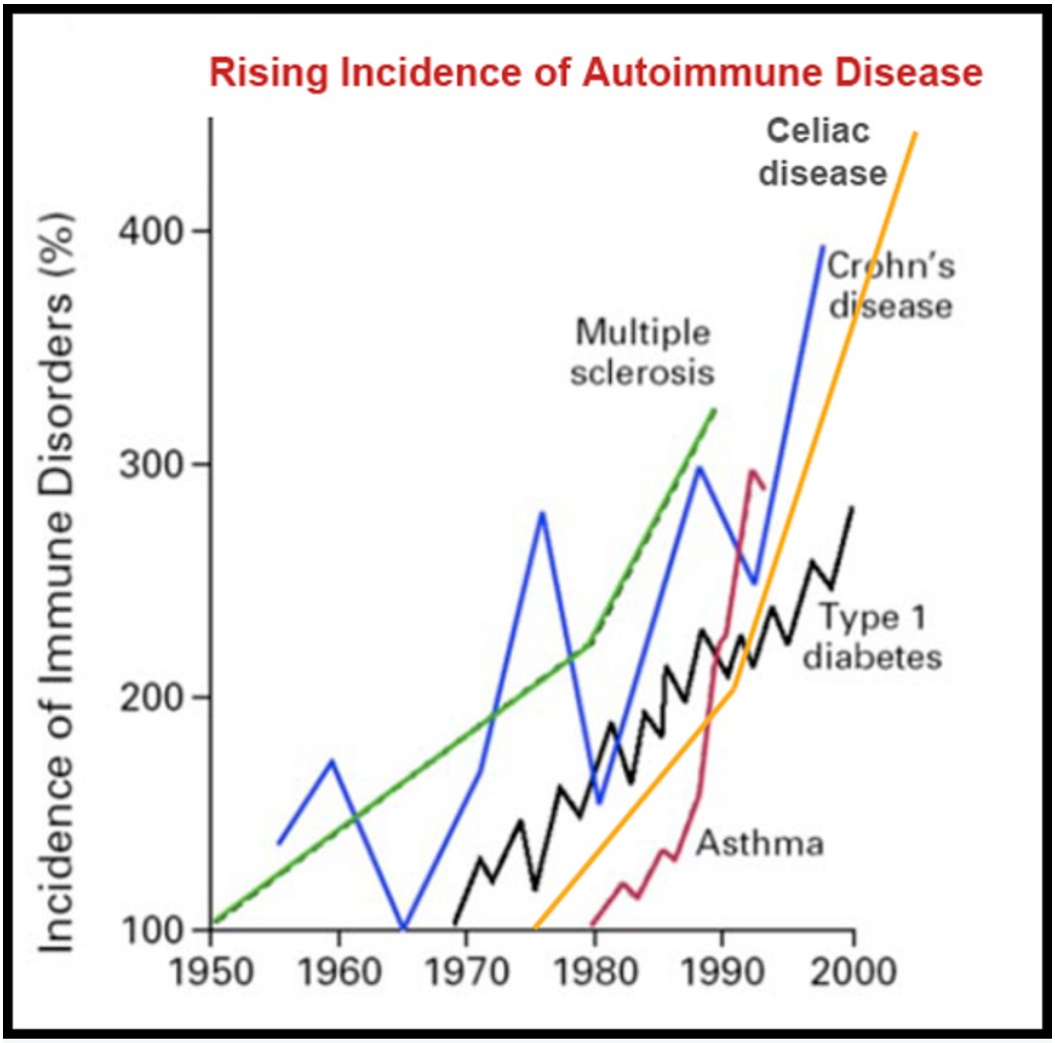

Figure 1. The incidence of autoimmune disease has exploded since the mid 1900s for both CrD (anti-mannan antibody) and CeD (anti-gluten antibody). Source: Alessio Fasano, MD, Center for Celiac Research, Massachusetts General Hospital.

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-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
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)

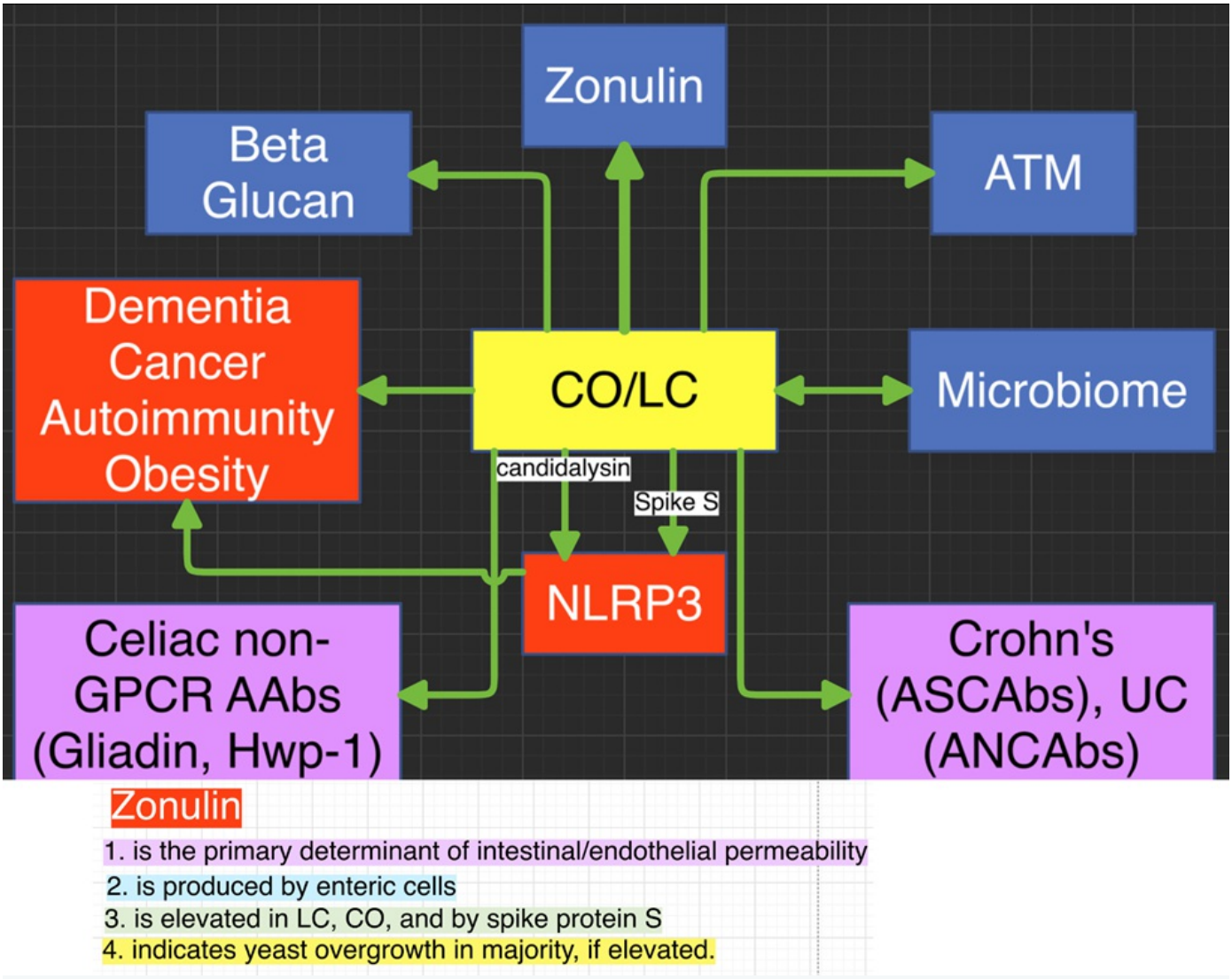

Figure 2. Candida and Spike S are co-conspirators in not only LC but also activation of the NLRP3 inflammasome and increased risk for dementia, cancer, autoimmunity, and obesity. Long Covid is more than just an autoimmune disease.

