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Review Article

Staunch the Age Related Decline into Dementia, Cancer, Autoimmunity (Long Covid), Obesity, and Other Diseases with a Prebiotic, Probiotic, Postbiotic Triple Play

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"All diseases originate in the gut." Hippocrates (400 BC)
A healthy gut microbiome via the gut-brain-axis elevates heart rate variability (HRV), a general measure of health and well-being. A dysbiotic gut microbiome, low in biodiversity and butyrate producers, can alter tryptophan metabolism (ATM) and increase the kynurenine to tryptophan ratio (KTR) with the release of proinflammatory cytokines, predominantly TNF-α, IL-6, and IL-1β. These also characterize chronic inflammation, oxidative stress, and a multitude of diseases. Also proposed is the gut-lung dysbiosis concept and the consequent degradation of ACE2 (richest in lungs and gut). Leaky gut (and lung) induced autoantibodies (AAs) related to G-protein coupled receptors (GPCRs), in combination with increased Ang II, further potentiate oxidative stress. The underappreciated pathogenic role of these receptors on invading Candida hyphae is explored. The efficacy of fecal microbiome transplantation (FMT) in treating dementia, cancer, and autoimmunity supports the plausibility of success with "FMT-lite". This triple play of prebiotic (d-mannose), probiotic (bifidobacteria and lactobacilli), and postbiotic (butyrate) might improve intestinal barrier integrity, oppose the entry of GPCR antigens (epitopes), suppress the inflammatory cytokine triad, balance IFN-γ and TGF-β, suppress oxidative stress, depress KTR, elevate HRV, and extend lifespan and its quality.

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Hypothesis

1. Gut dysbiosis (and SARS CoV2) depresses ACE2, vital to intestinal barrier integrity and tryptophan absorption
2. Tryptophan and vitamin D deficiencies promote pathogenic hyphal transition of commensal Candida yeast forms
3. Estrogen facilitates immune evasion by Candida

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4. Invasive Candida hyphae are rich in surface GPCRs (only present on eukaryotes) and can trigger GPCR AAs
5. LC symptoms are primarily due to GPCR AAs (~800 different candidates in humans)
6. Candida elicits a robust IFN-γ response that drives ATM, and females produce a more robust IFN-γ response
7. ATM upregulates IDO, linked to dementia and autoimmunity in females (IFN-γ) and cancer/organ fibrosis in males (TGF-β)
8. TGF-β (reciprocal cytokine to IFN-γ) regulates tolerogenesis; too little, self-antigens targeted; too much, tumor antigens not targeted
9. D-mannose enhances intestinal barrier integrity, and butyrate immunomodulates IFN-γ, TGF-β
10. Candida potentiates gut dysbiosis and is a major player in determining long-term health

1. Introduction

Pursuit of a healthier and happier lifestyle is a universal goal.

Better diet and more exercise are at the top of New Year's resolutions. But eating favorite foods is one of the great joys in life, and exercise, not so much. Balance is the key to achieving these goals, whether it be between the opposing enzymes ACE and ACE2 or the pleiotropic cytokines IFN-γ and TGF-β. However, several supplements readily available may assist in this pursuit of balance.

Although this article cites an abundance of recent research supporting its content, it is speculative, and the inferences are in part theoretical. It attempts to connect pleiotropic cytokines, gut dysbiosis, GPCR AAs, and disease with oxidative stress under the HRV umbrella (see figure 1). Prebiotic d-mannose (a dietary fiber substitute), a probiotic rich in bifidobacteria and lactobacilli, and postbiotic butyrate (the best short-chain fatty acid or SCFA) are proposed as partial solutions. HRV, a function of beat-to-beat interval, is proposed as a monitor of efficacy. It is the "fifth vital sign" and is more comprehensive and predictive in its assessment than the four traditional vital signs.

