Commentary

Candida, the Gut Microbiome, and the Epidemic Levels of Cancer and Autoimmune Disease in Young Women, Dementia, and Obesity

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Candida, especially C. albicans, has traditionally only been framed as an opportunistic infection. Unfortunately this rather limited view has impeded appreciation for this pathobiont and its growing role as a facilitator of gut dysbiosis and limited gut biodiversity. Candida overgrowth (CO) is linked to a gut microbiome that lacks biodiversity and sufficient butyrogenic bacteria. CO promotes intestinal permeability (leaky gut) and upregulates the estrobolome. The former is associated with dementia and autoimmune disease (AID) and the latter with many hormone driven cancers. Most appear to be estrogen receptor positive. Obesity predisposes to CO and to hormone driven cancers, dementia, AID, dementia, cardiovascular disease (CVD), and infectious disease. All report altered tryptophan metabolism (ATM). Candida can create its own indoleamine dioxygenase (IDO) to manipulate levels of this essential amino acid that otherwise inhibits hyphal morphogenesis. Candida releases numerous proteases and induces release of bacterial proteases as well. These proteases activate protease activated receptor (PAR2), linked to IBS (irritable bowel syndrome), IBD (inflammatory bowel disease), progression of estrogen receptor (ER) positive cancers, and AID. To quell proteolytic hyperactivity, gut microbiota produce an inhibitor - β-glucuronidase. This deconjugates estrogen in bilirubin otherwise destined for excretion, enabling its reabsorption. This Candida enabled increase in circulating estrogen may be the facilitator of this epidemic of cancer and AID in young women. Although the connection between CO and this unforgiving epidemic is enticing and supported by the pathophysiology, definitive clinical confirmation is required.

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I. Introduction

The Western diet, high in refined carbohydrates and low in fiber, promotes an imbalanced gut microbiome. The result is gut dysbiosis, characterized by low biodiversity. However, there are certain biomarkers that suggest a prominent role for CO in the development of gut dysbiosis and subsequent risks for cancer, dementia, AID, cardiovascular disease, infectious disease, and obesity. These include altered tryptophan metabolism (ATM) and increased kynurenine to tryptophan ratio, increased zonulin and intestinal permeability, and periodontitis linked to fungal biofilms. Both zonulin and periodontitis (gingivitis) have also been independently linked to these same human diseases (see figure 1).

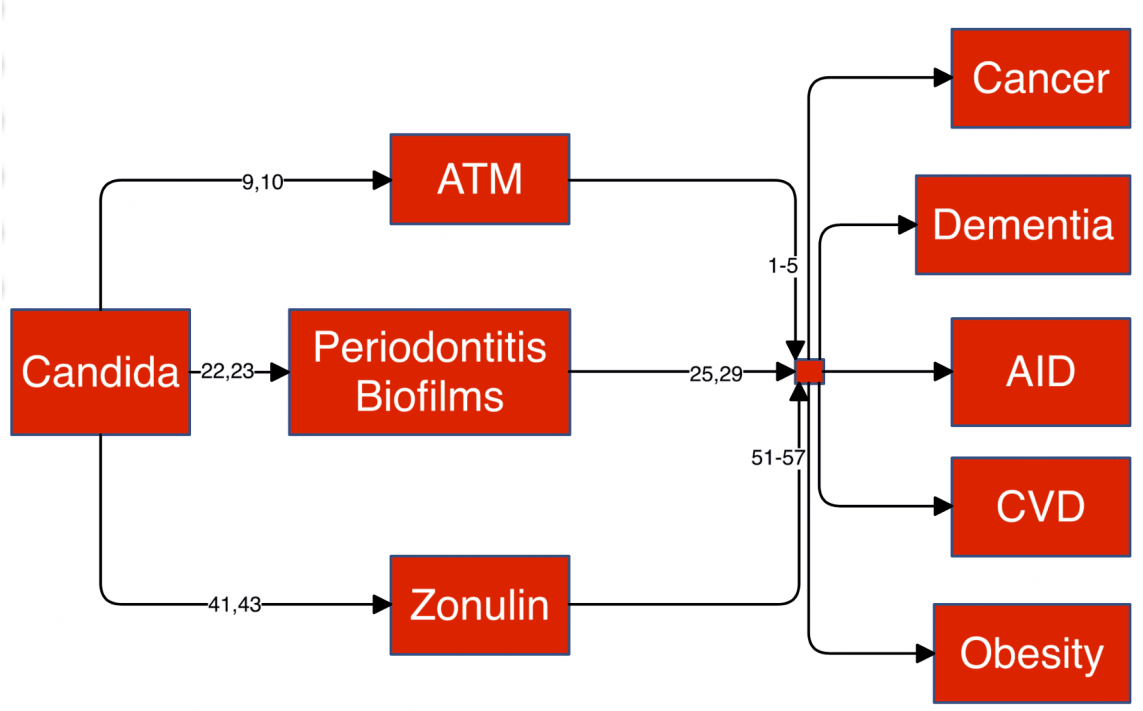

Figure 1. This hypothetical figure links Candida with cancer, AID, dementia, CVD, and obesity. Numbers are references.

Increased proteolytic activity characterizes gut dysbiosis, e.g., irritable bowel syndrome (IBS), leaky gut, celiac disease, inflammatory bowel disease (IBD). These proteases activate receptors (PAR2), linked to progression of ER+ cancers and AID. Gut microbial β-glucuronidase inactivates these microbial proteases by unconjugating bilirubin. This includes estrogen. Unconjugated estrogen, otherwise destined for excretion, can then be reabsorbed. Sustained exposure of estrogen receptor (ER) positive cells to elevated

levels of estrogen may hypothetically drive many hormone dependent cancers and AID, especially in young females, dementia in the elderly, and obesity in both (see figure 2). All are now globally epidemic.

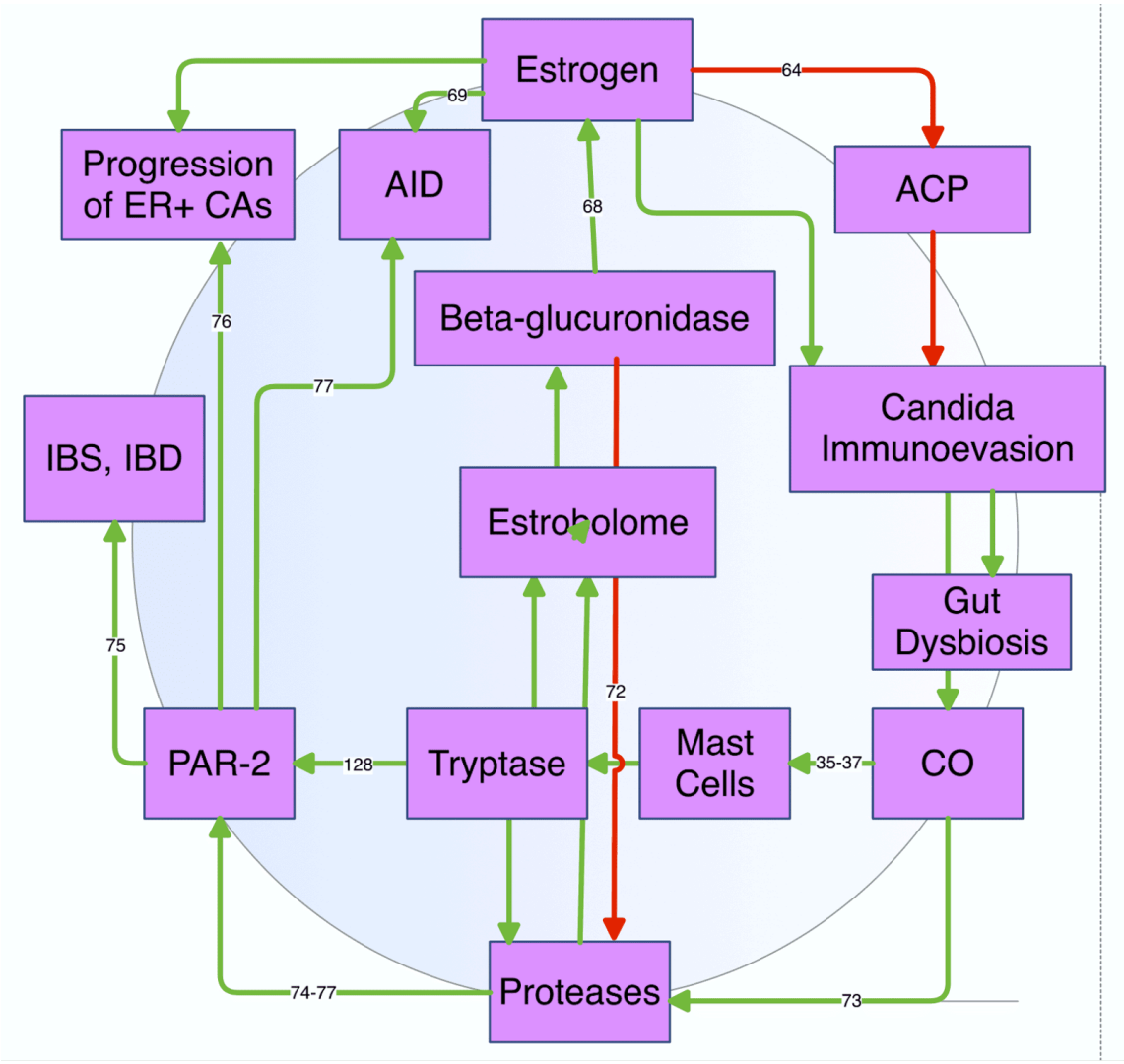

Figure 2. This is a hypothetical view for the vicious circle that CO (Candida overgrowth) may mediate. MCAS, POTS, and hEDS are each about three to four times more common in females. ACP is the alternative complement pathway, AID is autoimmune disease, PAR is protease activated receptor, IBS is irritable bowel syndrome, IBD is inflammatory bowel disease, ER is estrogen receptor, and CA is cancer.Numbers are references.