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.

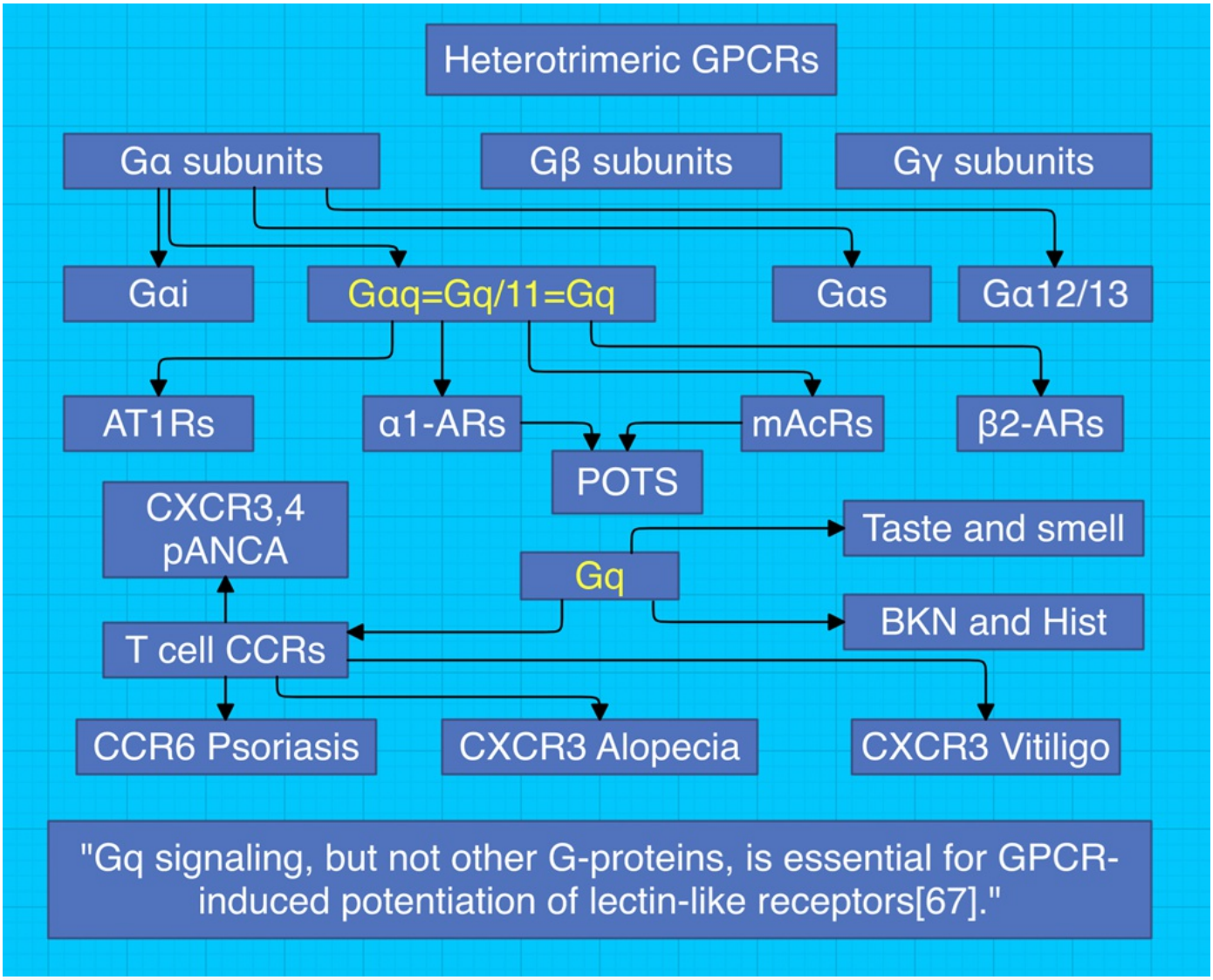

Figure 3. Gq coupled GPCRs mediate all CCR signals from T cells. Antibodies to Gq coupled GPCRs, induced by lectin bound hyphal mannans, may represent the pathway to LC, as the lectin receptor domain may be part of the Gq coupled GPCR platform. ASCAbs are anti-Saccharomyces cerevisiae antibodies, linked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