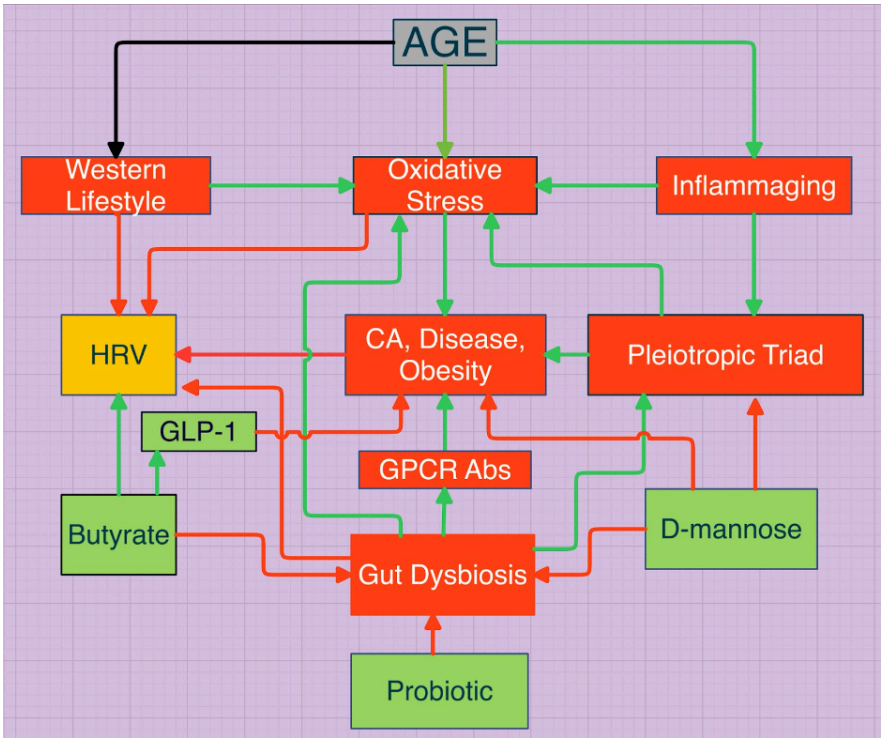

Figure 1. Pathways to a healthy HRV and enhanced lifespan are demonstrated. The Western Lifestyle includes an increased calcium to magnesium ratio, vitamin D deficiency, decreased antioxidants, toxins, e.g., smoking. TNF-α, IL-6, IL-1β comprise the triad. The trigger for the pleiotropic switch is not yet clear. Biologic individuality is also a prime determinant of differential pathway traffic.

2. Oxidative Stress and Gut Dysbiosis

Aging reflects the accumulated damage over a lifetime wrought by oxidative stress. This stress arises when energy needs increase and reactive oxygen species (ROS) generated within mitochondria remain unquenched due to insufficient onboard antioxidants. Psychological stress induces oxidative stress by increasing circulating cortisol and norepinephrine, which generate mitochondrial ROS[1]. Mental stress is also linked with gut dysbiosis[2], which upregulates oxidative stress[3]. Excess ROS compromise mitochondrial efficiency and gut microbial diversity. Gut microbes themselves impact ROS generation.

Gut dysbiosis occurs when the gut microbiome is unbalanced, i.e., gut microbiota are not diverse and SCFA-producing bacteria are in short supply. SCFAs are the end products of fermentation of dietary fibers by anaerobic intestinal bacteria and exert multiple beneficial effects on energy metabolism[4].

They are the primary energy substrate for colonic epithelial cells. Propionate and butyrate comprise 25% and 15%, respectively, of these SCFAs[5]. Acetate, which comprises ~60%, promotes obesity by stimulating insulin secretion and hyperphagia[6][7]. Propionate and butyrate stimulate the secretion of insulin and glucagon-like peptide 1 (GLP-1), which suppresses appetite[8][9]. Ozempic is a GLP-1 agonist. On the other hand, oxidative stress enhances acetate-dependent lipogenesis, i.e., promotes obesity[10]. Excess weight gain and obesity are features

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of Covid-19 and LC, which share the same gut microbiome, low in butyrates. Persistent low-grade oxidative stress is tightly linked to excitatory glutamate neurotransmission[11]. Glutamate-producing gut bacteria outperform their butyrate/γ-amino butyric acid-producing counterparts and create an imbalance in excitatory and inhibitory neurotransmission in the autonomic nervous system[12].

3. ATM and KTR

Tryptophan, an essential amino acid from the diet or synthesized by intestinal bacteria, can follow one of three major metabolic pathways: 1) intestinal bacterial indole synthesis, 2) the kynurenine pathway in immune and epithelial cells (95% of tryptophan), or 3) the serotonin pathway (90% of total body serotonin) in enteroendocrine, aka enterochromaffin, cells and initiation of vagal afferent signals[13]. During ATM, tryptophan pivots away from the serotonin pathway and the synthesis of serotonin and melatonin to the kynurenine pathway (see figure 2). Inhibitory parasympathetic signals are suppressed due to the increase in excitatory glutamate activity. This pivot down-regulates bacterial indole synthesis with the loss of indole-induced GLP-1. Benefits of GLP-1 include appetite suppression, stimulation of insulin[14], decrease in fasting blood sugar[15], and suppression of obesity and T2DM[16]. Many of the same bacteria that produce SCFAs, e.g., bifidobacteria and lactobacilli, also synthesize indoles from tryptophan[17]. Although the end product NAD+ (see figure 2) assists dysfunctional mitochondria in ATP production, what drives the ATM pivot is not clear. However, IFN-γ, upregulated in females, is a cofactor for many enzymes in the kynurenine pathway and may drive this pivot[18] (see figure 2). Tryptophan depletion lowers HRV (and increases KTR)[19]. Increased tryptophan intake (e.g., eggs) increases HRV, which appears to be due to the subsequent increase in serotonin[20]. KTR, an indicator of rate-limiting IDO activity, is positively correlated with cardiovascular disease mortality[21][22], depression, bipolar disorder, schizophrenia,[23] Alzheimer's disease, fronto-temporal dementia, [24] Parkinson's disease[25], and neurological disease in general[26]. Increased KTR has also been reported in cancer[27], autoimmune diseases, including rheumatoid arthritis (RA)[28], and systemic lupus erythematosus (SLE)[29]. Infectious diseases are also linked to an elevated KTR[30] with a ratio that directly reflects severity[31][32]. This includes SARS CoV2[33]. SARS CoV2-induced loss of ACE2 receptor-bearing intestinal epithelial cells depresses the absorption of the essential amino acid tryptophan[34] , and depressed tryptophan levels promote yeast-to-hyphal transition[35].