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II. Candida Overgrowth and ATM

The role of Candida and its impact on the gut microbiome as a pathobiont has been overlooked and marginalized in favor of its longstanding role as an opportunist in the immunocompromised.

However, one of the most persuasive arguments for its impact as a pathobiont is ATM, linked to cancer[1], dementia [2], CVD [3], AID [4], obesity [5], Covid-19 [6][7], and long Covid [8].

There are three pathways for tryptophan metabolism (see figures 3,5) - indole, a longevity agent produced by intestinal bacteria (<5%); serotonin, produced by the host (<5%); and kynurenine, production shared by the host and Candida, driven by indoleamine dioxygenase (IDO) and IFN gamma. IDO is the rate limiting step in the metabolism of tryptophan along the kynurenine pathway (95%). Candida can synthesize its own IDO, 31% homologous with human IDO [9].

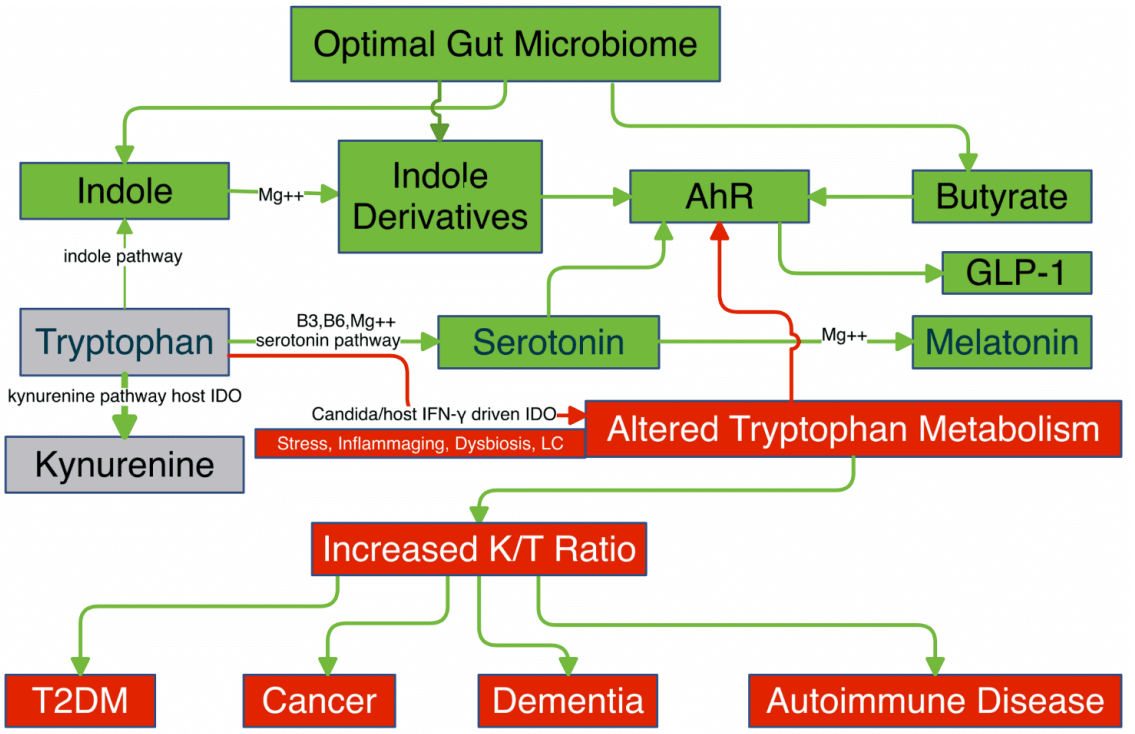

Figure 3. This figure proposes a model framework for the interrelationships between pro-inflammatory cytokines/inflammaging/oxidative stress and the major diseases afflicting humans, mediated by gut dysbiosis and Candida overgrowth. AhR is aryl hydrocarbon receptor; GLP is glucagon-like peptide; K/T is kynurenine to tryptophan ratio. Red boxes and arrows indicate unhealthful conditions and inhibition respectively.

Although some articles restrict the synthesis of IDO to eukaryotes (mammals and fungi), others contest this and include some bacteria, which may also produce TDO. However, ultimately only mammalian IDO and fungal IDO show high efficiency for Trp degradation along the kynurenine pathway [10].

The interplay between fungal and mammalian IDO seems to modulate tryptophan, permitting the benefits of Candida the commensal, while avoiding the dangers of Candida the pathobiont.

Butyrogenic bacteria can down regulate IDO [11] and suppress IFN gamma, TNF-alpha, IL-6, and IL-1 [12], all of which up-regulate IDO. Candidal IDO and host IDO oppose each other [9] but maintain a balance via luminal tryptophan between hyphal morphogenesis and bacterial overgrowth [13]

ATM reflects not only immune function but also neuroendocrine function. This cross linkage can be seen with cortisol, which responds to stress [14]. Lactobacilli [15] and Bifidobacteria [16] counts are negatively associated with cortisol levels. Unsurprisingly elevated cortisol is a risk factor for Candida overgrowth [17]. Cortisol suppresses gut microbiome diversity [18]. ATM is also associated with decreased gut biodiversity [19], which increases risks for AID and dementia [20]. This incriminates Candida as a central player in gut dysbiosis, as CO is tightly linked to ATM [19].

Candida Overgrowth and Biofilms

Gut dysbiosis and biofilm formation are linked. Biofilms are seen in irritable bowel syndrome, inflammatory bowel diseases, gastric cancer, and colorectal cancer [21], although they are most readily appreciated in the oral cavity. Candida is integral to the formation of tenacious biofilm structures, either alone or in mixed species communities [22]. These biofilms, composed of pathobionts, drive periodontitis aka gingivitis [23].

Unfortunately there is an unrecognized global epidemic of periodontitis [24]. It is a sentinel risk indicator for cancer, dementia, AID, CVD, and chronic diseases in general [25]. Periodontitis is linked to both CO and gut dysbiosis. Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola are not only pathobionts but also the majority of pathogenic bacteria involved in periodontitis [26]. All conspire with Candida to form biofilms [27]. Porphyromonas gingivalis mediated periodontitis has been linked to CVD, dementia, and AID [28]. Periodontitis is also linked with obesity [29]. The dysbiotic change in the oral cavity due to periodontitis is linked directly and indirectly to systemic diseases such as IBS, neurodegenerative diseases, muscle joint diseases, respiratory infections [30], cancer risks in general, especially GI cancers [31], dementia [32], and CVD [33]. Periodontitis increases the kynurenine to tryptophan ratio (K/T) [34]. Mast cells are biomarkers for periodontitis [35][36]. Hyphae linked to periodontitis can activate mast cells [37], which release histamine and tryptase. Hypermobility spectrum disorder, a genetic connective tissue disorder, is tightly linked to gut dysbiosis and can accompany MCAS and POTS, often referred to as the trifecta. Elevated tryptase links all three [38]. POTS patients exhibit low gut biodiversity [39]. Might intestinal dysmotility in hypermobility spectrum disorder [40] predispose CO and gut dysbiosis?

III. Candida Overgrowth and Zonulin

Zonulin is a biomarker for increased intestinal permeability and loss of barrier integrity. Yeast overgrowth is reported in the majority of those with elevated zonulin [41]. Zonulin is elevated in IBS [42] and celiac disease. The hyphal wall protein (Hwp1), expressed on Candida hyphae, resembles the gluten protein gliadin (celiac disease) and they exhibit humoral cross-reactivity [43]. Increased serum zonulin levels are linked with autism spectrum disorder [44], celiac disease [45], inflammatory bowel disease [46], especially Crohn's disease [47], type1 & 2 diabetes [48][49], and insulin resistant obesity [50]. Most of these AIDs have surged over recent decades (see figure 4). Zonulin mediated AID affects about one in ten and rates may be rising by 12-19 % annually worldwide [51].