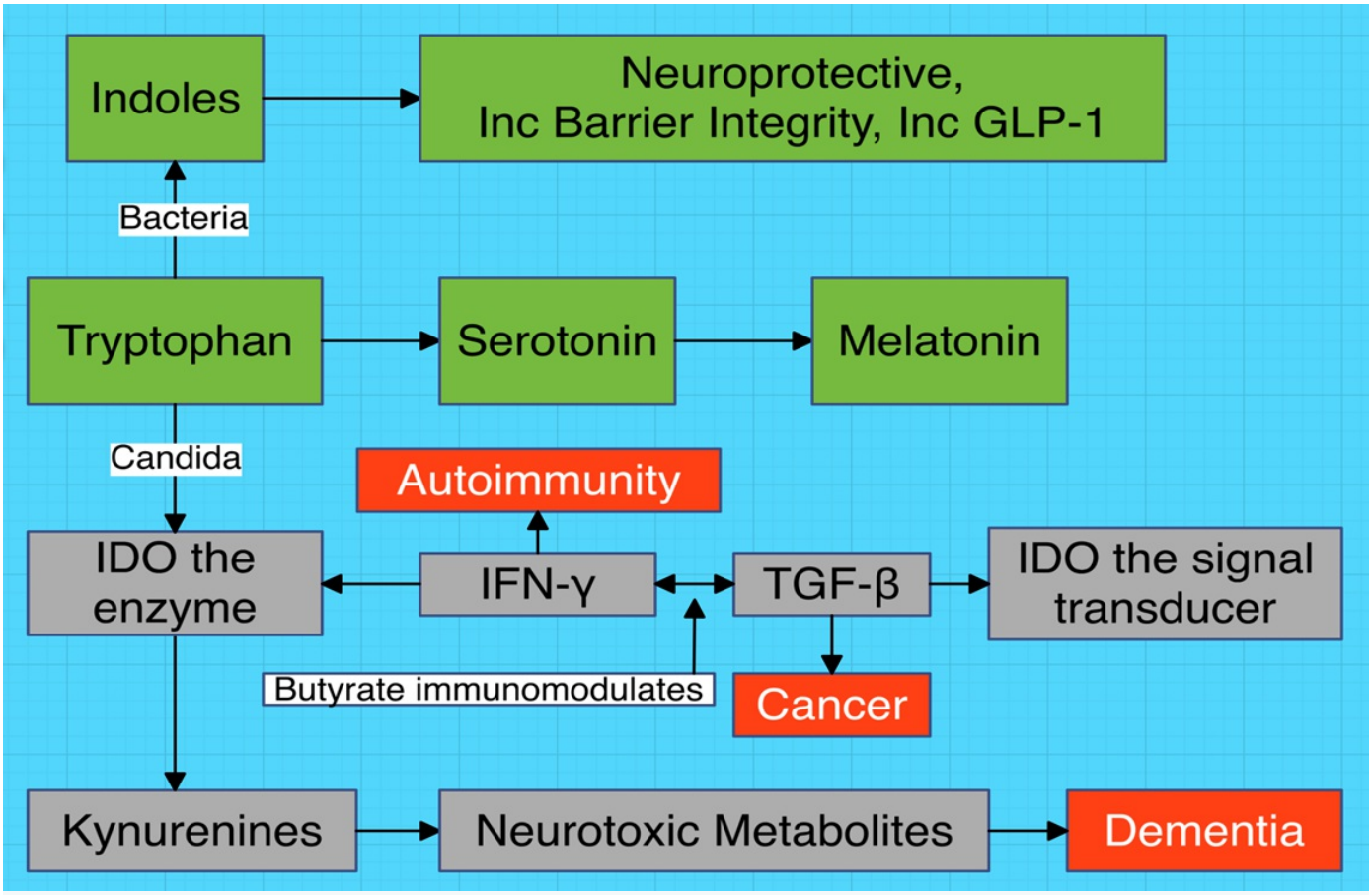

Figure 4. ATM characterizes LC (autoimmunity), cancer, dementia, obesity, and many other diseases. IFN-γ and TGF-β counterbalance each other. TGF-β oversees tolerogenesis - too much and cancer antigens are tolerated, too little and host antigens are not. Candida can release its own IDO.

Furthermore, ACE2 receptors must complex with $B^{0/+}$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 $B^{0/+}$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).

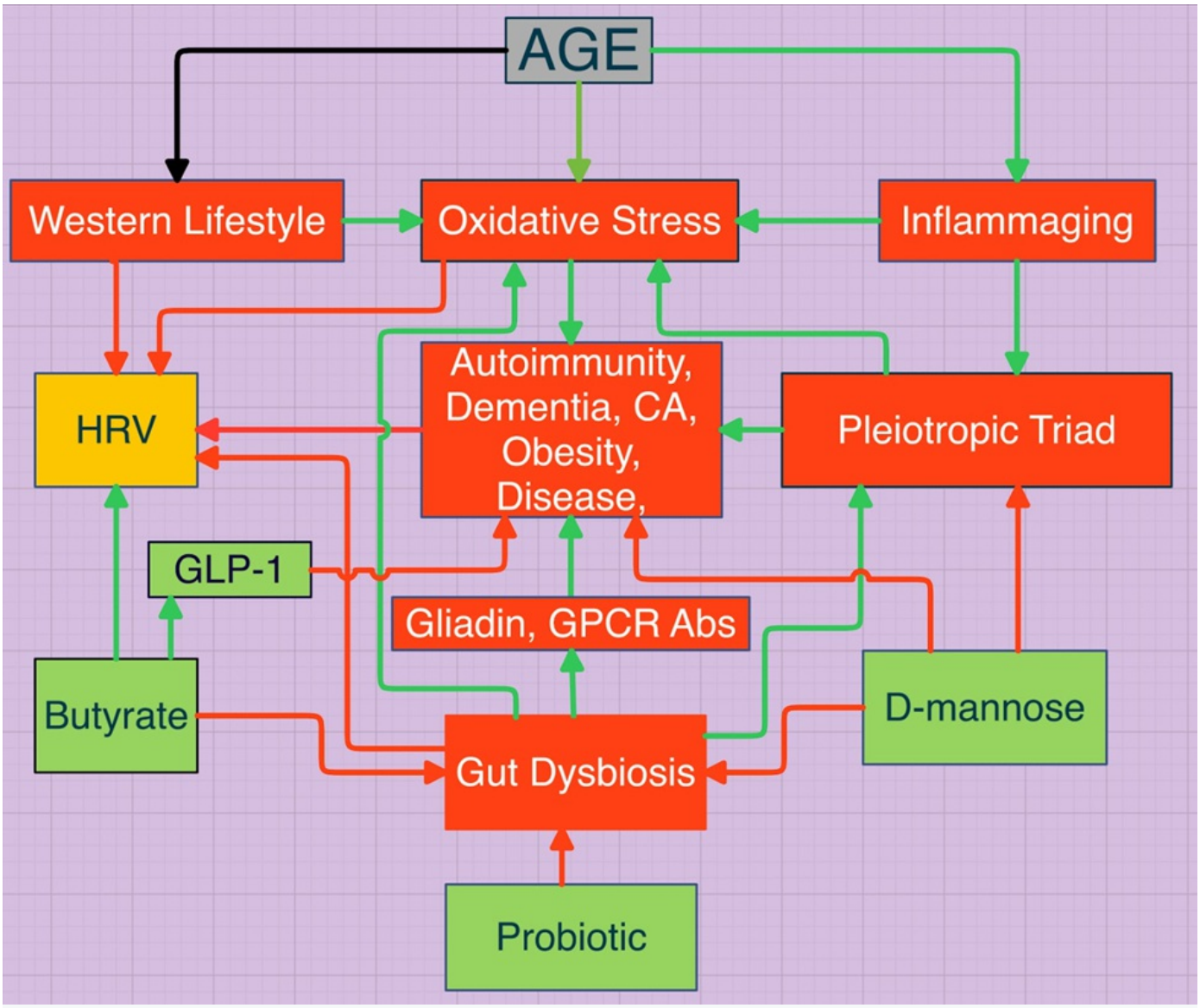

Figure 5. A prebiotic, probiotic, postbiotic approach may slow the inevitable age related decline in lifespan and healthspan, as reflected by decreasing heart rate variability (HRV). The pleiotropic triad is IL1-β, TNF-α, and IL-6.

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]) 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[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).

References

1. [a, b, c] *Llorens S, Nava E, Muñoz-López M, Sánchez-Larsen Á, Segura T. Neurological Symptoms of COVID-19: The Zonulin Hypothesis. Front Immunol. 2021 Apr 26;12:665300. https://doi.org/10.3389/fimmu.2021.665300*
2. [^] *Lammers KM, Lu R, Brownley J, Lu B, Gerard C, Thomas K, et al. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. Gastroenterology. 2008 Jul;135(1):194-204.e3. https://doi.org/10.1053/j.gastro.2008.03.023*
3. [^] *Cabral-Marques O, Moll G, Catar R, Preuß B, Bankamp L, Pecher AC, et al. Autoantibodies targeting G protein-coupled receptors: An evolving history in autoimmunity. Report of the 4th international symposium. Autoimmun Rev. 2023 May;22(5):103310. https://doi.org/10.1016/j.autrev.2023.103310*
4. [a, b] *Perez DM. α1-Adrenergic Receptors: Insights into Potential Therapeutic Opportunities for COVID-19, Heart Failure, and Alzheimer's Disease. International Journal of Molecular Sciences. 2023; 24(4):4188. https://doi.org/10.3390/ijms24044188*
5. [a, b] *Szewczykowski C, Mardin C, Lucio M, Wallukat G, Hoffmanns J, Schröder T, et al. Long COVID: Association of Functional Autoantibodies against G-Protein-Coupled Receptors with an Impaired Retinal Microcirculation. Int J Mol Sci. 2022 Jun 29;23(13):7209. https://doi.org/10.3390/ijms23137209*
6. [a, b] *Kumar R, Rojas IG, Edgerton M. Candida albicansSap6 Initiates Oral Mucosal Inflammation via the Protease Activated Receptor PAR2. Front Immunol. 2022 Jun 29;13:912748. https://doi.org/10.3389/fimmu.2022.912748*
7. [a, b, c] *Rahman, MT, Ghosh, C, Hossain, M, Linfield, D, Rezaee, F, Janigro, D, et al. IFN-γ, IL-17A, or zonulin rapidly increase the permeability of the blood-brain and small intestinal epithelial barriers: Relevance for neuro-inflammatory diseases. Biochem. Biophys. Res. Commun. 2018, 507, 274–279. https://doi.org/10.1016/j.bbrc.2018.11.021*
8. [^] *Zhao, Y., Kuang, M., Li, J. et al. SARS-CoV-2 spike protein interacts with and activates TLR41. Cell Res 31, 818–820 (2021). https://doi.org/10.1038/s41422-021-00495-9*
9. [^] *Liang, R., Qi, X., Cai, Q. et al. The role of NLRP3 inflammasome in aging and age-related diseases. Immun Ageing 21, 14 (2024). https://doi.org/10.1186/s12979-023-00395-z*
10. [^] *Fasano A. Zonulin, regulation of tight junctions, and autoimmune diseases. Ann N Y Acad Sci. 2012 Jul;1258(1):25-33. https://doi.org/10.1111/j.1749-6632.2012.06538.x*