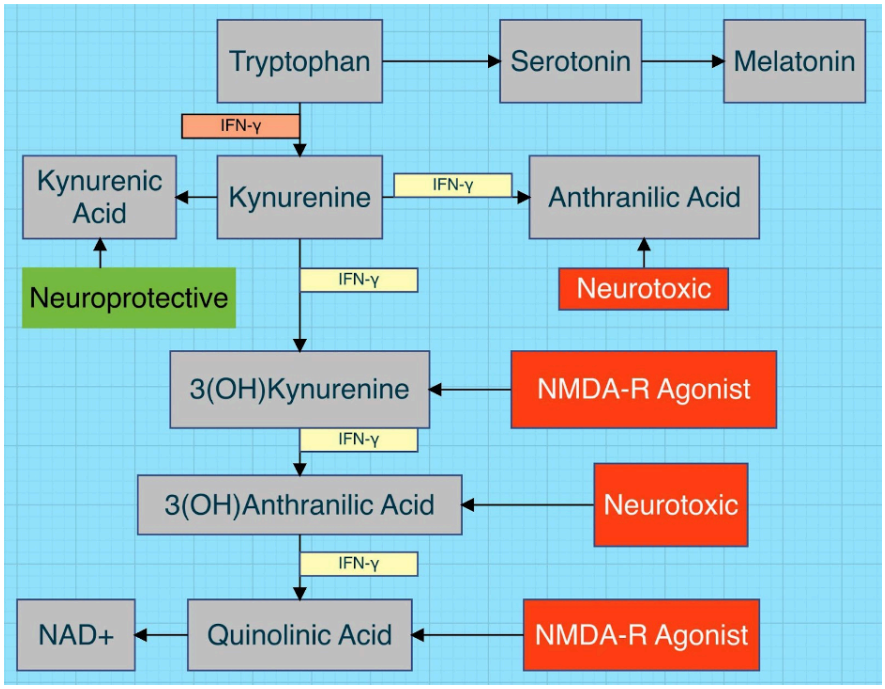

Figure 2. Altered tryptophan metabolism is demonstrated. NMDA-R=N-methyl-D-aspartate receptor is an excitatory glutamate receptor. Note the upregulating presence of the proinflammatory cytokine IFN-γ[36][23][37].

4. IFN-γ and TGF-β

IFN-γ and TGF-β are polarizing cytokines (reciprocal relationship)[38] and counterbalance each other[39]. IFN-γ is pro-inflammatory, and TGF-β is anti-inflammatory. When an imbalance arises, autoimmune disease/IFN-γ and cancer/TGF-β, two immunological opposites[40], can develop. These counterbalancing cytokines are in turn immuno-modulated by the gut microbiome. This is demonstrated by the utility of FMT in cancer[41], autoimmune disease[42], and dementia[43].

Reports on the efficacy of FMT for obesity are mixed. However, they include no concomitant prebiotic. Whether the microbiome is upgraded via probiotics or FMT, failure to simultaneously upgrade the diet or otherwise provide sustenance to the new microbiota compromises efficacy. Also, the postbiotic butyrate stimulates the release of GLP-1[8][9]. The highly popular weight loss drug Ozempic (semaglutide) is a GLP-1 agonist. Elevated IFN-γ characterizes parasitic infestations. In such patients, this cytokine was positively associated with a good prognosis in Covid-19[44]. A low baseline IFN-γ response could predict hospitalization[45] and post-discharge fibrosis in COVID-19 patients[43]. On the other hand, its reciprocal, TGF-β, was positively associated with Covid-19 severity[46] and fibrosis[47]. Even outside the TME, TGF-β promotes fibrosis, counterbalanced by IFN-γ. These cytokines are directly linked to the KTR and IDO. IDO, the enzyme, works to restrain excessive or inappropriate immune activation in the TME[48]

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However, IDO is not only an enzyme induced by IFN-γ (increased KTR) but also an intracellular signal transducer induced by TGF-β (TME)[49][50][51].