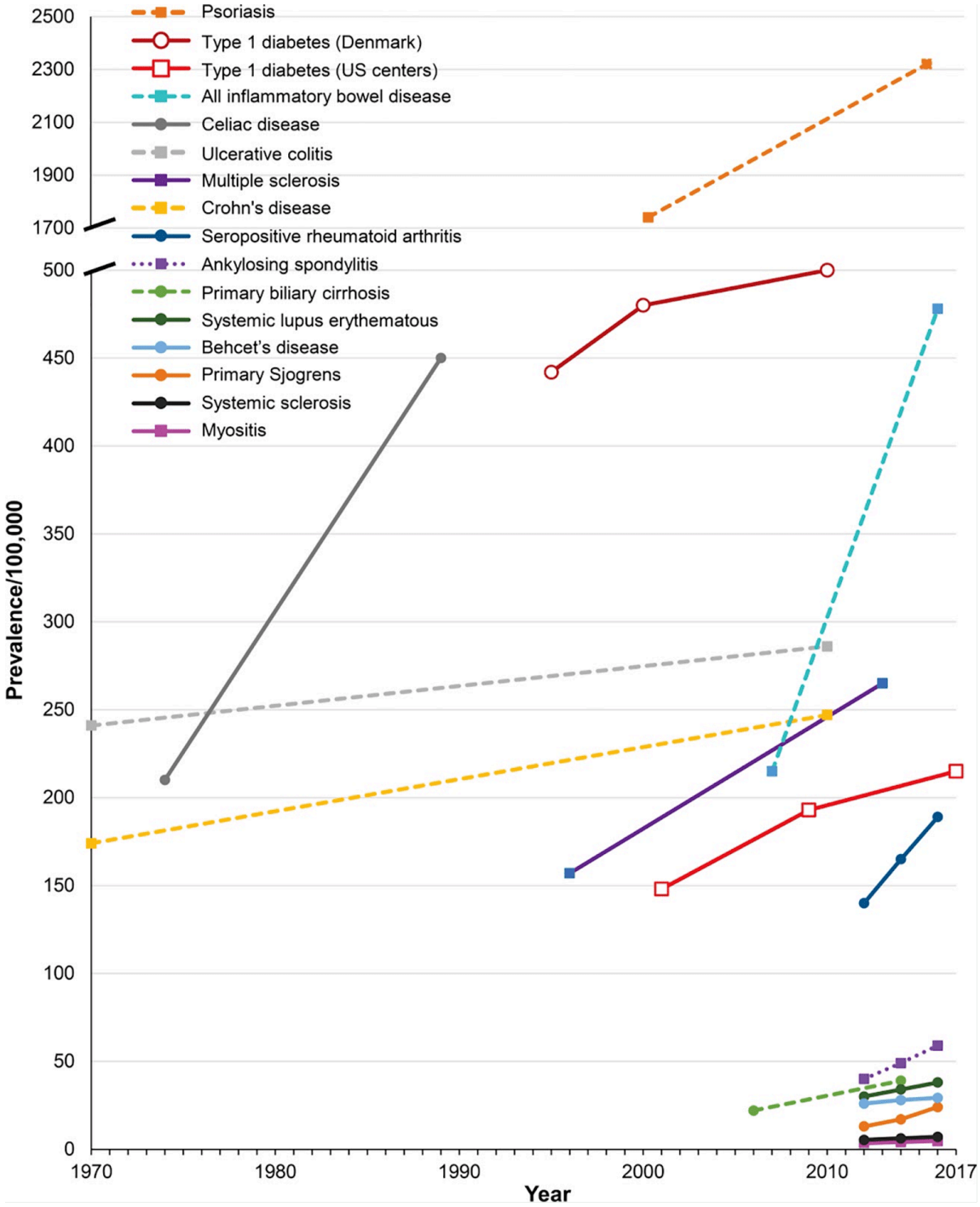

Figure 4. This figure from FW Miller [51] demonstrates the rapid escalation of AID, especially SLE, IBD, psoriasis, multiple sclerosis, rheumatoid arthritis, and celiac disease, over the last half century.

Zonulin also characterizes some cancers. e.g., glioblastoma multiforme (GBM) [52] and colorectal cancer [53], as well as dementia [54], CVD [55], AID [56], obesity [57], severe Covid-19 [52], and long Covid [58].

All of these entities are also linked to ATM, although there are no reports linking zonulin with ATM, other than via gut dysbiosis and CO.

As a biomarker for increased intestinal permeability, zonulin raises metabolic risks in the overweight [59]. Weight loss decreases zonulin levels [60]. Not surprisingly Candida overgrowth is more prevalent in the obese [61]. Unfortunately the incidence of obesity is increasing at an alarming rate. Fifty years ago only 5% of children were obese. That number is now over 12%. This grows to 22% during adolescence and 40% as adults [62]. Morbid obesity is 10% and growing [63].

Surprisingly estrogen promotes immunoevasion by Candida [64]. It suppresses the alternative complement pathway, but upregulates IFN gamma (see figure 2) [65]. Obesity enhances dysbiosis by reducing microbiome diversity. It also upregulates the estrobolome, leading to increased systemic estrogen levels [66], making the relationship between estrogen and obesity bidirectional [67]

IV. Gut Microbiome and the Estrobolome

The estrobolome is a collection of bacteria in the gut that can deconjugate estrogen. Estrogen is normally metabolized in the liver and excreted as conjugated bilirubin. Certain bacteria associated with gut dysbiosis can deconjugate this metabolite back to estrogen for intestinal reabsorption. β-glucuronidase is the enzyme that enables this deconjugation and is a key factor in regulating host estrogen metabolism [68]

This reabsorbed estrogen represents an excess that can stimulate estrogen receptor (ER) positive cells and upregulate cancer risks. Estrogen may also compromise intestinal epithelial tight junction integrity and increase permeability, potentiating AID risk [69]. This appears to involve zonulin disruption of the zonula occludens tight junctions. CO is associated with increased β-glucuronidase activity due to proteolytic activity of its secreted proteases, especially aspartic proteases [70] and to that of opposing bacteria induced by Candida (see figure 5).

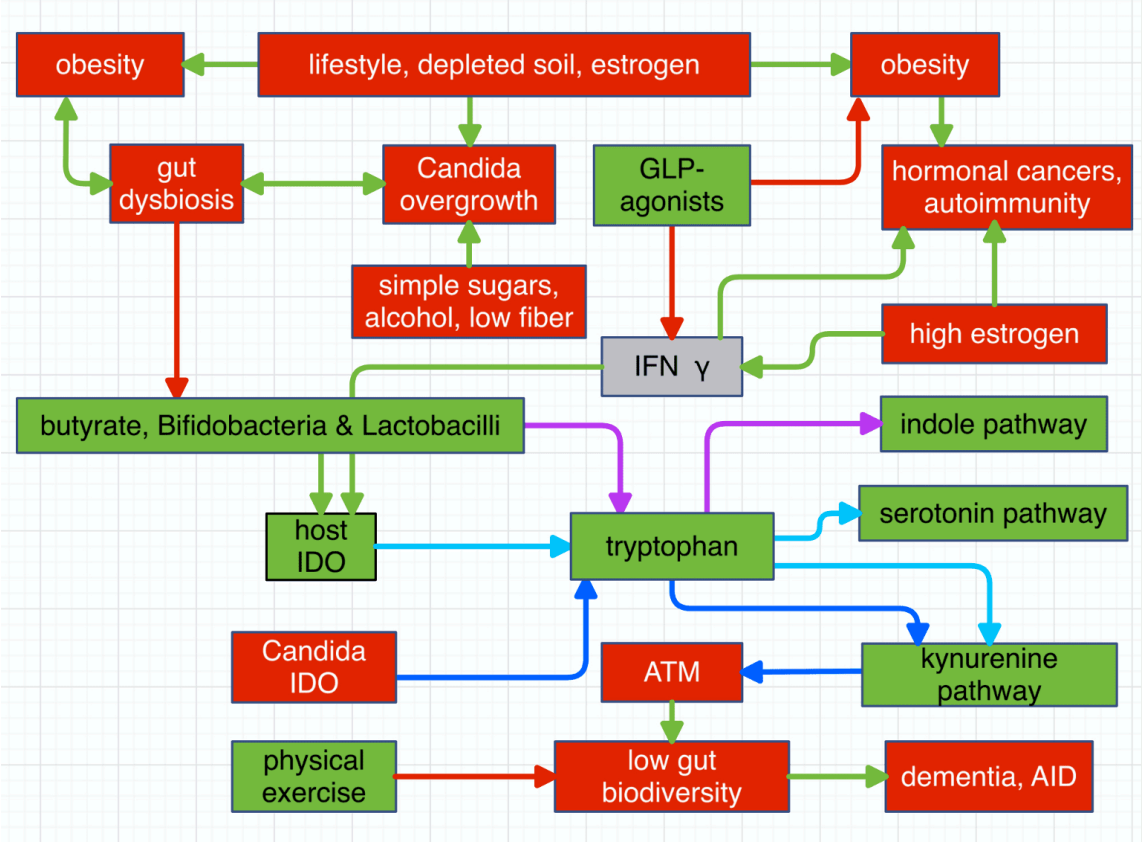

Figure 5. This figure proposes a hypothetical view connecting gut dysbiosis and the estrobolome driving hormone related cancers. Candida overgrowth may play a prominent role. The neutral gray box containing pleiotropic IFN-gamma can be either pro- or anti-inflammatory. Red boxes and arrows indicate unhealthful conditions and inhibition respectively.

Overactivity of bacterial proteases have emerged as crucial players in intestinal diseases [71]. Gut microbiota can suppress intestinal proteolytic activity through production of unconjugated bilirubin. This occurs via microbial β-glucuronidase. Proteases and β-glucuronidase are inverses and modulate each other [72].

Luminal proteases, e.g., aspartyl proteases, can initiate hyphal morphogenesis. These can arise directly from Candida albicans [73] or indirectly by protease secreting bacteria. Proteolytic bacterial expansion during colitis amplifies inflammation via host receptor (PAR2) tied to pain [74]. Activation of this receptor has been linked to IBS and IBD [75], progression of ER positive cancers [76], and AID [77].

Furthermore, candidalysin released by Candida is bactericidal and induces additional proteolytic activity, which exacerbates this proteolytic milieu [78]. This lowers gut biodiversity, entrenches gut dysbiosis, and

increases β-glucuronidase activity, upregulating the estrobolome [79]. SARS CoV2 driven host cathepsins (proteases) and serine proteases from immune cells [80] may exacerbate any pre-existing dysbiotic proteolytic activity due to CO. Indeed CO may drive long Covid [81]

Lactobacillus and Bifidobacterium keep β-glucuronidase levels in check, ensuring a proper balance between estrogen excretion and reabsorption. Butyrate producing intestinal bacteria, biomarkers for a healthy gut microbiome, can also reduce β-glucuronidase activity [82]. β-glucuronidase is a specific biomarker for colorectal [83] and breast cancer [84], which display ERs, and for pancreatic cancer [85]

ERs are present on non-small cell lung cancer (NSCLC) cells [86], which comprises 85% of all lung cancers. β-glucuronidase by "breath biopsy" has even been recommended for early detection of lung cancer [87]. ERs are also present on some pancreatic cancer cells [88], endometrial cancer cells [89], and gastric cancer cells [90]. The vast majority of prostate cancers are AR and/or ER positive [91]. Conjugated androgens are also secreted by the liver and can be deconjugated by bacterial β-glucuronidase.

These cancers - lung, breast, colon, and pancreas - constitute the top four most lethal cancers and their incidence and those of gastric, endometrial, and prostate have increased significantly over the past few decades and are predicted to increase 30% globally from 2019 to 2030 [92]

A 2025 report from the American Cancer Society demonstrated that women under age 50 had an 82% higher cancer rate than men in the same age group in 2021, up from 51% in 2002.

The increased incidence of breast, ovarian, and endometrial cancer in younger females has become mainstream. Thyroid, gastric, and pancreatic cancers can be added to this list. There is abundant circumstantial evidence that links greater ER positivity to all of these, otherwise present in less than 1% of non-gynecologic cancers. Many of these ER positive cancers are neuroendocrine tumors, e.g., carcinoids. Although less frequently encountered than in gynecologic malignancies, ER positivity in neuroendocrine tumors is an order of magnitude more frequent than in their non-gynecologic counterparts [93].