11. [a, b]*Sturgeon C, Fasano A. Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases. Tissue Barriers. 2016 Oct 21;4(4):e1251384. https://doi.org/10.1080/21688370.2016.1251384*
12. [a, b]*Fasano A. Intestinal permeability and its regulation by zonulin: diagnostic and therapeutic implications. Clin Gastroenterol Hepatol. 2012 Oct;10(10):1096-100. https://doi.org/10.1016/j.cgh.2012.08.012*
13. [^]*LJ Walker, MC Aldhous, HE Drummond, BRK Smith, ER Nimmo, IDR Arnott, et al. Anti-Saccharomyces cerevisiae antibodies (ASCA) in Crohn's disease are associated with disease severity but not NOD2/CARD15 mutations, Clinical and Experimental Immunology, March 2004, 135 (3):490–496, https://doi.org/10.1111/j.1365-2249.2003.02392*
14. [^]*Kohan DE, Barratt J, Heerspink HJL, Campbell KN, Camargo M, Ogbaa I, et al. Targeting the Endothelin A Receptor in IgA Nephropathy. Kidney Int Rep. 2023 Aug 4;8(11):2198-2210. https://doi.org/10.1016/j.ekir.2023.07.023*
15. [^]*Mitsuyama K, Niwa M, Takedatsu H, Yamasaki H, Kuwaki K, Yoshioka S, et al. Antibody markers in the diagnosis of inflammatory bowel disease. World J Gastroenterol. 2016 Jan 21;22(3):1304-10. https://doi.org/10.3748/wjg.v22.i3.1304*
16. [^]*Zhang L, Shi G. Gq-Coupled Receptors in Autoimmunity. J Immunol Res. 2016;2016:3969023. https://doi.org/10.1155/2016/3969023.*
17. [^]*Kuwabara T, Ishikawa F, Kondo M, Kakiuchi T. The Role of IL-17 and Related Cytokines in Inflammatory Autoimmune Diseases. Mediators Inflamm. 2017;2017:3908061. https://doi.org/10.1155/2017/3908061*
18. [a, b]*Krishna BA, Lim EY, Metaxaki M, Jackson S, Mactavous L, Lyons PA, et al. Spontaneous, persistent, T cell-dependent IFN-γ release in patients who progress to Long Covid. Sci Adv. 2024 Feb 23;10(8):eadi9379. https://doi.org/10.1126/sciadv.adi9379*
19. [^]*Boschetti E, Caio G, Cervellati C, Costanzini A, Rosta V, Caputo F, et al. Serum zonulin levels are increased in Alzheimer's disease but not in vascular dementia. Aging Clin Exp Res. 2023 Sep;35(9):1835-1843. https://doi.org/10.1007%2Fs40520-023-02463-2*
20. [^]*van IJzendoorn SCD, Derkinderen P. The Intestinal Barrier in Parkinson's Disease: Current State of Knowledge. J Parkinsons Dis. 2019;9(s2):S323-S329. https://doi.org/10.3233/JPD-191707*
21. [^]*Boncuk Ulaş S, Güzey Aras Y, Irmak Gözükara S, Acar T, Acar BA. Correlates of Zonulin and Claudin-5, markers of intestinal and brain endothelial permeability, in Parkinson's Disease: A pilot study. Parkinsonism Relat Disord. 2023 May;110:105361. https://doi.org/10.1016/j.parkreldis.2023.105361*
22. [^]*Kushlinskii, N.E., Gershtein, E.S., Zybina, N.N. et al. Blood Serum Zonulin in Colorectal Cancer, Autoimmune Bowel Diseases, and Irritable Bowel Syndrome. Bull Exp Biol Med 173, 376–379 (2022). https://doi.org/10.1007/s10517-022-05552-w*
23. [^]*Onwuzo S, Boustany A, Saleh M, Gupta R, Onwuzo C, Mascarenhas Monteiro J, et al. Increased Risk of Colorectal Cancer in Patients With Celiac Disease: A Population-Based Study. Cureus. 2023 Mar 31;15(3):e36964. https://doi.org/10.7759/cureus.36964*
24. [a, b, c, d]*Fasano, A. All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. F1000Res. 2020 Jan 31;9:F1000 Faculty Rev-69. https://doi.org/10.12688/f1000research.20510.1*