Pleiotropism is the expression of different traits by the same gene. IFN-γ can pivot from pro-inflammatory and anti-proliferative to tumor promoter, and TGF-β can pivot from tumor suppressor to tumor promoter. What triggers the pleiotropic switch from tumor suppressor to tumor promoter for either IFN-γ or TGF-β is not clear, but it may be related to the TME milieu, where TGF-β appears to dominate[52]. In an imbalanced (elevated TGF-β/IFN-γ) TGF-β may trigger fibrosis and the TME via paracrine transmission. IFN-γ is generally considered pro-inflammatory but anti-proliferative. However, in the TME, it can induce programmed cell death protein-1 (PD-1) expression linked to metastasis (see figure 3)[53]. TGF-β is generally considered anti-inflammatory and a tumor suppressor, but in the TME, it becomes a tumor promoter, triggering cancer-associated fibroblasts (CAF), epithelial/endothelial mesenchymal transformation (EMT), and vascular endothelial growth factor (VEGF), possibly mediated by methylation of its epigenome. The switch seems to occur in the TME. The relative concentrations of IFN-γ and TGF-β[54] or local hypoxia[55] may instigate this. Interestingly, tumors treated with low-dose IFN-γ acquired metastatic properties, while tumors infused with a high dose of IFN-γ regressed[54].

Perhaps the TGF-β concentration in the TME can trigger a pleiotropic switch in low-dose IFN-γ, but at a higher dose, IFN-γ can modulate its reciprocal in the TME. Cancer cells can also produce TGF-β. Pleiotropic IFN-γ is linked with metastatic behavior via upregulation of PD-1[56]. Angiotensin II stimulates the TGF-β signaling pathway[57]. This may in part explain the predilection for and severity of Covid-19 in males with comorbidities and for recurrent cancer in those previously in remission (see figure 3). On the other hand, females are robust producers of type I interferon[58]. Type 1 IFNs (IFN-α and IFN-β) are first responders to any invading pathogen and trigger the release of interferon-stimulated genes for the synthesis of IFN-γ.

Its reciprocal, TGF-β, is vital to the maintenance of tolerogenesis and avoidance of autoimmunity. If TGF-β/IFN-γ is low, self-recognition and tolerance may be compromised (autoimmunity)[59]. If TGF-β/IFN-γ is high, tumor-associated antigens may be tolerated (cancer)[60]. An increased TGF-β/IFN-γ is also a risk factor for tissue fibrosis[61][62][63].

