Hyphae and Healthspan

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Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

Candida overgrowth (CO) can induce an avalanche of health problems. Its hyphal wall contains epitopes that can trigger not only gluten type antibodies (celiac disease) but also a plethora of mannan related antibodies targeting Gq coupled GPCRs. These latter can disrupt autonomic receptors, inducing POTS, loss of taste and smell, and many other symptoms. These mannan auto-antibodies also disrupt chemotactic cytokine receptors (CCRs) that can induce pain, psoriasis, alopecia areata, vitiligo and many other maladies. They also target T cells that otherwise suppress latent viruses, e.g., EBV. Hyphae also release candidalysin, a toxin that suppresses growth of competing intestinal bacteria, triggers inflammasomes, and causes hypercitrullination. Anti-citrullinated peptide antibodies (ACPAs) are produced. B cells exposed to hyper citrullination develop citrullinated receptors. ACPAs and CCRs may jointly induce viral reactivation from infected B cells. EBV, latent in virtually all humans and now free to circulate, is targeted by these same ACPAs. EBV nuclear material is released and antinuclear antibodies (ANAs) may emerge. Hyphae also trigger the release of histamine and tryptase from mast cells. Tryptase and mast cells have been tightly linked to the trifecta of mast cell activation syndrome (MCAS), hypermobility spectrum disorder (HSD), and POTS in addition to long Covid (LC) and probably anti-phospholipid syndrome (APS). Hyphae are also linked to periodontitis. Bacteria are generally considered to be the culprits, but Candida hyphae and its biofilm facilitate their pathogenesis. Periodontitis is linked with and may be a sentinel risk indicator for cancer, dementia, autoimmune disease, ASCVD and chronic disease in general. D3 and tryptophan oppose the invasive hyphal transition of Candida, which responds by releasing indoleamine dioxygenase that degrades tryptophan. This altered tryptophan metabolism is characteristic of all of these. Ultimately hyphae may be directly or indirectly involved in gut dysbiosis, including periodontitis, to the detriment of healthspan. The approach is conceptual not empirical.

Keywords: Periodontitis, Mast cell, Cancer, Dementia, Zonulin, EBV.

Introduction

The overarching goal for all humankind is to enhance quality and length of life. Although the latter has generally

lengthened, thanks to technology, the former has deteriorated. A growing shortfall in diet and exercise has boosted the “dwindles”. Appreciation for the paramount significance of the gut microbiome is now recognized as a primary determinant of our health. The LC induced data deluge has catapulted Candida from opportunist to key player in healthspan. It has traditionally been considered incidental or opportunistic. More recent data suggests that invasive Candida has played a critical wide ranging pathogenic role in those not obviously immunocompromised. It has now been exposed as a co-conspirator with many other pathogens. Refined carbohydrates and alcohol have unleashed Candida, the primary hyphae producing gut fungus, normally present as a commensal in yeast form. These hyphae also release candidalysin that induce auto-antibodies. All disease begins in the gut (Hippocrates) and the gut begins in the mouth. Here Candida potentiates oral bacteria. Not surprisingly periodontitis (and Candida) have been linked with subsequent pervasive health issues, such as autoimmune disease, cancer, dementia, ASCVD and other systemic diseases.

Discussion

I. Inflammaging, Candida, and Periodontitis

Aging is characterized by systemic chronic inflammation, known as inflammaging[1], and is associated with autoimmunity[2], dementia[3], and cancer[4]. Periodontitis triggers inflammaging[5] and is directly linked to cancer risk[6], dementia[7][8], and autoimmune disease, including SLE[9][10], systemic sclerosis[11], Hashimoto’s disease[12], and multiple sclerosis (MS)[13]

Porphyromonas gingivalis has been implicated in the generation of ACPAbs in RA patients, suggesting a direct biological intersection between periodontitis and RA[14].

Periodontitis is also linked to ASCVD[15] and obesity[16]. Gut profiling revealed elevated abundance and diversity of Candida species among obese[17]. Indeed periodontitis is linked with systemic disease in general[18] and specifically with the NLRP3 inflammasome[19] and transglutaminase[20], both markers for CO[21]. Periodontitis is directly related to Covid-19 severity[22] and is also tied to LC[23]. Candida is directly associated with periodontitis, dysphagia, and hyposalivation[24]. CO may precede and potentiate Porphyromonas gingivalis[25] in addition to Treponema denticola, Tannerella forsythia, and many other periothodontopathic bacteria, inducing periodontitis[26]. Refined carbohydrates increase risk for periodontitis and CO[27]. CO can be both cause and effect of xerostomia[28], a frequent oral complaint in LC[29]. Candida and periodontitis are also linked to zonulin[30], the primary determinant of intestinal and endothelial permeability. 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[31]. Additional links between zonulin, autoimmune disease, and Candida have recently been reported. Zonulin is a biomarker for the development of CeD[32] and is elevated in IBD[33]. CO has recently been implicated in the etiology of ulcerative colitis[34]. It may be a primary determinant of chronic disease, as its invading hyphae present mannan epitopes that appear to elicit Gq coupled GPCR antibodies[35]. These latter are associated with chronic disease[36]. They can also induce pain[37][38] and loss of taste/smell[39]. The impact of histamine[40] and bradykinin[41] are also Gq coupled GPCR dependent. These interconnecting linkages can be seen in

figure 1.