25. ^Fasano, A. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. Physiol Rev. 2011 Jan;91(1):151-75. https://doi.org/10.1152/physrev.00003.2008
26. ^Kara H, Burak Açıkel S, Çetinkaya M, Çiğdem Tuncer S. Serum Zonulin Levels Are Higher Among Children with Autism Spectrum Disorders and Correlated with Social Impairment. Alpha Psychiatry. 2021 Sep 1;22(5):250-256. https://doi.org/10.1530/alphapsychiatry.2021.21152
27. ^Tajik, N., Frech, M., Schulz, O. et al. Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis. Nat Commun 11, 1995 (2020). https://doi.org/10.1038/s41467-020-15831-7
28. ^DaFonte TM, Valitutti F, Kenyon V, Locascio JJ, Montuori M, Francavilla R, et al; CD-GEMM Study Group. Zonulin as a Biomarker for the Development of Celiac Disease. Pediatrics. 2024 Jan 1;153(1):e2023063050. https://doi.org/10.1542/peds.2023-063050
29. a, b Trovato CM, Montuori M, Pietropaoli N, Oliva S. COVID-19 and celiac disease: A pathogenetic hypothesis for a celiac outbreak. Int J Clin Pract. 2021 Sep;75(9):e14452. https://doi.org/10.1111/ijcp.14452
30. ^Benson BC, Mulder CJ, Laczek JT. Anti-gliadin antibodies identify celiac patients overlooked by tissue transglutaminase antibodies. Hawaii J Med Public Health. 2013 Sep;72(9 Suppl 4):14-7 https://pubmed.ncbi.nlm.nih.gov/24052912
31. ^Hua L, Xiang S, Xu R, Xu X, Liu T, Shi Y, et al. Causal association between rheumatoid arthritis and celiac disease: A bidirectional two-sample mendelian randomization study. Front Genet. 2022 Oct 18;13:976579. https://doi.org/10.3389/fgene.2022.976579
32. ^Balaban DV, Mihai A, Dima A, Popp A, Jinga M, Jurcut C. Celiac disease and Sjögren's syndrome: A case report and review of literature. World J Clin Cases. 2020 Sep 26;8(18):4151-4161. https://doi.org/10.12998/wjcc.v8.i18.4151
33. ^Taraghikhah N, Ashtari S, Asri N, Shahbazkhani B, Al-Dulaimi D, Rostami-Nejad M, et al. An updated overview of spectrum of gluten-related disorders: clinical and diagnostic aspects. BMC Gastroenterol. 2020 Aug 6;20(1):258. https://doi.org/10.1186/s12876-020-01390-0
34. ^(Wijarnpreecha K, Panjawatanan P, Corral JE, Lukens FJ, Ungprasert P. Celiac disease and risk of sarcoidosis: A systematic review and meta-analysis. J Evid Based Med. 2019 Aug;12(3):194-199. https://doi.org/10.1111/jebm.12355
35. ^Flores Monar GV, Islam H, Puttagunta SM, Islam R, Kundu S, Jha SB, et al. Association Between Type 1 Diabetes Mellitus and Celiac Disease: Autoimmune Disorders With a Shared Genetic Background. Cureus. 2022 Mar 7;14(3):e22912. https://doi.org/10.7759/cureus.22912
36. ^Passali M, Josefsen K, Frederiksen JL, Antvorskov JC. Current Evidence on the Efficacy of Gluten-Free Diets in Multiple Sclerosis, Psoriasis, Type 1 Diabetes and Autoimmune Thyroid Diseases. Nutrients. 2020 Aug 1;12(8):2316. https://doi.org/10.3390/nu12082316
37. ^Joshi AS, Varthakavi PK, Bhagwat NM, Thiruvengadam NR. Graves' disease and coeliac disease: screening and treatment dilemmas. BMJ Case Rep. 2014 Oct 23;2014:bcr2013201386. https://doi.org/10.1136/bcr-2013-201386
38. ^Starchl C, Scherkl M, Amrein K. Celiac Disease and the Thyroid: Highlighting the Roles of Vitamin D and Iron. Nutrients. 2021 May 21;13(6):1755. https://doi.org/10.3390/nu13061755
39. ^Beas R, Altamirano-Farfan E, Izquierdo-Veraza D, Norwood DA, Riva-Moscoso A, Godoy A, et al. Prevalence of celiac disease in systemic lupus erythematosus, sjogren syndrome and systemic sclerosis: A systematic review and

meta-analysis. Dig Liver Dis. 2024 Apr 6:S1590-8658(24)00316-5. https://doi.org/10.1016/j.dld.2024.03.015

40. [a, b]*Iqbal U, Chaudhary A, Karim MA, Siddiqui MA, Anwar H, Merrell N. Association of Autoimmune Hepatitis and Celiac Disease: Role of Gluten-Free Diet in Reversing Liver Dysfunction. J Investig Med High Impact Case Rep. 2017 Apr 19;5(2):2324709617705679. https://doi.org/10.1177/2324709617705679*
41. ^*Vashist S, Mahajan VK, Mehta KS, Chauhan PS, Yadav RS, Sharma SB, et al. Association of Psoriasis with Autoimmune Disorders: Results of a Pilot Study. Indian Dermatol Online J. 2020 Sep 19;11(5):753-759. https://doi.org/10.4103/idoj.IDOJ_648_19*
42. ^*Zahra, H., Maryam, A., Amirhooshang, E., Pedram, N., Fatemeh, G., Mohammad, B., & Javad, J.S. (2011). Prevalence of anti-gliadin antibody and patients with alopecia areata: A case control study Tehran University Medical Journal, 68(12):738-742 https://core.ac.uk/display/26848935*
43. ^*Zhang JZ, Abudoureyimu D, Wang M, Yu SR, Kang XJ. Association between celiac disease and vitiligo: A review of the literature. World J Clin Cases. 2021 Dec 6;9(34):10430-10437. https://doi..org/10.12998/wjcc.v9.i34.10430*
44. ^*Ito T, Kageyama R, Nakazawa S, Honda T. Understanding the significance of cytokines and chemokines in the pathogenesis of alopecia areata. Exp Dermatol. 2020 Aug;29(8):726-732. https://doi.org/10.1111/exd.14129*
45. ^*He, Q., Yuan, Q., Shan, H. et al. Mechanisms of ligand recognition and activation of melanin-concentrating hormone receptors. Cell Discov 10, 48 (2024). https://doi.org/10.1038/s41421-024-00679-8*
46. ^*Hedrick MN, Lonsdorf AS, Hwang ST, Farber JM. CCR6 as a possible therapeutic target in psoriasis. Expert Opin Ther Targets. 2010 Sep;14(9):911-22. https://doi.org/10.1517/14728222.2010.504716.*
47. ^*Sendid B, Cornu M, Cordier C, Bouckaert J, Colombel JF, Poulain D. From ASCA breakthrough in Crohn's disease and Candida albicans research to thirty years of investigations about their meaning in human health. Autoimmun Rev. 2024 Feb;23(2):103486. https://doi.org/10.1016/j.autrev.2023.103486*
48. ^*Jangi S, Hsia K, Zhao N, Kumamoto CA, Friedman S, Singh S, Michaud DS. Dynamics of the Gut Mycobiome in Patients With Ulcerative Colitis. Clin Gastroenterol Hepatol. 2024 Apr;22(4):821-830.e7. https://doi.org/10.1016/j.cgh.2023.09.023*
49. [a, b]*Afzal MS. G proteins: binary switches in health and disease. Cent Eur J Immunol. 2020;45(3):364-367. https://doi.org/10.5114%2Fceji.2020.101271*
50. ^*Qi, F., Li, D. & Zhang, Z. The kinetics of chemokine autoantibodies in COVID-19. Nat Immunol 24, 567–569 (2023). https://doi.org/10.1038/s41590-023-01455-8*
51. ^*Tang T, Gong T, Jiang W, Zhou R. GPCRs in NLRP3 Inflammasome Activation, Regulation, and Therapeutics. Trends Pharmacol Sci. 2018 Sep;39(9):798-811. https://doi.org/10.1016/j.tips.2018.07.002*
52. ^*Tesch, F., Ehm, F., Vivirito, A. et al. Incident autoimmune diseases in association with SARS-CoV-2 infection: a matched cohort study. Clin Rheumatol 42, 2905–2914 (2023). https://doi.org/10.1007/s10067-023-06670-0*
53. ^*Farooq H, Aemaz Ur Rehman M, Asmar A, Asif S, Mushtaq A, Qureshi MA. The pathogenesis of COVID-19-induced IgA nephropathy and IgA vasculitis: A systematic review. J Taibah Univ Med Sci. 2022 Feb;17(1):1-13. https://doi..org/10.1016/j.jtumed.2021.08.012*
54. ^*Gracia-Ramos AE, Martin-Nares E, Hernández-Molina G. New Onset of Autoimmune Diseases Following COVID-19 Diagnosis. Cells. 2021; 10(12):3592. https://doi.org/10.3390/cells10123592*