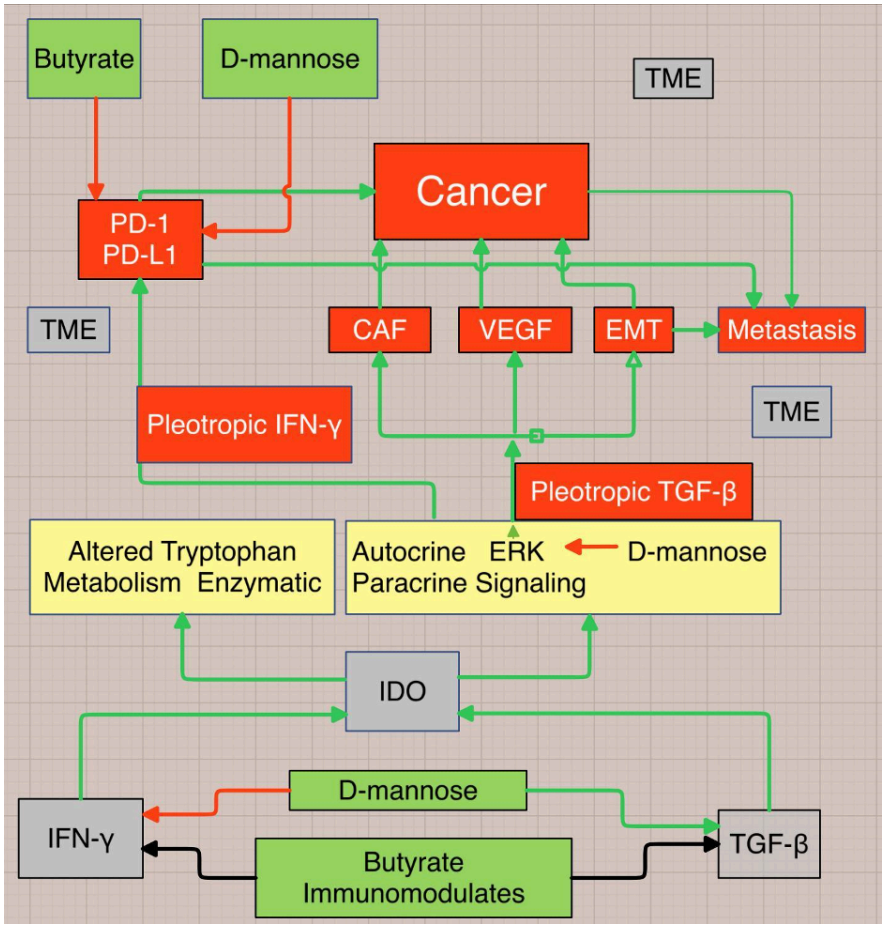

Figure 3. Proposed flow chart leading to cancer, demonstrating the behavior of the cytokines TGF-β and IFN-γ in the tumor microenvironment (TME) that pleiotropically pivot from anti-inflammatory/tumor suppressor to tumor promoter (TGF-β) and from pro-inflammatory/tumor suppressor to tumor promoter (IFN-γ). TME=tumor microenvironment, CAF=cancer-associated fibroblast, VEGF=vascular endothelial growth factor, EMT=epithelial or endothelial mesenchymal transformation, PD=programmed cell death protein-1, ERK=extracellular signal-regulated kinase, IDO=indoleamine 2,3-dioxygenase. Figure 3 complements Figure 2.

5. GPCR

A. GPCR and SARS Cov2

Recent research, including a 2023 international symposium, has focused on AAs targeting G-protein coupled receptors[64]. Their roles in Covid-19[65] and LC have been reported[66]. More than 800 different GPCRs had been identified as of 2020[67]. In one study, a majority of those with POTS possessed adrenergic and muscarinic cholinergic receptor AAs. These are all G-protein coupled receptors, as is AT1R. Antibodies to these receptors are also associated with chronic fatigue syndrome (CFS), fibromyalgia (FM), Covid, LC[68],[69] and with other autoimmune diseases (including SLE, RA, Crohn's disease[70]). Many of these did poorly during the pandemic[71]. POTS or POTS-like symptoms develop in 10-50% of

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long haulers, yet there are significant hormonal differences, e.g., low cortisol in LC[72] but high cortisol in POTS[73],[74]. In POTS, the adrenals respond to ACTH[75], but in LC, they do not, and symptoms can mimic adrenal insufficiency. ACTH receptors are GPCRs, and AAs might inactivate receptors, as GPCR antibodies can activate or inactivate[76]. POTS is easily diagnosed, and pathogenesis points to the baroreflex and the neurohypophysis (see figure 4). The wealth of GPCRs in the involved CNS nuclei[77] and the link between GPCRs and autoimmunity underscore the probable GPCR-induced autoimmune pathogenesis for LC.

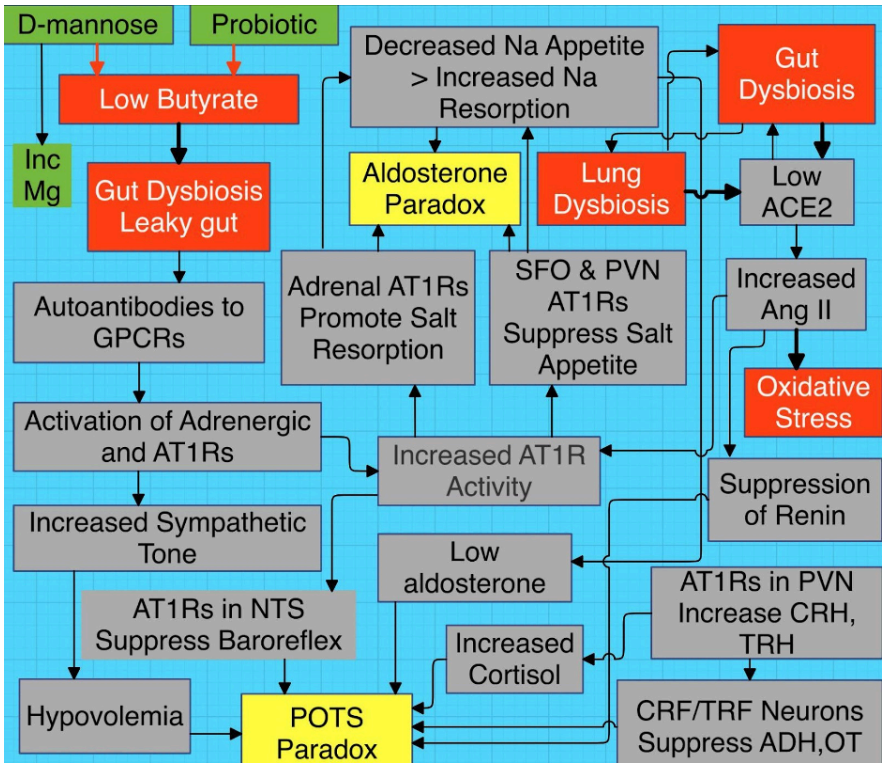

Figure 4. Proposed schema connecting gut dysbiosis (leaky gut) with elevated Ang II, elevated AT1R activity, and oxidative stress. Input from the aldosterone and POTS paradoxes is emphasized. PVN ADH/OT secreting neurons are type 1 magnocellular neurons, and CRH/TRH are type 2. Activation of type 2 inhibits the release of type 1's[78][79]. GPCR=G-protein coupled receptors, NTS=nucleus tractus solitarius, PVN= paraventricular nucleus, SFO=subfornical organ, CRF= corticotropin releasing factor, TRF=thyroid releasing factor, AVP=arginine vasopressin, OT=oxytocin, Mg=magnesium