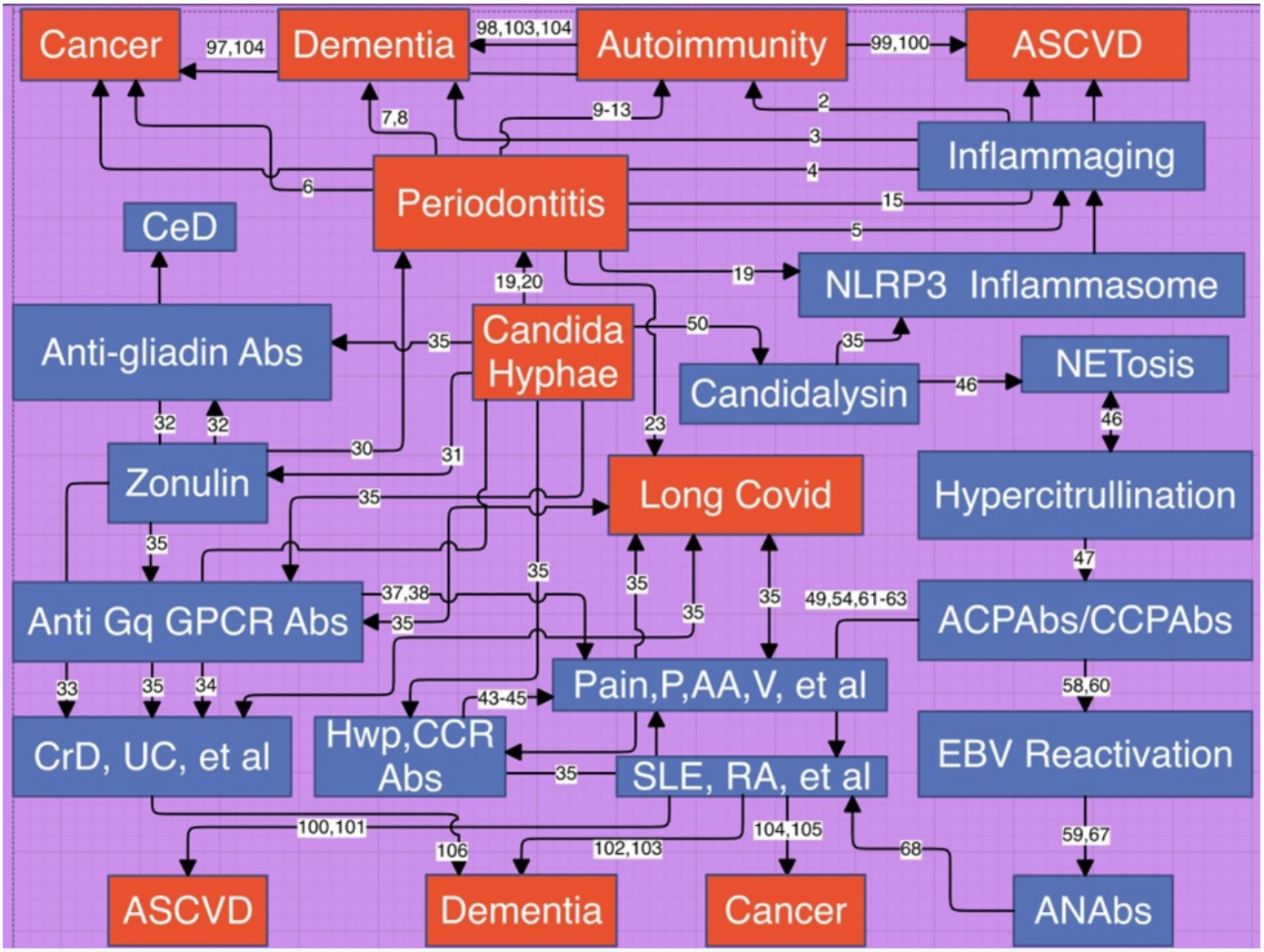

Figure 1. This is an incomplete diagrammatic representation of sections I, II, III. CeD=celiac disease, CrD=Crohn's disease, UC=ulcerative colitis, GPCR=G-protein coupled receptor, ACP=anti-citrullinated peptide, CCP=cyclic citrullinated peptide, P=psoriasis, AA=alopecia areata, V=vitiligo, Hwp=hyphal wall protein, CCR=chemotactic cytokine, EBV=Epstein-Barr virus, ANA=antinuclear antibody; numbers are references.