Neuroendocrine tumors are primarily gastrointestinal, including the pancreas, and pulmonary in origin. The relative frequency of neuroendocrine cancers versus that of epithelial cancers in these organs with increasing cancer rates is not clear.

Establishing a correlation between ER positivity and the cancer epidemic in young women is complex. For example, there has also been an increase in oral cavity cancers due to HPV and in melanoma,

frequently over diagnosed. These tumors are rarely ER positive. The increase in thyroid cancers is predominantly due to the increase in papillary carcinoma, which is not considered a neuroendocrine tumor. Yet 50% of the tumors are ER positive [94].

On the other hand, ERs are present in GBM [95], which, unlike other brain tumors, may be increasing [96]. According to the French Public Health Agency (2019), the incidence of glioblastoma multiforme increased fourfold between 1990 and 2015. Similar increases were noted in the US and Australia. The increase in young adults was noteworthy. The incidence of carcinoids has also increased in recent decades, especially in women [97] and Covid-19 may have boosted this. The SARS CoV2 virus enters ACE2 receptor bearing intestinal epithelial cells. This receptor is integral to absorption of neutral amino acids [98] and their loss compromises absorption of tryptophan and methionine, two of the eight neutral (nonpolar) essential amino acids. Loss of tryptophan promotes ATM and loss of methionine down regulates methylation (see figure 6). According to the CDC, the MTHFR variant allele that dictates this folate cycle rate limiting step is present in more than 50% of Americans. Methionine synthase (MS) is inhibited by acetaldehyde, a metabolite of alcohol, produced in abundance by Candida. Methylation is critical to the operation of the epigenome. Methylation helps prevent DNA mutations and activates many proteins.

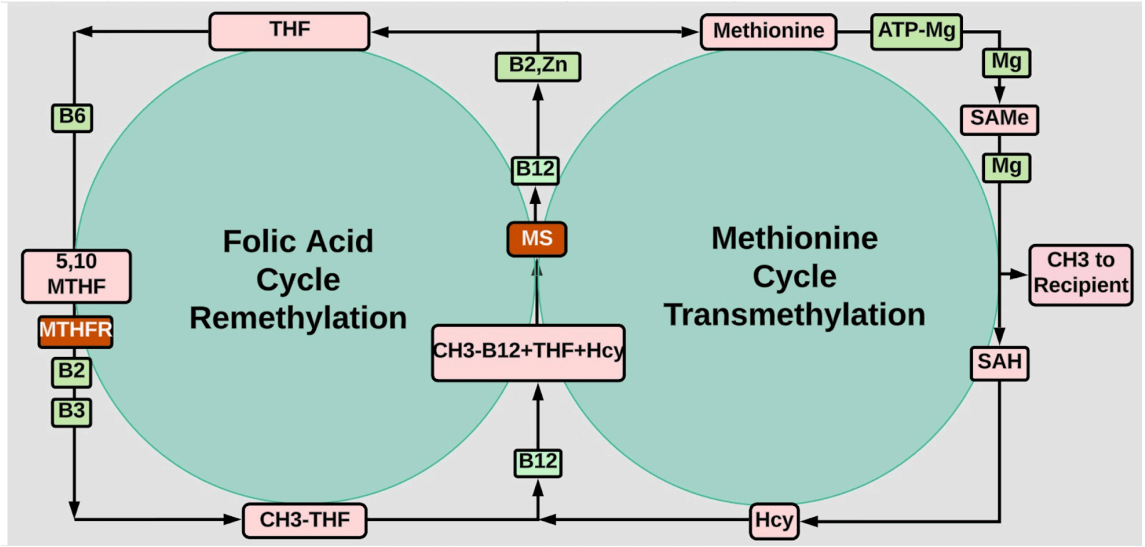

Figure 6. MTHFR is methylene tetrahydrofolate reductase from a variant allele, present in 50% of the population (35% reduction in activity with single allele, 70% with homozygous state), MS is methionine synthase, inhibited by acetaldehyde, SAMe is S-adenosyl methionine, required for virtually 100% of methylation needs. Note the importance of Mg and Mg dependent B2,3,6,9,12.

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Elevated levels of β-glucuronidase are linked to the Western diet of processed food, especially high meat and fat [99]. A diet high in plant-based foods, particularly complex carbohydrates, and lower in fat and animal proteins prevents inflammation and positively modulates gut microbiota [100]. Hunter gatherers exhibit greater gut microbiome diversity compared to those predominantly on a processed fast food type diet [101].

V. Therapeutic Interventions

As recognized by Hippocrates (400 BC), the gut microbiome and its biodiversity are the primary determinants of human health.

Avoiding processed/ultra processed foods (low in fiber) and refined carbohydrates is extremely difficult. Consequently, the most rational approach invokes some degree of supplementation.

Prebiotics, e.g., dietary fiber or supplemental d-mannose, probiotics, e.g., yogurt or other sources rich in Bifidobacteria and Lactobacilli, and postbiotics, e.g., butyrate, constitute excellent support for a healthy gut microbiome. Fermented foods (kimchi and sauerkraut) increase microbiome diversity and decrease markers of inflammation [102]. Probiotics with lactobacilli and bifidobacteria increase intestinal lactate and are recommended for possible prevention of and/or survival from breast cancer [103]. L. acidophilus is especially effective at suppressing CO [104][105]. Lactate producing bacteria crossfeed butyrogenic bacteria. Butyrate reduces appetite by upregulating glucagon-like peptide 1 (GLP1) [106]. GLP-1 also downregulates the production of pro-inflammatory cytokines, such as IFN-γ, TNF-α, IL-6, and IL-8, thereby opposing inflammaging and oxidative stress [12]. The chronic low grade inflammation of gut dysbiosis drives this pro-inflammatory cytokine production. The consequent increase in ROS creates oxidative stress [107].

Candida and cancer cells (Warburg effect) thrive on sugar. Candida ferments simple sugars to alcohol and acetaldehyde, toxic to the rate limiting step in the methionine cycle, critical to one carbon metabolism (methylation). Candida and cancer cells also produce histone deacetylase (HDAC) [108][109], which damages DNA/RNA. Butyrate also inhibits HDAC [110] and is a beneficial aryl hydrocarbon receptor (AhR) ligand that promotes an optimal gut microbiome. Butyrate producing intestinal bacteria, biomarkers for a healthy gut microbiome, can also reduce β-glucuronidase [82]

Low Mg impedes intestinal biodiversity [111], promotes oxidative stress and inflammaging [112], and increases the pro-inflammatory state [113]. Mg supplementation reduces these pro-inflammatory

cytokines [114]

Increasing B vitamins that require Mg dependent activation is an antifungal strategy [115]. These B vitamins include Mg dependent phosphorylation for B1,2,3,5,6 and Mg dependent methylation for B9,12. Bacteria and Candida compete for luminal Mg. Candida overgrowth can deplete ingested Mg, making less available for the host. Lower levels of Mg dependent B5 are associated with a higher preference for sugar [116]. Mg dependent B5 dependent acetate CoA-transferase is the final enzyme required for the synthesis of butyrate by gut bacteria [117].

D3 is the primary supplemental form for vitamin D. Most of the benefits of vitamin flow through its Mg dependent active form $1,25(OH)_2D$. However, luminal D3 [118] and tryptophan [9] inhibit Candida hyphal morphogenesis and glutamine can prevent acetaldehyde induced damage to intestinal barrier integrity [119]. Physical exercise enhances biodiversity [120] and associated increases in lactate provide food for butyrogenic bacteria [121].

Antibiotics indiscriminately eliminate gut microbiota, lowering biodiversity. The microbiome is established early in life [122]. The use of antibiotics in children under one is rising [123] and this is linked to greater risk for obesity [124][125], gut dysbiosis [126] and inflammatory bowel disease [127].

Candida is resistant to most broad spectrum antibiotics and their use eliminates many beneficial enteric bacteria, e.g., lactobacilli. This creates a vacuum that Candida can fill. Peptidoglycan subunits released by bacteria upon antibiotic treatment can promote C. albicans dissemination from the intestine [128]. Broad spectrum antibiotics also enhance Candida biofilm formation and dissemination [129]

VI. Conclusion

Levels of circulating estrogen depend on a balanced gut microbiome. Estrogen facilitates immunoevasion by Candida. Candida upregulates intestinal proteolytic activity and activates PAR2, linked to progression of ER positive cancers and autoimmunity. This increase in proteolytic activity is opposed by microbial β-glucuronidase, which deconjugates bilirubin. This enzyme is a biomarker for increased estrobolome activity. Sustained elevation of estrogen is linked to many hormone dependent cancers, e.g., breast cancer, colorectal cancer, and AID in the young and dementia in the elderly. Not all ER positive cancers are gynecologic, e.g., papillary thyroid carcinoma, GBM.

CO driven gut dysbiosis and low biodiversity upregulate the estrobolome, increase intestinal permeability, alter tryptophan metabolism, and facilitate biofilm formation. Candida overgrowth is linked not only to ATM but also to zonulin and oral biofilms (periodontitis). These in turn share linkages with cancer/dementia/CVD/AID/infectious disease/obesity. However, associations do not prove causation, although the implications are enticing. Nonetheless, there is circumstantial evidence that the growing role of refined carbohydrates and low fiber in the western diet may contribute to the epidemic of cancer and autoimmune disease in young women, dementia, and obesity. Gut dysbiosis of bacterial origin, e.g., small intestine bacterial overgrowth (SIBO) without concomitant small intestine fungal overgrowth (SIFO) and absent antibiotic therapy, does not appear to target females. Candida does, possibly linking Candida overgrowth and its estrogen enabled immuno-evasion to this epidemic.

There are many intersecting pathophysiologic pathways and discerning a pattern is difficult. Accordingly, the views discussed are speculative and subject to more definitive clinical correlation.