Although LC and POTS are distinctly different and considered autoimmune, perhaps the wide variety of GPCR AAs in combination with biological individuality explains how one can be a subset of the other. It also appears, not surprisingly, that Covid-19 is also of autoimmune etiology in those with suboptimal gut microbiomes. The gut microbiome in LC[78]>[80] reflects that of Covid-19[81]. Mast Cell Activation Syndrome and Ehlers Danlos Syndrome are linked to POTS[67]. Mast cells are activated by GPCR[82] and GPCRs are involved in the synthesis of collagen[83], as well as the perception of pain[84]. The

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microthrombosis in Covid-19 may be due to AAs to GPCR-bearing platelets[85][86] or phospholipids[87], perhaps reflecting some degree of gut dysbiosis. AAs were present in 50% of those with Covid-19 versus only 15% in healthy controls[88].

B. GPCR and Gut Dysbiosis

The gut-lung axis is based on the concept of continuity between their microbiota, forming a microbial community[89][90]. Cutaneous, nasopharyngeal, and vaginal microbiomes are members of this community. ACE2 receptors are highest in the lung and GI tract[91], primary targets for SARS CoV2. But ACE2 is more than just an enzyme. It is negatively associated with gut dysbiosis[92] and positively associated with tryptophan absorption[34].

G-protein-coupled receptors (GPCRs) are the largest class of cell surface receptors in fungi[93] and Candida is tightly linked to gut dysbiosis and LC[94]. Tryptophan[35] and vitamin D[95] inhibit the commensal yeast-to-pathogenic hyphae transition. GPCRs induce the transition of commensal yeast forms to pathogenic hyphal forms[96] and are required for Candida biofilm formation[97]. Hyphal cell walls are rich in GPCRs[98] that may breach the intestinal barrier and trigger the production of anti-GPCR AAs. Surprisingly, estrogen promotes innate immune evasion of Candida albicans through inactivation of the alternative complement system[99]. Candida and SARS CoV2 may conspire in this process. SARS CoV2 can initiate not only gut dysbiosis through the loss of ACE2-bearing intestinal epithelial cells but also LC symptoms through GPCR AAs induced by Candida-associated gut dysbiosis (see figure 4).

This may also occur in the lungs of ARDS patients, where both invasive Candida[100] and GPCR antibody-mediated lung edema[101] have been reported. Although cell wall/membrane surface GPCRs are only present on eukaryotes, i.e., not on viruses or bacteria, SARS CoV2 appears to be a ligand for some GPCRs[102][103], especially those in the brain[104], e.g., NMDA-Rs (see figure 2) that control taste, smell, and baroreflex and symptoms like brain fog and fatigue[105]. As a ligand, SARS CoV2 can disrupt GPCR signaling[106]. GPCR signaling can also be disrupted by AAs. Why do GPCR AAs figure so prominently, and what is prompting the TGB-β/IFN-γ imbalance? Animals infected with SARS CoV2 generate GPCR AAs to the same AT1Rs, β2 adrenergic, and muscarinic cholinergic receptors encountered in LC[107]. Furthermore, the receptors most frequently targeted by AAs in LC[108] are at least partially regulated by GPCRs - autoimmune thyroiditis (Graves disease, Hashimoto's thyroiditis)[109][110], celiac disease[111][112], inflammatory bowel disease[113], myasthenia gravis[114], pernicious anemia[115], psoriasis[116], RA[117], Sjogren's syndrome[118], SLE[119], type 1 diabetes mellitus (T1DM)[120], and vitiligo[121]. Many of these autoimmune diseases have been escalating for decades before the pandemic (see figure 5). SARS CoV2-induced loss of ACE2-bearing cells and associated gut dysbiosis may have accelerated this. For many of these autoimmune diseases, similar gut microbiomes and concomitant Candida overgrowth have been reported. The linkages are clear, and the notion of causation (Candida) is provocative.