55. ^Sachdeva M, Mufti A, Maliyar K, Lara-Corrales I, Salcido R, Sibbald C. A Review of COVID-19 Chilblains-like Lesions and Their Differential Diagnoses. Adv Skin Wound Care. 2021 Jul 1;34(7):348-354. https://doi.org/10.1097/01.ASW.0000752692.72055
56. ^Mills JL, Taylor LM Jr, Porter JM. Buerger's disease in the modern era. Am J Surg. 1987 Jul;154(1):123-9. https://doi.org/10.1016/0002-9610(87)90301-1
57. ^Song Y, Huang X, Yu G, Qiao J, Cheng J, Wu J, Chen J. Pathogenesis of IgA Vasculitis: An Up-To-Date Review. Front Immunol. 2021 Nov 9;12:771619. https://doi.org/10.3389/fimmu.2021.771619
58. ^Liu, Y., Ebinger, J.E., Mostafa, R. et al. Paradoxical sex-specific patterns of autoantibody response to SARS-CoV-2 infection. J Transl Med 19, 524 (2021). https://doi.org/10.1186/s12967-021-03184-8
59. a, b, cFerreira-Gomes, M., Kruglov, A., Durek, P. et al. SARS-CoV-2 in severe COVID-19 induces a TGF-β-dominated chronic immune response that does not target itself. Nat Commun 12, 1961 (2021). https://doi.org/10.1038/s41467-021-22210-3
60. ^Dubey RK, Jackson EK, Keller PJ, Imthurn B, Rosselli M. Estradiol metabolites inhibit endothelin synthesis by an estrogen receptor-independent mechanism. Hypertension. 2001 Feb;37(2 Pt 2):640-4. https://doi.org/10.1161/01.hyp.37.2.640
61. ^Sendid B, Cao C, Colombel JF, Poulain D. Coincidence of antibodies against Hwp1 and ASCA, two distinct molecular targets of Candida albicans, reinforces the link between this fungal species and coeliac disease. Virulence. 2024 Dec;15(1):2334085. https://doi.org/10.1080/21505594.2024.2334085
62. ^Al-Janabi AAHS, Mohammed MJ. Correlation of Celiac Diseases with Candida Spp. Based on Anti-gliadin Antibodies. Kurume Med J. 2023 Jul 3;68(2):63-68. https://doi.org/10.2739/kurumemedj.MS682018
63. ^Naglik JR, Challacombe SJ, Hube B. Candida albicans secreted aspartyl proteinases in virulence and pathogenesis. Microbiol Mol Biol Rev. 2003 Sep;67(3):400-28, table of contents. https://doi.org/10.1128/MMBR.67.3.400-428.2003
64. ^Abigail, E., & Haytham, E. (2018). Assessment of the relevance of intestinal Zonulin test for inflammatory conditions in an integrated clinical setting. https://api.semanticscholar.org/CorpusID:53624540
65. ^Ocana-Ortega A, Perez-Flores G, Torres-Tirado D, Perez-Garcia LA. O-Linked Glycans of Candida albicans Interact with Specific GPCRs in the Coronary Endothelium and Inhibit the Cardiac Response to Agonists. Journal of Fungi. 2023; 9(2):141. https://doi.org/10.3390/jof9020141
66. ^Lu, S., He, X., Yang, Z. et al. Activation pathway of a G protein-coupled receptor uncovers conformational intermediates as targets for allosteric drug design. Nat Commun 12, 4721 (2021). https://doi.org/10.1038/s41467-021-25020-9
67. a, bBadolia R, Inamdar V, Manne BK, Dangelmaier C, Eble JA, Kunapuli SP. Gq pathway regulates proximal C-type lectin-like receptor-2 (CLEC-2) signaling in platelets. J Biol Chem. 2017 Sep 1;292(35):14516-31. https://doi.org/10.1074/jbc.M117.791012
68. ^Myagmar BE, Ismaili T, Swigart PM, Raghunathan A, Baker AJ, Sahdeo S, et al. Coupling to Gq Signaling Is Required for Cardioprotection by an Alpha-1A-Adrenergic Receptor Agonist. Circ Res. 2019 Sep 13;125(7):699-706. https://doi.org/10.1161/CIRCRESAHA.118.314416
69. ^McGraw DW, Liggett SB. Molecular mechanisms of beta2-adrenergic receptor function and regulation. Proc Am

Thorac Soc. 2005;2(4):292-6; discussion 311-2. https://doi.org/10.1513/pats.200504-027SR

70. ^*Kim, YS., Yeon, JH., Ko, W. et al. Two-step structural changes in M3 muscarinic receptor activation rely on the coupled Gq protein cycle. Nat Commun 14, 1276 (2023). https://doi.org/10.1038/s41467-023-36911-4*
71. ^*Li H, Kem DC, Reim S, Khan M, Vanderlinde-Wood M, Zillner C, Collier D, Liles C, Hill MA, Cunningham MW, Aston CE, Yu X. Agonistic autoantibodies as vasodilators in orthostatic hypotension: a new mechanism. Hypertension. 2012 Feb;59(2):402-8. https://doi.org/10.1161/HYPERTENSIONAHA.111.184937*
72. ^*Rodrigues AR, Almeida H, Gouveia AM. Intracellular signaling mechanisms of the melanocortin receptors: current state of the art. Cell Mol Life Sci. 2015 Apr;72(7):1331-45. https://doi.org/10.1007/s00018-014-1800-3*
73. ^*Unger L, Skoluda S, Backman E, Amulic B, Ponce-Garcia FM, Etiaba CN, Yellagunda S, Krüger R, von Bernuth H, Bylund J, Hube B, Naglik JR, Urban CF. Candida albicans induces neutrophil extracellular traps and leucotoxic hypercitrullination via candidalysin. EMBO Rep. 2023 Nov 6;24(11):e57571. https://doi.org/10.15252/embr.202357571*
74. ^*Sawadogo SA, Dighero-Kemp B, Ouédraogo DD, Hensley L, Sakandé J. How NETosis could drive "Post-COVID-19 syndrome" among survivors. Immunol Lett. 2020 Dec;228:35-37. https://doi.org/10.1016/j.imlet.2020.09.005*
75. ^*Darrah E, Andrade F. Rheumatoid arthritis and citrullination. Curr Opin Rheumatol. 2018 Jan;30(1):72-78. https://doi.org/10.1097/BOR.0000000000000452*
76. ^*Zaccardelli A, Wallace ZS, Sparks JA. Acute and postacute COVID-19 outcomes for patients with rheumatoid arthritis: lessons learned and emerging directions 3 years into the pandemic. Curr Opin Rheumatol. 2023 May 1;35(3):175-184. https://doi.org/10.1097/BOR.0000000000000930*
77. ^*Lingel H, Meltendorf S, Billing U, Thurm C, Vogel K, Majer C, Prätsch F, Roggenbuck D, Heuft HG, Hachenberg T, Feist E, Reinhold D, Brunner-Weinzierl MC. Unique autoantibody prevalence in long-term recovered SARS-CoV-2-infected individuals. J Autoimmun. 2021 Aug;122:102682. https://doi.org/10.1016/j.jaut.2021.102682*
78. ^*Hemgren, C., Martinsson, K., Rooney, C. et al. (4 more authors) (2024) Elevated Serum Levels of Zonulin Family Peptides in Anticitrullinated Protein Antibody–Positive At-Risk Individuals Without Arthritis. The Journal of Rheumatology, 51 (2). pp. 134-138. ISSN 0315-162X. https://eprints.whiterose.ac.uk/212889/*
79. ^*Martos R, Tar I, Nagy AC, Csősz É, Kiss C, Márton I. Hypercitrullination and anti-citrullinated protein antibodies in chronic apical periodontitis, a laboratory investigation. Does autoimmunity contribute to the pathogenesis? Int Endod J. 2023 May;56(5):584-592. https://doi.org/10.1111/iej.13903*
80. ^*Suresh Unniachan A, Krishnavilasom Jayakumari N, Sethuraman S. Association between Candidaspecies and periodontal disease: A systematic review. Curr Med Mycol. 2020 Jun;6(2):63-68. https://doi.org/10.18502/CMM.6.2.3420*
81. ^*Makol, AK, Chakravorty, B, Heller. MB, Riley, B The Association Between Hypermobility Ehlers–Danlos Syndrome and Other Rheumatologic Diseases." European Medical Journal (2021) https://doi.org/10.33590/emj/21-00078R2*
82. ^*Mathias CJ, Owens A, Iodice V, Hakim A. Dysautonomia in the Ehlers-Danlos syndromes and hypermobility spectrum disorders-with a focus on the postural tachycardia syndrome. Am J Med Genet C Semin Med Genet. 2021;187(4):510-519. https://doi.org/10.1002/ajmg.c.31951*
83. ^*Khan HF, Ambreen S, Raziq H, Hayat A. Comparison of cortisol levels in patients with vasovagal syncope and postural tachycardia syndrome. Pak J Med Sci. 2022 Jan-Feb;38(1):185-189. https://doi.org/10.12669/pjms.38.1.4122*