References

1. ^ *Zhao J, Bai X, Du J, Chen Y, Guo X, Zhang J, et al. (2025). "Tryptophan Metabolism: From Physiological Functions to Key Roles and Therapeutic Targets in Cancer (Review)." Oncol Rep. **54**(1):1–16. doi:10.3892/or.2025.8919.*
2. ^ *Li D, Yu S, Long Y, Shi A, Deng J, Ma Y, et al. (2022). "Tryptophan Metabolism: Mechanism-Oriented Therapy for Neurological and Psychiatric Disorders." Front Immunol. **13**:985378. doi:10.3389/fimmu.2022.985378.*
3. ^ *Zhang J, Jiang X, Pang B, Li D, Kang L, Zhou T, et al. (2024). "Association Between Tryptophan Concentrations and the Risk of Developing Cardiovascular Diseases: A Systematic Review and Meta-Analysis." Nutr Metab (Lond). **21**(1):82. doi:10.1186/s12986-024-00857-1.*
4. ^ *Brown J, Robusto B, Morel L (2020). "Intestinal Dysbiosis and Tryptophan Metabolism in Autoimmunity." Front Immunol. **11**:1741. doi:10.3389/fimmu.2020.01741.*
5. ^ *Cussotto S, Delgado I, Anesi A, Dexpert S, Aubert A, Beau C, et al. (2020). "Tryptophan Metabolic Pathways Are Altered in Obesity and Are Associated With Systemic Inflammation." Front Immunol. **11**:557. doi:10.3389/fimmu.2020.00557.*
6. ^ *Takeshita H, Yamamoto K (2022). "Tryptophan Metabolism and COVID-19-Induced Skeletal Muscle Damage: Is ACE2 a Key Regulator?" Front Nutr. **9**:868845. doi:10.3389/fnut.2022.868845.*

7. ^Essex M, Millet Pascual-Leone B, Löber U, Kuhring M, Zhang B, Brüning U, et al. (2024). "Gut Microbiota Dysbiosis Is Associated with Altered Tryptophan Metabolism and Dysregulated Inflammatory Response in COVID-19." npj Biofilms Microbiomes. **10**(1):66. doi:10.1038/s41522-024-00538-0.
8. ^Al-Hakeim HK, Abed AK, Moustafa SR, Almulla AF, Maes M (2023). "Tryptophan Catabolites, Inflammation, and Insulin Resistance as Determinants of Chronic Fatigue Syndrome and Affective Symptoms in Long COVID." Front Mol Neurosci. **16**:1194769. doi:10.3389/fnmol.2023.1194769.
9. a, b, cBozza S, Fallarino F, Pitzurra L, Zelante T, Montagnoli C, Bellocchio S, et al. (2005). "A Crucial Role for Tryptophan Catabolism at the Host/Candida albicans Interface." J Immunol. **174**(5):2910–2918. https://www.researchgate.net/publication/8004194.
10. ^Yuasa HJ, Ball HJ (2015). "Efficient Tryptophan-Catabolizing Activity Is Consistently Conserved Through Evolution of TDO Enzymes, But Not IDO Enzymes." J Exp Zool Pt B. **324**(2):128–140. doi:10.1002/jez.b.22608.
11. ^Martin-Gallausiaux C, Larraufie P, Jarry A, Béguet-Crespel F, Marinelli L, Ledue F, et al. (2018). "Butyrate Produced by Commensal Bacteria Down-Regulates Indolamine 2,3-Dioxygenase 1 (IDO-1) Expression via a Dual Mechanism in Human Intestinal Epithelial Cells." Front Immunol. **9**:2838. doi:10.3389/fimmu.2018.02838.
12. a, bSun H, Hao Y, Liu H, Gao F (2025). "The Immunomodulatory Effects of GLP-1 Receptor Agonists in Neurogenerative Diseases and Ischemic Stroke Treatment." Front Immunol. **16**:1525623. doi:10.3389/fimmu.2025.1525623.
13. ^Bozza S, Fallarino F, Pitzurra L, Zelante T, Montagnoli C, Bellocchio S, et al. (2005). "A Crucial Role for Tryptophan Catabolism at the Host/Candida albicans Interface." The Journal of Immunology. **174**(5):2910–2918. doi:10.4049/jimmunol.174.5.2910.
14. ^Myint K, Jacobs K, Myint AM, Lam SK, Henden L, Hoe SZ, et al. (2021). "Effects of Stress Associated with Academic Examination on the Kynurenine Pathway Profile in Healthy Students." PLoS ONE. **16**(6):e0252668. doi:10.1371/journal.pone.0252668.
15. ^Chong HX, Yusoff NAA, Hor YY, Lew LC, Jaafar MH, Choi SB, et al. (2019). "Lactobacillus Plantarum DR7 Alleviates Stress and Anxiety in Adults: A Randomised, Double-Blind, Placebo-Controlled Study." BM. **10**(4):355–373. doi:10.3920/bm2018.0135.
16. ^Aizawa E, Tsuji H, Asahara T, Takahashi T, Teraishi T, Yoshida S, et al. (2019). "Bifidobacterium and Lactobacillus Counts in the Gut Microbiota of Patients With Bipolar Disorder and Healthy Controls." Front Psychiatry. **9**:730. doi:10.3389/fpsyt.2018.00730.

17. ^Li Z, Denning DW (2023). "The Impact of Corticosteroids on the Outcome of Fungal Disease: A Systematic Review and Meta-Analysis." Curr Fungal Infect Rep. **17**(1):54–70. doi:10.1007/s12281-023-00456-2.

18. ^Hickmott AJ, Boose KJ, Wakefield ML, Brand CM, Snodgrass JJ, Ting N, et al. (2022). "A Comparison of Faecal Glucocorticoid Metabolite Concentration and Gut Microbiota Diversity in Bonobos (Pan Paniscus)." Microbiology. **168**(8). doi:10.1099/mic.0.001226.

19. a, bTaleb S (2019). "Tryptophan Dietary Impacts Gut Barrier and Metabolic Diseases." Front Immunol. **10**:2113. doi:10.3389/fimmu.2019.02113.

20. ^Zhang R, Ding N, Feng X, Liao W (2025). "The Gut Microbiome, Immune Modulation, and Cognitive Decline: Insights on the Gut-Brain Axis." Front Immunol. **16**:1529958. doi:10.3389/fimmu.2025.1529958.

21. ^Jandl B, Dighe S, Baumgartner M, Makristathis A, Gasche C, Muttenthaler M (2024). "Gastrointestinal Biofilms: Endoscopic Detection, Disease Relevance, and Therapeutic Strategies." Gastroenterology. **167**(6):1098–1112.e5. doi:10.1053/j.gastro.2024.04.032.

22. ^Ramage G, Borghi E, Rodrigues CF, Kean R, Williams C, Lopez-Ribot J (2023). "Our Current Clinical Understanding of Candida Biofilms: Where Are We Two Decades On?" APMIS. **131**(11):636–653. doi:10.1111/apm.13310.

23. ^Unniachan SA, Jayakumari NK, Sethuraman S. (2020). "Association Between Candida Species and Periodontal Disease: A Systematic Review." Curr Med Mycol. 6(2):63–68. doi:10.18502/CMM.6.2.3420

24. ^Nazir M, Al-Ansari A, Al-Khalifa K, Alhareky M, Gaffar B, Almas K (2020). "Global Prevalence of Periodontal Disease and Lack of Its Surveillance." ScientificWorldJournal. **2020**:2146160. doi:10.1155/2020/2146160.

25. ^Chambers PW (2024). "Candida Hyphae and Healthspan: Hypothesis." Microbes & Immunity. **2**(3):145. doi:10.36922/mi.4736.

26. ^Prado MM, Figueiredo N, Pimenta AL, Miranda TS, Feres M, Figueiredo LC, et al. (2022). "Recent Updates on Microbial Biofilms in Periodontitis: An Analysis of In Vitro Biofilm Models." In: Periodontitis. Advances in Experimental Medicine and Biology, vol 1373. Cham: Springer. 159–174. doi:10.1007/978-3-030-96881-6_8.

27. ^Hwang G (2022). "In It Together: Candida–Bacterial Oral Biofilms and Therapeutic Strategies." Environ Microbiol Rep. **14**(2):183–196. doi:10.1111/1758-2229.13053.

28. ^de Jongh CA, Bikker FJ, de Vries TJ, Werner A, Gibbs S, Krom BP (2023). "Porphyromonas Gingivalis Interaction with Candida Albicans Allows for Aerobic Escape, Virulence and Adherence." Biofilm. **7**:100172. doi:10.1016/j.bioflm.2023.100172.