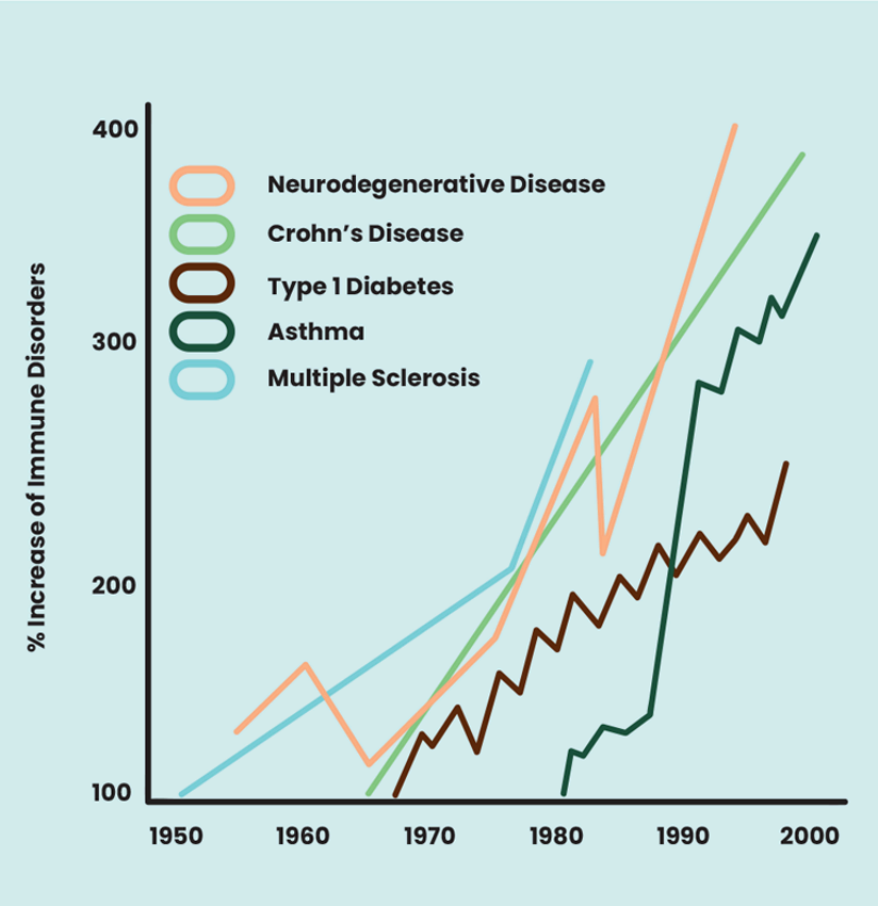

Figure 5. From: Bach, JF, The Effect of Infections on Susceptibility to Autoimmune and Allergic Diseases, NEJM 347(12):911-920.

SARS CoV2 may trigger AAs to GPCRs even in the absence of severe disease[107]. GPCR AAs are associated with dysautonomia and post-viral fatigue disorders[70]. Pre-existing gut dysbiosis, e.g., Candida overgrowth after antibiotics or driven by simple sugars or alcohol, enhanced by a GPCR-related viral assault like SARS CoV2 or HIV[122], may trigger or worsen symptomatic expression, e.g., dysautonomia[123]. But females exhibit more robust T cell activation than males[124] and produce higher levels of interferon[125], predisposing to autoimmunity (see figure 2). Fungal infections, especially Candida, elicit a robust IFN-γ response[126][127] and drive the serotonin to kynurenine pathway pivot (see figure 2). New onset T2DM has been reported post Covid-19[128]. Pancreatic β-cells have numerous GPCRs that can activate or inhibit β-cell insulin secretion[129]. Several autoimmune skin diseases have also been reported post Covid-19. These include alopecia areata in addition to psoriasis and vitiligo. G-protein coupled receptors stimulate hair follicle stem cells and promote activation of the hair cycle[130]. GPCR activity is decreased in psoriatic skin and can be alleviated by topical butyrate[131][132]. Not surprisingly, cutaneous Candida colonization is linked to psoriasis[133]. GPCRs that augment melanocyte growth are depressed in Covid-19/LC-induced vitiligo[134].

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GPCR autoantibody-induced upregulation of AT1R activity also activates JAK/STAT pathways[135]. JAK/STAT pathways are strongly linked to cancer, autoimmunity, and dementia. Cytokine receptors targeted by JAK/STAT signaling are GPCRs[136] and can be activated by AAs[76]. The role of GPCRs in driving cancer has been acknowledged but remains unexplained. Perhaps the gut microbiome might provide answers[137]. JAK inhibitors are very popular in the treatment of autoimmune disease, cancer, and dementia, all linked to the inflammatory triad of TGF-β, IL-6, IL-1β. Interestingly, subclinical AAs to GPCR can be present in otherwise healthy individuals[2].

6. HRV and the Triple Play

A. HRV

The cytokine triad of TNF-α[7][138][139], IL-6[79][140], and IL-1β[79] are negatively linked to HRV and positively linked to CRP[65]. Cancer diagnosis and prognosis are linked to TNF-α[141], IL-1β[142][143], and IL-6. Low HRV can alert one to asymptomatic infection and inflammation[144][145], anxiety[146], depression[147][148], cognition and neurodegenerative disorders[149][150], psychosis spectrum disorders[151], cancer[152][153], cardiovascular disease[154][155], stroke[156][157], T2DM[158][159], severe Covid-19[160], Long Covid[161][162][163], MS[164], SLE[165], and RA[166]. Central, aka visceral, adiposity (waist-hip ratio, waist circumference) is negatively related to HRV and is a much more sensitive indicator than BMI[167][168][169]. Peripheral obesity is not only not associated with a low HRV but is protective with elevated HRV[170].