84. ^Hakim A, O'Callaghan C, De Wandele I, Stiles L, Pocinki A, Rowe P. Cardiovascular autonomic dysfunction in Ehlers-Danlos syndrome-Hypermobile type. Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):168-174. https://doi.org/10.1002/ajmg.c.31543
85. ^Garcia-Campayo, J., Asso, E. & Alda, M. Joint Hypermobility and Anxiety: The State of the Art. Curr Psychiatry Rep 13, 18–25 (2011). https://doi.org/10.1007/s11920-010-0164-0
86. ^Hakim, A.J., Simmonds, J.V., Kaul, A. (2021). Rheumatology and Postural Tachycardia Syndrome. In: Gall, N., Kavi, L., Lobo, M.D. (eds) Postural Tachycardia Syndrome. Springer, Cham. https://doi.org/10.1007/978-3-030-54165-1_12
87. ^Zhang Q, Xu B, Du J. Update of Individualized Treatment Strategies for Postural Orthostatic Tachycardia Syndrome in Children. Front Neurol. 2020 Jun 11;11:525. https://doi.org/10.3389/fneur.2020.00525
88. ^Steiner L, Bodensteiner A, Johnson NR (2023) Gastrointestinal Manifestations of Hypermobile Ehlers-Danlos Syndrome and Dietary Approaches Related to Their Management. J Orthop Res Ther 8: 1313. https://doi.org/10.29011/2575-8241.001313
89. ^Ryan L, Beer H, Thomson E, Philcox E, Kelly C. Autistic Traits Correlate with Chronic Musculoskeletal Pain: A Self-Selected Population Based Survey. OBM Neurobiology 2023; 7(1): 155; https://doi.org/10.21926/obm.neurobiol.2301155
90. ^Gutowski Ł, Kanikowski S, Formanowicz D. Mast Cell Involvement in the Pathogenesis of Selected Musculoskeletal Diseases. Life (Basel). 2023 Aug 5;13(8):1690. https://doi.org/10.3390/life13081690
91. ^Logarbo BP, Yang M, Longo MT, Kingry C, Courseault J. Long COVID and the diagnosis of underlying hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders. PM R. 2023 Dec 20. https://doi.org/10.1002/pmrj.13120
92. ^Yu M, Song XT, Liu B, Luan TT, Liao SL, Zhao ZT. The Emerging Role of Mast Cells in Response to Fungal Infection. Front Immunol. 2021 Jun 3;12:688659. https://doi.org/10.3389/fimmu.2021.688659
93. ^Monaco A, Choi D, Uzun S, Maitland A, Riley B. Association of mast-cell-related conditions with hypermobile syndromes: a review of the literature. Immunol Res. 2022 Aug;70(4):419-431. https://doi.org/10.1007/s12026-022-09280-1
94. ^Weinstock LB, Brook JB, Walters AS, Goris A, Afrin LB, Molderings GJ. Mast cell activation symptoms are prevalent in Long-COVID. Int J Infect Dis. 2021 Nov;112:217-226. https://doi.org/10.1016/j.ijid.2021.09.043
95. ^Arun S, Storan A, Myers B. Mast cell activation syndrome and the link with long COVID. Br J Hosp Med (Lond). 2022 Jul 2;83(7):1-10. https://doi.org/10.12968/hmed.2022.0123
96. ^Wang E, Ganti T, Vaou E, Hohler A. The relationship between mast cell activation syndrome, postural tachycardia syndrome, and Ehlers-Danlos syndrome. Allergy Asthma Proc. 2021 May 1;42(3):243-246. https://doi.org/10.2500/aap.2021.42.210022
97. ^Seeley MC, Gallagher C, Ong E, Langdon A, Chieng J, Bailey D, Page A, Lim HS, Lau DH. High Incidence of Autonomic Dysfunction and Postural Orthostatic Tachycardia Syndrome in Patients with Long COVID: Implications for Management and Health Care Planning. Am J Med. 2023 Jun 29:S0002-9343(23)00402-3. https://%doi.org/10.1016/j.amjmed.2023.06.010
98. ^Lagree, K., Chen, P. Candida makes a lasting impression in COVID-19.Nat Immunol 24, 1782–1784 (2023).