29. ^Reytor-González C, Parise-Vasco JM, González N, Simancas-Racines A, Zambrano-Villacres R, Zambrano AK, et al. (2024). "Obesity and Periodontitis: A Comprehensive Review of Their Interconnected Pathophysiolo

gy and Clinical Implications." Front Nutr. ***11****:1440216. doi:10.3389/fnut.2024.1440216.*

30. ^*Sulaiman Y, Pacauskienė IM, Šadzevičienė R, Anuzyte R (2024). "Oral and Gut Microbiota Dysbiosis Due to Periodontitis: Systemic Implications and Links to Gastrointestinal Cancer: A Narrative Review." Medicina.* ***60****(9):1416. doi:10.3390/medicina60091416.*
31. ^*Nwizu N, Wactawski-Wende J, Genco RJ (2020). "Periodontal Disease and Cancer: Epidemiologic Studies and Possible Mechanisms." Periodontol 2000.* ***83****(1):213–233. doi:10.1111/prd.12329.*
32. ^*Beydoun MA, Beydoun HA, Hossain S, El-Hajj ZW, Weiss J, Zonderman AB (2020). "Clinical and Bacterial Markers of Periodontitis and Their Association with Incident All-Cause and Alzheimer's Disease Dementia in a Large National Survey." J Alzheimers Dis.* ***75****(1):157–172. doi:10.3233/jad-200064.*
33. ^*Leng Y, Hu Q, Ling Q, Yao X, Liu M, Chen J, et al. (2023). "Periodontal Disease Is Associated with the Risk of Cardiovascular Disease Independent of Sex: A Meta-Analysis." Front Cardiovasc Med.* ***10****:1114927. doi:10.3389/fcvm.2023.1114927.*
34. ^*Kurgan Ş, Önder C, Balcı N, Akdoğan N, Altıngöz SM, Serdar MA, et al. (2022). "Influence of Periodontal Inflammation on Tryptophan-Kynurenine Metabolism: A Cross-Sectional Study." Clin Oral Invest.* ***26****(9):5721–5732. doi:10.1007/s00784-022-04528-4.*
35. ^*Trimarchi M, Lauritano D, Ronconi G, Caraffa A, Gallenga C, Frydas I, et al. (2022). "Mast Cell Cytokines in Acute and Chronic Gingival Tissue Inflammation: Role of IL-33 and IL-37." International Journal of Molecular Sciences.* ***23****(21):13242. doi:10.3390/ijms232113242.*
36. ^*Lagdive SS, Lagdive SB, Mani A, Anarthe R, Pendyala G, Pawar B, et al. (2013). "Correlation of Mast Cells in Periodontal Diseases." J Indian Soc Periodontol.* ***17****(1):63–67. doi:10.4103/0972-124x.107500.*
37. ^*Yu M, Song XT, Liu B, Luan TT, Liao SL, Zhao ZT (2021). "The Emerging Role of Mast Cells in Response to Fungal Infection." Front Immunol.* ***12****:688659. doi:10.3389/fimmu.2021.688659.*
38. ^*Bonamichi-Santos R, Yoshimi-Kanamori K, Giavina-Bianchi P, Aun MV (2018). "Association of Postural Tachycardia Syndrome and Ehlers-Danlos Syndrome with Mast Cell Activation Disorders." Immunology and Allergy Clinics of North America.* ***38****(3):497–504. doi:10.1016/j.iac.2018.04.004.*
39. ^*Hamrefors V, Kahn F, Holmqvist M, Carlson K, Varjus R, Gudjonsson A, et al. (2024). "Gut Microbiota Composition Is Altered in Postural Orthostatic Tachycardia Syndrome and Post-Acute COVID-19 Syndrome." Sci Rep.* ***14****(1):3389. doi:10.1038/s41598-024-53784-9.*
40. ^*Alomari M, Hitawala A, Chadalavada P, Covut F, Al Momani L, Khazaaleh S, et al. (2020). "Prevalence and Predictors of Gastrointestinal Dysmotility in Patients with Hypermobile Ehlers-Danlos Syndrome: A Tertiary Care Center Experience." Cureus.* ***12****(4):e7881. doi:10.7759/cureus.7881.*

41. ^ Abigail E, Haytham E (2018). "Assessment of the Relevance of Intestinal Zonulin Test for Inflammatory Conditions in an Integrated Clinical Setting." S2CID 53624540.

42. ^ Singh P, Silvester J, Chen X, Xu H, Sawhney V, Rangan V, et al. (2019). "Serum Zonulin Is Elevated in IBS and Correlates with Stool Frequency in IBS-D." UEG Journal. **7**(5):709–715. doi:10.1177/2050640619826419.

43. ^ Corouge M, Loridant S, Fradin C, Salleron J, Damiens S, Moragues MD, et al. (2015). "Humoral Immunity Links Candida Albicans Infection and Celiac Disease." PLoS ONE. **10**(3):e0121776. doi:10.1371/journal.pone.0121776.

44. ^ de Magistris L, Familiari V, Pascotto A, Sapone A, Frolli A, Iardino P, et al. (2010). "Alterations of the Intestinal Barrier in Patients With Autism Spectrum Disorders and in Their First-Degree Relatives." J Pediatr Gastroenterol Nutr. **51**(4):418–424. doi:10.1097/mpg.0b013e3181dcc4a5.

45. ^ Fasano A, Not T, Wang W, Uzzau S, Berti I, Tommasini A, et al. (2000). "Zonulin, a Newly Discovered Modulator of Intestinal Permeability, and Its Expression in Coeliac Disease." The Lancet. **355**(9214):1518–1519. doi:10.1016/s0140-6736(00)02169-3.

46. ^ Vanuytsel T, Vermeire S, Cleynen I (2013). "The Role of Haptoglobin and Its Related Protein, Zonulin, in Inflammatory Bowel Disease." Tissue Barriers. **1**(5):e27321. doi:10.4161/tisb.27321.

47. ^ Malíčková K, Francová I, Lukáš M, Kolář M, Králíková E, Bortlík M, et al. (2017). "Fecal Zonulin Is Elevated in Crohn's Disease and in Cigarette Smokers." Pract Lab Med. **9**:39–44. doi:10.1016/j.plabm.2017.09.001.

48. ^ de Kort S, Keszthelyi D, Masclee AAM (2011). "Leaky Gut and Diabetes Mellitus: What Is the Link?" Obesity Reviews. **12**(6):449–458. doi:10.1111/j.1467-789x.2010.00845.x.

49. ^ Zhang D, Zhang L, Zheng Y, Yue F, Russell RD, Zeng Y (2014). "Circulating Zonulin Levels in Newly Diagnosed Chinese Type 2 Diabetes Patients." Diabetes Research and Clinical Practice. **106**(2):312–318. doi:10.1016/j.diabres.2014.08.017.

50. ^ Damms-Machado A, Louis S, Schnitzer A, Volynets V, Rings A, Basrai M, et al. (2017). "Gut Permeability Is Related to Body Weight, Fatty Liver Disease, and Insulin Resistance in Obese Individuals Undergoing Weight Reduction." The American Journal of Clinical Nutrition. **105**(1):127–135. doi:10.3945/ajcn.116.131110.

51. ^ a, b Miller FW (2022). "The Increasing Prevalence of Autoimmunity and Autoimmune Diseases: An Urgent Call to Action for Improved Understanding, Diagnosis, Treatment, and Prevention." Current Opinion in Immunology. **80**:102266. doi:10.1016/j.coi.2022.102266.

52. ^ a, b Giron LB, Dweep H, Yin X, Wang H, Damra M, Goldman AR, et al. (2021). "Plasma Markers of Disrupted Gut Permeability in Severe COVID-19 Patients." Front Immunol. **12**:686240. doi:10.3389/fimmu.2021.686240.

53. ^Marino M, Mignozzi S, Michels KB, Cintolo M, Penagini R, Gargari G, et al. (2024). "Serum Zonulin and Colorectal Cancer Risk." Sci Rep. **14**(1):28171. doi:10.1038/s41598-024-76697-z.

54. ^Boschetti E, Caio G, Cervellati C, Costanzini A, Rosta V, Caputo F, et al. (2023). "Serum Zonulin Levels Are Increased in Alzheimer's Disease But Not in Vascular Dementia." Aging Clin Exp Res. **35**(9):1835–1843. doi:10.1007/s40520-023-02463-2.

55. ^Violi F, Nocella C (2023). "Editorial: Gut Permeability-Related Endotoxemia and Cardiovascular Disease: A New Clinical Challenge." Front Cardiovasc Med. **10**:1118625. doi:10.3389/fcvm.2023.1118625.

56. ^Kinashi Y, Hase K (2021). "Partners in Leaky Gut Syndrome: Intestinal Dysbiosis and Autoimmunity." Front Immunol. **12**:673708. doi:10.3389/fimmu.2021.673708.

57. ^Moreno-Navarrete JM, Sabater M, Ortega F, Ricart W, Fernández-Real JM (2012). "Circulating Zonulin, a Marker of Intestinal Permeability, Is Increased in Association with Obesity-Associated Insulin Resistance." PLoS ONE. **7**(5):e37160. doi:10.1371/journal.pone.0037160.

58. ^Mouchati C, Durieux JC, Zisis SN, Labbato D, Rodgers MA, Ailstock K, et al. (2023). "Increase in Gut Permeability and Oxidized LDL Is Associated with Post-Acute Sequelae of SARS-CoV-2." Front Immunol. **14**:1182544. doi:10.3389/fimmu.2023.1182544.

59. ^Mokkala K, Pellonperä O, Röytiö H, Pussinen P, Rönnemaa T, Laitinen K (2017). "Increased Intestinal Permeability, Measured by Serum Zonulin, Is Associated with Metabolic Risk Markers in Overweight Pregnant Women." Metabolism. **69**:43–50. doi:10.1016/j.metabol.2016.12.015.

60. ^Aasbrenn M, Lydersen S, Farup PG (2020). "Changes in Serum Zonulin in Individuals with Morbid Obesity After Weight-Loss Interventions: A Prospective Cohort Study." BMC Endocr Disord. **20**(1):108. doi:10.1186/s12902-020-00594-5.

61. ^García-Gamboa R, Kirchmayr MR, Gradilla-Hernández MS, Pérez-Brocal V, Moya A, González-Avila M (2021). "The Intestinal Mycobiota and Its Relationship with Overweight, Obesity and Nutritional Aspects." J Hum Nutr Diet. **34**(4):645–655. doi:10.1111/jhn.12864.

62. ^CDC (2024). "Childhood Obesity Facts." CDC. https://www.cdc.gov/obesity/childhood-obesity-facts/childhood-obesity-facts.html.

63. ^Emmerich SD, Fryar CD, Stierman B, Ogden CL (2024). "Obesity and Severe Obesity Prevalence in Adults: United States, August 2021–August 2023." NCHS Data Brief. (508):10.15620/cdc/159281. doi:10.15620/cdc/159281.

64. ^Kumwenda P, Cottier F, Hendry AC, Kneafsey D, Keevan B, Gallagher H, et al. (2022). "Estrogen Promotes Innate Immune Evasion of Candida Albicans Through Inactivation of the Alternative Complement System."

Cell Reports. **38**(1):110183. doi:10.1016/j.celrep.2021.110183.