II. Hyphae Epitopes and Candidalysin

Candida hyphae epitopes include hyphal wall protein that mimics gliadin (CeD) and mannan that binds lectin linked to Gq coupled GPCRs and chemotactic cytokine receptors (CCRs). Gq coupled GPCRAbs may cause dysfunction in not only taste, smell, histamine/bradykinin release but also many other LC symptoms. CCRs are also Gq coupled GPCRs and may mediate pain[42], as well as psoriasis[43], alopecia areata[44], and vitiligo[45], all common in LC. These hyphae also release candidalysin, triggering citrullination that drives NETosis (neutrophil extracellular traps) and additional citrullination[46]. Candidalysin induced hypercitrullination can then lead to ACPAbs linked to autoimmune disease[47] and periodontitis[48]. ACPAbs have been implicated in RA, multiple sclerosis, Alzheimer's disease, psoriatic arthritis, SLE, and juvenile idiopathic arthritis[49]. NETs release a large amount of citrullinated antigens to drive ACPA production, which can form more NETs[50]. Cyclic citrullinated peptide antibodies (CCPAbs), a subset of ACPAbs, are related to severe Covid-

19[51] and are a hallmark of RA. ACPAs are reported in 5-10% of primary Sjögren's syndrome[52]. Candida, periodontal pathogens, and EBV are associated with RA and periodontitis[53]. ACPAbs are even seen in up to 50% of SLE with arthritis (Rhupus)[54]. Alopecia areata and vitiligo, reported in both SLE and LC, involve aberrant CCRs[55] that bind to gliadin, mimicked by hyphal wall epitopes (see figure 1), specifically CXCR3[56], also reported in both SLE. Candida and candidalysin are not only linked with inflammation and autoimmune disease but also with cancer[57].

III. EBV and ANAs

B lymphocytes bearing CCP receptors normally tolerate circulating CCP antigens[58], but when exposed to hypercitrullination produce CCPAbs[47]. Although EBV laden B lymphocytes are present in virtually all humans[59], activity is generally latent. EBV reactivation could involve hypercitrullination induced CCPAbs and EBV laden B cells with release of ENA into the general circulation. This correlates with the coincident appearance of ANAs and ENA (EBV nuclear antigen)[60]. Such ACPAb activity can be seen in RA[61] and SLE[62][63]. ANAs are also prevalent in POTS, where ANA levels are positive in one fourth of POTS[64]. EBV reactivation is seen in up to 27% of those with Covid-19[65] and 68% with LC[66]. Released but viable EBV might not only generate ANAs to ENA, secreted by the virus, but also shuttle between immune cells and epithelial cells[59] to induce autoimmune diseases related to intracellular ENA, e.g., SLE, MS, RA, IBD, CeD, T1DM, and juvenile idiopathic arthritis[67]. Autoantibodies induced by different regions of ENA cross-react with SLE autoantigens SmB, SmD, as well as Ro[68]

IV. Hyphae and Tryptase

This section will further link hyphae, periodontitis, candidalysin induced antibodies, and the POTS, MCAS, HSD trifecta. Mast cells are biomarkers for periodontitis[69][70]. Candida hyphae linked to periodontitis can also activate mast cells[71]. The incidence of periodontitis in LC is reportedly greater in patients with LC[72]. Anti-cardiolipin Abs (anti-phospholipid antibodies) are seen in 15-20% of those with periodontitis[73]. Oral symptoms in POTS include refractory periodontitis, xerostomia, dysgeusia, and burning mouth[74]. Periodontal disease in HSD is considered to be primarily genetic in origin[75], but CO may exacerbate this. Mast cells are key players in periodontitis[76]. Mast cells play a prominent role in dementia[77], cancer[78], ASCVD[79], and autoimmunity. Tryptase and chymase positive mast cells are prominent in skin biopsies from both systemic and cutaneous lupus[80]. Mast cells collaborate with ACPAbs in RA[81] and are significant in Sjögren's syndrome[82], Grave's disease[83], inflammatory bowel disease (IBD)[84], and many other autoimmune diseases, such as MS, psoriasis, and atopic dermatitis[85]. Mast cells and tryptase link the trifecta of HSD/MCAS/POTS and possibly APS[86] (see figure 2).