https://doi.org/10.1038/s41590-023-01648-1

99. ^Schofield J, Blitshteyn S, Shoenfeld Y, Hughes G. Postural tachycardia syndrome (POTS) and other autonomic disorders in antiphospholipid (Hughes) syndrome (APS). Lupus. 2014;23(7):697-702. https://doi.org/10.1177/0961203314524468
100. ^Alessandri C, Agmon-Levin N, Conti F, Perricone C, Ortona E, Pendolino M, et al. Anti-mutated citrullinated vimentin antibodies in antiphospholipid syndrome: diagnostic value and relationship with clinical features. Immunol Res. 2017 Apr;65(2):524-531. https://doi.org/10.1007/s12026-017-8899-x
101. ^Giron, L. B., Peluso, M. J., Ding, J., Kenny, G., Zilberstein, N. F., Koshy, J., et al. (2022). Markers of fungal translocation are elevated during post-acute sequelae of SARS-CoV-2 and induce NF-κB signaling. JCI Insight 7 (15), e164813 https://doi.org/10.1172/jci.insight.160989
102. ^Liang, SH., Sircaik, S., Dainis, J. et al. The hyphal-specific toxin candidalysin promotes fungal gut commensalism. Nature 627, 620–627 (2024). https://doi.org/10.1038/s41586-024-07142-4
103. ^Palakkott AR, Alneyadi A, Muhammad K, Eid AH, Amiri KMA, Akli Ayoub M, Iratni R. The SARS-CoV-2 Spike Protein Activates the Epidermal Growth Factor Receptor-Mediated Signaling. Vaccines (Basel). 2023 Mar 30;11(4):768. https://doi.org/10.3390/vaccines11040768
104. ^Carnevale R, Cammisotto V, Bartimoccia S, Nocella C, Castellani V, Bufano M, et al. Toll-Like Receptor 4-Dependent Platelet-Related Thrombosis in SARS-CoV-2 Infection. Circ Res. 2023 Feb 3;132(3):290-305. https://doi.org/10.1161/CIRCRESAHA.122.321541
105. a, b Veres-Székely A, Szász C, Pap D, Szebeni B, Bokrossy P, Vannay Á. Zonulin as a Potential Therapeutic Target in Microbiota-Gut-Brain Axis Disorders: Encouraging Results and Emerging Questions. Int J Mol Sci. 2023 Apr 19;24(8):7548. https://doi.org/10.3390/ijms24087548
106. ^Zhang Y, Yan R, Zhou Q. ACE2, B0AT1, and SARS-CoV-2 spike protein: Structural and functional implications. Curr Opin Struct Biol. 2022 Jun;74:102388. https://doi.org/10.1016/j.sbi.2022.102388
107. ^Pallotta MT, Rossini S, Suvieri C, Coletti A, Orabona C, Macchiarulo A, et al. Indoleamine 2,3-dioxygenase 1 (IDO1): an up-to-date overview of an eclectic immunoregulatory enzyme. FEBS J. 2022 Oct;289(20):6099-6118 https://doi.org/10.1111/febs.16086
108. ^Chen, W. IDO: more than an enzyme. Nat Immunol 12, 809–811 (2011). https://doi.org/10.1038/ni.2088
109. ^Ye Z, Yue L, Shi J, Shao M, Wu T. Role of IDO and TDO in Cancers and Related Diseases and the Therapeutic Implications. J Cancer. 2019 Jun 2;10(12):2771-2782. https://doi.org/10.7150/jca.31727
110. ^Shirey KA, Jung JY, Maeder GS, Carlin JM. Upregulation of IFN-gamma receptor expression by proinflammatory cytokines influences IDO activation in epithelial cells. J Interferon Cytokine Res. 2006 Jan;26(1):53-62. https://doi.org/10.1089/jir.2006.26.53
111. a, b Strober W, Kelsall B, Fuss I, Marth T, Ludviksson B, Ehrhardt R, Neurath M. Reciprocal IFN-gamma and TGF-beta responses regulate the occurrence of mucosal inflammation. Immunol Today. 1997 Feb;18(2):61-4. https://doi.org/10.1016/s0167-5699(97)01000-1
112. a, b Gauthier T, Chen W. IFN-γ and TGF-β, Crucial Players in Immune Responses: A Tribute to Howard Young. J Interferon Cytokine Res. 2022 Dec;42(12):643-654. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9917322/

113. [a, b]*Bozza, S, Fallarino, F, Pitzurra, L, Zelante, T, Montagnoli, C, Bellocchio, S, et al; A Crucial Role for Tryptophan Catabolism at the Host/Candida albicans Interface. J Immunol 1 March 2005; 174 (5): 2910–2918. https://doi.org/10.4049/jimmunol.174.5.2910*

114. [^]*Siddiqui MT, Cresci GAM. The Immunomodulatory Functions of Butyrate. J Inflamm Res. 2021 Nov 18;14:6025-6041. https://doi.org/10.2147/JIR.S300989*

115. [a, b]*Ngai J, Methi T, Andressen KW, Levy FO, Torgersen KM, Vang T, et al. The heterotrimeric G-protein α-subunit Gαq regulates TCR-mediated immune responses through an Lck-dependent pathway. Eur J Immunol. 2008 Nov;38(11):3208-18. https://doi.org/10.1002/eji.200838195.*

116. [^]*Kherad Z, Yazdanpanah S, Saadat F, Pakshir K, Zomorodian K. Vitamin D3: A promising antifungal and antibiofilm agent against Candida species. Curr Med Mycol. 2023 Jun;9(2):17-22. https://pubmed.ncbi.nlm.nih.gov/38375518/*

117. [^]*Korkmaz, H., Sirin, F.B. & Torus, B. Could there be a role of serum zonulin increase in the development of hypercalcemia in primary hyperparathyroidism. Endocrine 72, 234–238 (2021). https://doi.org/10.1007/s12020-020-02504-0*

118. [^]*Hans S, Fatima Z, Ahmad A, Hameed S. Magnesium impairs Candida albicans immune evasion by reduced hyphal damage, enhanced β-glucan exposure and altered vacuole homeostasis. PLoS One. 2022 Jul 14;17(7):e0270676. https://doi.org/10.1371/journal.pone.0270676*

119. [^]*Walkon LL, Strubbe-Rivera JO, Bazil JN. Calcium Overload and Mitochondrial Metabolism. Biomolecules. 2022 Dec 17;12(12):1891. https://doi.org/10.3390/biom12121891*

120. [^]*Dominguez LJ, Veronese N, Barbagallo M. Magnesium and the Hallmarks of Aging. Nutrients. 2024 Feb 9;16(4):496. https://doi.org/10.3390/nu16040496*

121. [^]*Jaana van Gastel, Hanne Leysen, Jan Boddaert, Laura vangenechten, Louis M. Luttrell, Bronwen Martin, et al. Aging-related modifications to G protein-coupled receptor signaling diversity, Pharmacology&Therapeutics (2021) v 223, 107793 https://doi.org/10.1016/j.pharmthera.2020.107793*

122. [^]*Kim HJ, Kim H, Lee JH, Hwangbo C. Toll-like receptor 4 (TLR4): new insight immune and aging. Immun Ageing. 2023 Nov 24;20(1):67. https://doi.org/10.1186/s12979-023-00383-3*

123. [^]*Kaushal, A., Noor, R. Association of Gut Microbiota with Inflammatory Bowel Disease and COVID-19 Severity: A Possible Outcome of the Altered Immune Response. Curr Microbiol 79, 184 (2022). https://doi.org/10.1007/s00284-022-02877-7*

124. [^]*Liu W, Shi LJ, Li SG. The Immunomodulatory Effect of Alpha-Lipoic Acid in Autoimmune Diseases. Biomed Res Int. 2019 Mar 20;2019:8086257. https://doi.org/10.1155/2019/8086257*

125. [^]*Tripathi AK, Ray AK, Mishra SK, Bishen SM, Mishra H, Khurana A. Molecular and Therapeutic Insights of Alpha-Lipoic Acid as a Potential Molecule for Disease Prevention. Rev Bras Farmacogn. 2023;33(2):272-287. https://doi.org/10.1007/s43450-023-00370-1*

126. [^]*Chambers, P. (2024). Staunch the Age Related Decline into Dementia, Cancer, Autoimmunity (Long Covid), Obesity, and Other Diseases with a Prebiotic, Probiotic, Postbiotic Triple Play. Qeios. https://doi.org/10.32388/X0TQ1D.6*

127. [^]*Nguyen, LN, Lopes, LCL, Radames, JBC, Nosanchuk, JD. Sodium butyrate inhibits pathogenic yeast growth and enhances the functions of macrophages, Journal of Antimicrobial Chemotherapy, Volume 66, Issue 11, November*

2011, pp 2573-80, https://doi.org/10.1093/jac/dkr358

128. ^*Souza PB, de Araujo Borba L, Castro de Jesus L, Valverde AP, Gil-Mohapel J, Rodrigues ALS. Major Depressive Disorder and Gut Microbiota: Role of Physical Exercise. Int J Mol Sci. 2023 Nov 28;24(23):16870. https://doi.org/10.3390/ijms242316870*