65. ^Karpuzoglu-Sahin E, Hissong BD, Ansar Ahmed S (2001). "Interferon-γ Levels Are Upregulated by 17-β-Estradiol and Diethylstilbestrol." *Journal of Reproductive Immunology*. **52**(1-2):113–127. doi:10.1016/s0165-0378(01)00117-6.

66. ^Schreurs MPH, de Vos van Steenwijk PJ, Romano A, Dieleman S, Werner HMJ (2021). "How the Gut Microbiome Links to Menopause and Obesity, with Possible Implications for Endometrial Cancer Development." *Journal of Clinical Medicine*. **10**(13):2916. doi:10.3390/jcm10132916.

67. ^Kuryłowicz A (2023). "Estrogens in Adipose Tissue Physiology and Obesity-Related Dysfunction." *Biomedicines*. **11**(3):690. doi:10.3390/biomedicines11030690.

68. ^Hu S, Ding Q, Zhang W, Kang M, Ma J, Zhao L (2023). "Gut Microbial Beta-Glucuronidase: A Vital Regulator in Female Estrogen Metabolism." *Gut Microbes*. **15**(1). doi:10.1080/19490976.2023.2236749.

69. ^Zhou Z, Zhang L, Ding M, Luo Z, Yuan S, Bansal MB, et al. (2017). "Estrogen Decreases Tight Junction Protein ZO-1 Expression in Human Primary Gut Tissues." *Clinical Immunology*. **183**:174–180. doi:10.1016/j.clim.2017.08.019.

70. ^Bras G, Satala D, Juszczak M, Kulig K, Wronowska E, Bednarek A, et al. (2024). "Secreted Aspartic Proteinases: Key Factors in Candida Infections and Host-Pathogen Interactions." *International Journal of Molecular Sciences*. **25**(9):4775. doi:10.3390/ijms25094775.

71. ^Caminero A, Guzman M, Libertucci J, Lomax AE (2023). "The Emerging Roles of Bacterial Proteases in Intestinal Diseases." *Gut Microbes*. **15**(1). doi:10.1080/19490976.2023.2181922.

72. ^Edwinson AL, Yang L, Peters S, Hanning N, Jeraldo P, Jagtap P, et al. (2022). "Gut Microbial β-Glucuronidases Regulate Host Luminal Proteases and Are Depleted in Irritable Bowel Syndrome." *Nat Microbiol*. **7**(5):680–694. doi:10.1038/s41564-022-01103-1.

73. ^Kumar R, Rojas IG, Edgerton M (2022). "Candida AlbicansSap6 Initiates Oral Mucosal Inflammation via the Protease Activated Receptor PAR2." *Front Immunol*. **13**:912748. doi:10.3389/fimmu.2022.912748.

74. ^Rondeau LE, Da Luz BB, Santiago A, Bermudez-Brito M, Hann A, De Palma G, et al. (2024). "Proteolytic Bacteria Expansion During Colitis Amplifies Inflammation Through Cleavage of the External Domain of PAR 2." *Gut Microbes*. **16**(1). doi:10.1080/19490976.2024.2387857.

75. ^Lakemeyer M, Latorre R, Blazkova K, Jensen D, Wood HM, Shakil N, et al. (2025). "Identification of a Secreted Protease from Bacteroides Fragilis That Induces Intestinal Pain and Inflammation by Cleavage of PAR 2." doi:10.1101/2025.01.15.633241.

76. ^Shah H, Fairlie DP, Lim J (2025). "Protease-Activated Receptor 2: A Promising Therapeutic Target for Women's Cancers." The Journal of Pharmacology and Experimental Therapeutics. **392**(1):100016. doi:10.1124/jpet.124.002176.

77. ^Khoon L, Piran R (2025). "A New Strategy in Modulating the Protease-Activated Receptor 2 (PAR2) in Autoimmune Diseases." International Journal of Molecular Sciences. **26**(1):410. doi:10.3390/ijms26010410.

78. ^Kasper L, König A, Koenig PA, Gresnigt MS, Westman J, Drummond RA, et al. (2018). "The Fungal Peptide Toxin Candidalysin Activates the NLRP3 Inflammasome and Causes Cytolysis in Mononuclear Phagocytes." Nat Commun. **9**(1):4260. doi:10.1038/s41467-018-06607-1.

79. ^Kumari N, Kumari R, Dua A, Singh M, Kumar R, Singh P, et al. (2024). "From Gut to Hormones: Unraveling the Role of Gut Microbiota in (Phyto)Estrogen Modulation in Health and Disease." Molecular Nutrition & Food Research. **68**(6):e2300688. doi:10.1002/mnfr.202300688.

80. ^Nejat R, Torshizi MF, Najafi DJ (2023). "S Protein, ACE2 and Host Cell Proteases in SARS-CoV-2 Cell Entry and Infectivity; Is Soluble ACE2 a Two Blade Sword? A Narrative Review." Vaccines. **11**(2):204. doi:10.3390/vaccines11020204.

81. ^Chambers PW (2023). "The Candida Covid Connection: Preexisting Candida Overgrowth and Gut Dysbiosis Drives Long COVID." Neuroscience and Neurological Surgery. **13**(7):01–09. doi:10.31579/2578-8868/283.

82. a, bZhang J, Lacroix C, Wortmann E, Ruscheweyh HJ, Sunagawa S, Sturla SJ, et al. (2019). "Gut Microbial Beta-Glucuronidase and Glycerol/Diol Dehydratase Activity Contribute to Dietary Heterocyclic Amine Biotransformation." BMC Microbiol. **19**(1):99. doi:10.1186/s12866-019-1483-x.

83. ^Hillege LE, Stevens MAM, Kristen PAJ, de Vos-Geelen J, Penders J, Redinbo MR, et al. (2024). "The Role of Gut Microbial β-Glucuronidases in Carcinogenesis and Cancer Treatment: A Scoping Review." J Cancer Res Clin Oncol. **150**(11):495. doi:10.1007/s00432-024-06028-2.

84. ^Fernández-Murga ML, Gil-Ortiz F, Serrano-García L, Llombart-Cussac A (2023). "A New Paradigm in the Relationship Between Gut Microbiota and Breast Cancer: β-Glucuronidase Enzyme Identified as Potential Therapeutic Target." Pathogens. **12**(9):1086. doi:10.3390/pathogens12091086.

85. ^Sperker B, Werner U, Mürdter TE, Tekkaya C, Fritz P, Wacke R, et al. (2000). "Expression and Function of β-Glucuronidase in Pancreatic Cancer: Potential Role in Drug Targeting." Naunyn-Schmied Arch Pharmacol. **362**(2):110–115. doi:10.1007/s002100000260.

86. ^Kawai H (2014). "Estrogen Receptors as the Novel Therapeutic Biomarker in Non-Small Cell Lung Cancer." World J Clin Oncol. **5**(5):1020–1027. doi:10.5306/wjco.v5.i5.1020.

87. ^ Labuschagne CF, Smith R, Kumar N, Allsworth M, Boyle B, Janes S, et al. (2022). "Breath Biopsy Early Detection of Lung Cancer Using an EVOC Probe Targeting Tumor-Specific Extracellular β-Glucuronidase." Journal of Clinical Oncology. **40**(16 suppl):2569–2569. doi:10.1200/JCO.2022.40.16_suppl.2569.

88. ^ Seeliger H, Pozios I, Assmann G, Zhao Y, Müller MH, Knösel T, et al. (2018). "Expression of Estrogen Receptor Beta Correlates with Adverse Prognosis in Resected Pancreatic Adenocarcinoma." BMC Cancer. **18**(1):1049. doi:10.1186/s12885-018-4973-6.

89. ^ Ge Y, Ni X, Li J, Ye M, Jin X (2023). "Roles of Estrogen Receptor α in Endometrial Carcinoma (Review)." Oncol Lett. **26**(6):530. doi:10.3892/ol.2023.14117.

90. ^ Tang W, Liu R, Yan Y, Pan X, Wang M, Han X, et al. (2017). "Expression of Estrogen Receptors and Androgen Receptors and Their Clinical Significance in Gastric Cancer." Oncotarget. **8**(25):40765–40777. doi:10.18632/oncotarget.16582.

91. ^ Su R, Chen L, Jiang Z, Yu M, Zhang W, Ma Z, et al. (2022). "Comprehensive Analysis of Androgen Receptor Status in Prostate Cancer with Neuroendocrine Differentiation." Front Oncol. **12**:955166. doi:10.3389/fonc.2022.955166.

92. ^ Zhao J, Xu L, Sun J, Song M, Wang L, Yuan S, et al. (2023). "Global Trends in Incidence, Death, Burden and Risk Factors of Early-Onset Cancer from 1990 to 2019." BMJ Oncology. **2**:e000049. https://bmjoncology.bmj.com/content/2/1/e000049.

93. ^ Viehweger F, Gusinde J, Leege N, Tinger LM, Gorbokon N, Menz A, et al. (2025). "Estrogen Receptor Expression in Human Tumors: A Tissue Microarray Study Evaluating More Than 18,000 Tumors from 149 Different Entities." Human Pathology. **157**:105757. doi:10.1016/j.humpath.2025.105757.

94. ^ Jalali-Nadoushan MR, Amirtouri R, Davati A, Askari S, Siadati S (2016). "Expression of Estrogen and Progesterone Receptors in Papillary Thyroid Carcinoma." Caspian J Intern Med. **7**(3):183–187. PMID 27757203.

95. ^ Madeshwaran A, Vijayalakshmi P, Umapathy VR, Shanmugam R, Selvaraj C (2024). "Unlocking Estrogen Receptor: Structural Insights into Agonists and Antagonists for Glioblastoma Therapy." Advances in Protein Chemistry and Structural Biology. **142**:1–24. doi:10.1016/bs.apcsb.2024.06.001.

96. ^ Sarwar SA, Maddali A, Adams D, Kumar RP, O'Malley GR, Szymanski LJ, et al. (2024). "Glioblastoma Multiforme Incidence Is Increasing: An Epidemiological Investigation of 100,000 Cases Across the United States." doi:10.21203/rs.3.rs-5423792/v1.