B. Triple Play

Butyrate enhances mitochondrial function during oxidative stress[171] and rescues tryptophan[172]. Serotonin cannot cross the BBB, but tryptophan can, and by rescuing tryptophan, butyrate can increase brain serotonin (an inhibitory neurotransmitter). Butyrate also suppresses IDO activity[173] and immuno-modulates IFN-γ and TGF-β[174]. Butyrate-producing gut microbiota[175], gut biodiversity, and production of SCFAs[176] are associated with elevated HRV. Unfortunately, butyrate-producing Bacteroidetes species decline with age[177]. Butyrate alleviates obesity and related comorbidities[178][179][180]. But not all SCFAs have beneficial effects on human health. Acetate not only promotes obesity[7][181] but can also be used by tumor cells as an energy substrate during oxidative stress[182]. Postbiotic butyrate bypasses the negative effects[6] of Bacteroides-produced acetate[183].

Prebiotic D-mannose assists dietary fiber in propagating butyrate producers[184]. It enhances intestinal barrier integrity[185] and opposes the proinflammatory effects of glucose and fructose[186]. D-mannose opposes diet-induced obesity[187], which is positively associated with CRP and negatively associated with HRV[188]. Central adiposity is adverse and linked to elevated CRP, while peripheral adiposity is favorable and not so linked[189][190]. D-mannose not only downregulates gut dysbiosis by enhancing intestinal barrier integrity[184][185] but also suppresses the adipokine and cytokine triad (TNF-α, IL-6, IL-1β)[191]

[192][193], linked to cancer[194][195], cardiovascular disease[196], stroke[197], obesity[198], diabetes[199], neurodegenerative disease[200], and autoimmune disease[201][202]. D-mannose suppresses autoimmune diseases, e.g., T1DM, asthma[203], and SLE[203]>[204] by suppressing IFN-γ[39][148]. D-mannose can suppress ERK (extracellular signal regulated kinase) signaling pathways (see figure 3)[205] integral to TGF-β induced organ fibrosis[206], transformation of fibroblasts into CAFs[207], epithelial/endothelial mesenchymal transformation (EMT)[208], and VEGF synthesis[209]. D-mannose inhibits PD-1 (see figure 3)[210], upregulated in Covid-19[211]. This pathway to tumorigenesis is separate but complementary to that induced by TGF-β[212] (see figure 3). Probiotics also increase HRV and have proven efficacious in LC[213][79]. Probiotics and antioxidants are nutraceuticals that have proven most effective in Covid-19 and LC[214]. *Prebiotic is more important than postbiotic*, as SCFA-producing bacteria cannot flourish without dietary fiber or its equivalent (D-mannose).

7. Conclusion

Gut (and lung) dysbiosis and Candida overgrowth-induced GPCR AAs may be at the root of the vast majority of our health problems, including cancer, dementia, autoimmunity, obesity, post-viral fatigue syndrome (LC, CFS, FM, Epstein Barr Virus), and many infectious diseases. A gut leaking Candida hyphae laden with GPCRs stimulates the production of host AAs that activate AT1Rs, adrenergic, and muscarinic receptors, and others at the heart of many comorbidities.

The growing epidemic of LC has spawned tremendous suffering and economic loss. The bidirectional correlations between gut dysbiosis and inflammatory cytokines, disease, and HRV/KTR/CRP make supplementation the most feasible path to better health. This triple play of prebiotic d-mannose, a probiotic of diverse butyrate-producing bacteria, and postbiotic butyrate can provide a strong assist. Limit inflammaging and oxidative stress (see figures 1,4) and embrace antioxidants to maintain mitochondrial health.

Adding exercise to this regimen further energizes HRV[215]. Monitoring a rising HRV and possibly a falling waistline[167][168] due to butyrate[9] and indole[14][15][16] induced GLP-1 can provide positive feedback and boost incentive during the effort. This approach affords the individual an inexpensive and convenient path to a more healthful existence without necessarily forcing dietary and other lifestyle changes. Changing one's diet may be more difficult than changing one's religion.

Obtaining an accurate HRV via a Bluetooth-enabled chest strap, armband, finger sensor, or wristwatch can be tedious, but HRV is especially useful in following the benefits of dietary changes,[216] and significant benefits to a more healthful lifestyle and lifespan[217] await.

Although the ideas proposed in this review are in part speculative and underscore associations, they do not prove causation. That remains for randomized controlled trials.

> "Death sits in the bowel." Hippocrates (400 BC)
>
> "Mouths affected with aphthous ulcerations" Hippocrates' description of oral candidiasis (400 BC)[218]

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