97. ^ Ruggeri RM, Altieri B, Razzore P, Retta F, Sperti E, Scotto G, et al. (2024). "Gender-Related Differences in Patients with Carcinoid Syndrome: New Insights from an Italian Multicenter Cohort Study." J Endocrinol Invest. **47**(4):959–971. doi:10.1007/s40618-023-02213-1.

98. ^ Penninger JM, Grant MB, Sung JJY (2021). "The Role of Angiotensin Converting Enzyme 2 in Modulating Gut Microbiota, Intestinal Inflammation, and Coronavirus Infection." Gastroenterology. **160**(1):39–46. doi:10.1053/j.gastro.2020.07.067.

99. ^ Reddy BS, Weisburger JH, Wynder EL (1974). "Fecal Bacterial β-Glucuronidase: Control by Diet." Science. **183**(4123):416–417. doi:10.1126/science.183.4123.416.

100. ^ Walsh CJ, Guinane CM, O'Toole PW, Cotter PD (2014). "Beneficial Modulation of the Gut Microbiota." FEBS Letters. **588**(22):4120–4130. doi:10.1016/j.febslet.2014.03.035.

101. ^ Schnorr S, Candela M, Rampelli S, Centanni M, Consolandi C, Basaglia G, et al. (2014). "Gut Microbiome of the Hadza Hunter-Gatherers." Nat Commun. **5**(1):3654. doi:10.1038/ncomms4654.

102. ^ Wastyk HC, Fragiadakis GK, Perelman D, Dahan D, Merrill BD, Yu FB, et al. (2021). "Gut-Microbiota-Targeted Diets Modulate Human Immune Status." Cell. **184**(16):4137-4153.e14. doi:10.1016/j.cell.2021.06.019.

103. ^ Thu MS, Ondee T, Nopsopon T, Farzana IAK, Fothergill JL, Hirankarn N, et al. (2023). "Effect of Probiotics in Breast Cancer: A Systematic Review and Meta-Analysis." Biology. **12**(2):280. doi:10.3390/biology12020280.

104. ^ Salari S, Ghasemi Nejad Almani P (2020). "Antifungal Effects of Lactobacillus Acidophilus and Lactobacillus Plantarum Against Different Oral Candida Species Isolated from HIV/AIDS Patients: An In Vitro Study." J Oral Microbiol. **12**(1):1769386. doi:10.1080/20002297.2020.1769386.

105. ^ Zangl I, Pap IJ, Aspöck C, Schüller C (2020). "The Role of Lactobacillus Species in the Control of Candida Via Biotroph Interactions." Microb Cell. **7**(1):1-14. doi:10.15698/mic2020.01.702.

106. ^ Amiri P, Hosseini SA, Ghaffari S, Tutunchi H, Ghaffari S, Mosharkesh E, et al. (2022). "Role of Butyrate, a Gut Microbiota Derived Metabolite, in Cardiovascular Diseases: A Comprehensive Narrative Review." Front Pharmacol. **12**:837509. doi:10.3389/fphar.2021.837509.

107. ^ Bhol NK, Bhanjadeo MM, Singh AK, Dash UC, Ojha RR, Majhi S, et al. (2024). "The Interplay Between Cytokines, Inflammation, and Antioxidants: Mechanistic Insights and Therapeutic Potentials of Various Antioxidants and Anti-Cytokine Compounds." Biomed Pharmacother. **178**:117177. doi:10.1016/j.biopha.2024.117177.

108. ^ Su S, Li X, Yang X, Li Y, Chen X, Sun S, et al. (2020). "Histone Acetylation/Deacetylation in Candida Albicans and Their Potential as Antifungal Targets." Future Microbiol. **15**(11):1075–1090. doi:10.2217/fmb-2019-0343.

109. ^ Alseksek RK, Ramadan WS, Saleh E, El-Awady R (2022). "The Role of HDACs in the Response of Cancer Cells to Cellular Stress and the Potential for Therapeutic Intervention." Int J Mol Sci. **23**(15):8141. doi:10.3390/ijms23158141.

110. ^ Chakraborty P, Laird AS (2025). "Understanding Activity of Butyrate at a Cellular Level." Neural Regeneration Research. **20**(8):2323-2324. doi:10.4103/NRR.NRR-D-24-00468.

111. ^ Gommers LMM, Ederveen THA, van der Wijst J, Overmars-Bos C, Kortman GAM, Boekhorst J, et al. (2019). "Low Gut Microbiota Diversity and Dietary Magnesium Intake Are Associated with the Development of PPI-Induced Hypomagnesemia." FASEB J. **33**(10):11235-11246. doi:10.1096/fj.201900839R.

112. ^ Fatima G, Dzupina A, B Alhmadi H, Magomedova A, Siddiqui Z, Mehdi A, et al. (2024). "Magnesium Matters: A Comprehensive Review of Its Vital Role in Health and Diseases." Cureus. **16**(10):e71392. doi:10.7759/cureus.71392.

113. ^ Ashique S, Kumar S, Hussain A, Mishra N, Garg A, Gowda BHJ, et al. (2023). "A Narrative Review on the Role of Magnesium in Immune Regulation, Inflammation, Infectious Diseases, and Cancer." J Health Popul Nutr. **42**(1):74. doi:10.1186/s41043-023-00423-0.

114. ^ Veronese N, Pizzol D, Smith L, Dominguez LJ, Barbagallo M (2022). "Effect of Magnesium Supplementation on Inflammatory Parameters: A Meta-Analysis of Randomized Controlled Trials." Nutrients. **14**(3):679. doi:10.3390/nu14030679.

115. ^ Meir Z, Osherov N (2018). "Vitamin Biosynthesis as an Antifungal Target." J Fungi. **4**(2):72. doi:10.3390/jof4020072.

116. ^ Zhang T, Wang W, Li J, Ye X, Wang Z, Cui S, et al. (2025). "Free Fatty Acid Receptor 4 Modulates Dietary Sugar Preference Via the Gut Microbiota." Nat Microbiol. **10**(2):348–361. doi:10.1038/s41564-024-01902-8.

117. ^ Trachsel J, Bayles DO, Looft T, Levine UY, Allen HK (2016). "Function and Phylogeny of Bacterial Butyryl Coenzyme A:Acetate Transferases and Their Diversity in the Proximal Colon of Swine." Appl Environ Microbiol. **82**(22):6788-6798. doi:10.1128/AEM.02307-16.

118. ^ Kherad Z, Yazdanpanah S, Saadat F, Pakshir K, Zomorodian K (2023). "Vitamin D3: A Promising Antifungal and Antibiofilm Agent Against Candida Species." Curr Med Mycol. **9**(2):17-22. PMID 10874479.

119. ^ Chaudhry KK, Shukla PK, Mir H, Manda B, Gangwar R, Yadav N, et al. (2016). "Glutamine Supplementation Attenuates Ethanol-Induced Disruption of Apical Junctional Complexes in Colonic Epithelium and Ameliorates Gut Barrier Dysfunction and Fatty Liver in Mice." J Nutr Biochem. **27**:16-26. doi:10.1016/j.jnutbio.2015.08.012.

120. ^ Sohail MU, Yassine HM, Sohail A, Thani AAA (2019). "Impact of Physical Exercise on Gut Microbiome, Inflammation, and the Pathobiology of Metabolic Disorders." Rev Diabet Stud. **15**:35-48. PMID 31380886.

121. ^ Louis P, Duncan SH, Sheridan PO, Walker AW, Flint HJ (2022). "Microbial Lactate Utilisation and the Stability of the Gut Microbiome." Gut Microbiome. **3**:e3. doi:10.1017/gmb.2022.3.

122. ^ Aurora R, Sanford T (2024). "The Microbiome: From the Beginning to the End." Mo Med. **121**(4):310-316. https://pmc.ncbi.nlm.nih.gov/articles/PMC11578570/.

123. ^Petersen MR, Cosgrove SE, Quinn TC, Patel EU, Grabowski MK, Tobian AAR (2021). "Prescription Antibiotic Use Among the US Population 1999–2018: National Health and Nutrition Examination Surveys." Open Forum Infectious Diseases. **8**(7):ofab224. doi:10.1093/ofid/ofab224.

124. ^Aghaali M, Hashemi-Nazari SS (2019). "Association Between Early Antibiotic Exposure and Risk of Childhood Weight Gain and Obesity: A Systematic Review and Meta-Analysis." J Pediatr Endocrinol Metab. **32**(5):439-445. doi:10.1515/jpem-2018-0437.

125. ^Li P, Chang X, Chen X, Wang C, Shang Y, Zheng D, et al. (2022). "Early-Life Antibiotic Exposure Increases the Risk of Childhood Overweight and Obesity in Relation to Dysbiosis of Gut Microbiota: A Birth Cohort Study." Ann Clin Microbiol Antimicrob. **21**(1):46. doi:10.1186/s12941-022-00535-1.

126. ^Kesavelu D, Jog P (2023). "Current Understanding of Antibiotic-Associated Dysbiosis and Approaches for Its Management." Ther Adv Infect Dis. **10**:20499361231154443. doi:10.1177/20499361231154443.

127. ^Jawad AB, Jansson S, Wewer V, Malham M (2023). "Early Life Oral Antibiotics Are Associated With Pediatric-Onset Inflammatory Bowel Disease—A Nationwide Study." J Pediatr Gastroenterol Nutr. **77**(3):366-372. doi:10.1097/MPG.0000000000003861.

128. ^Pérez JC (2021). "The Interplay Between Gut Bacteria and the Yeast Candida Albicans." Gut Microbes. **13**(1). doi:10.1080/19490976.2021.1979877.

129. ^Cordeiro RA, Evangelista AJJ, Serpa R, de Andrade ARC, Mendes PBL, de Oliveira JS, et al. (2019). "Cefepime and Amoxicillin Increase Metabolism and Enhance Caspofungin Tolerance of Candida Albicans Biofilms." Front Microbiol. **10**:1337. doi:10.3389/fmicb.2019.01337.

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