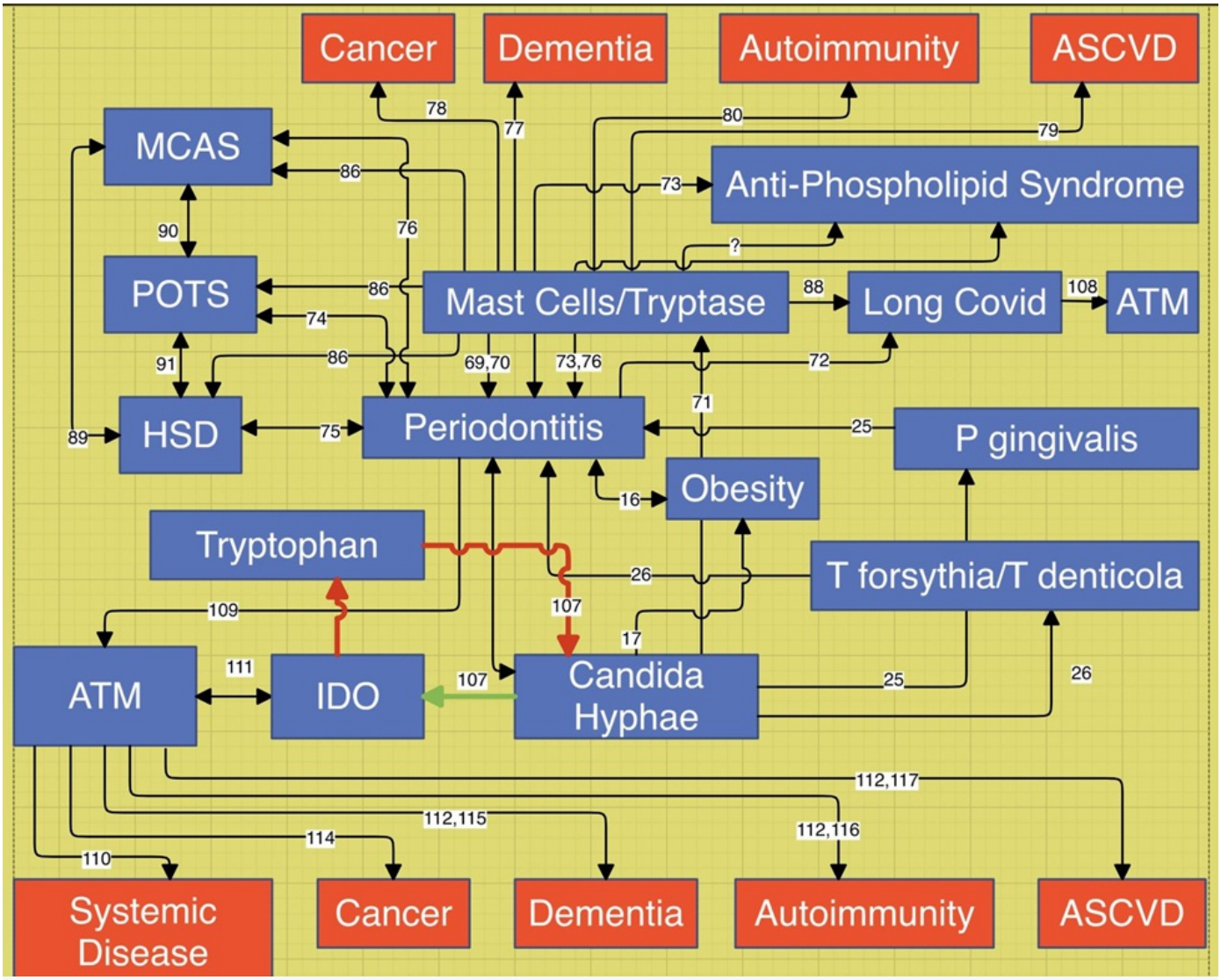

Figure 2. This is an incomplete diagrammatic representation of sections IV, V. MCAS= mast cell activation syndrome, POTS=postural, orthostatic tachycardia syndrome, ATM=altered tryptophan metabolism, IDO= indoleamine dioxygenase, numbers are references.

ACPAs activate mast cells, which are associated with RA, spondyloarthritis, psoriatic arthritis, and HSD[87], all seen in LC[88]. MCAS and HSD are linked[89], as are POTS/MCAS[90] and POTS/HSD. Almost 80% of patients with HSD displayed POTS[91]. MCAS[92], HSD[93], and POTS[94] are all linked to SLE, as is APS[95][96]. In a large community-based survey, the most common autoimmune conditions coexistent with SLE were Hashimoto thyroiditis (present in 6%), celiac disease (3%), Sjögren syndrome (3%), rheumatoid arthritis (2%) and systemic lupus erythematosus (2%)[94]

V. Altered Tryptophan Metabolism in Cancer, Dementia, Autoimmunity, and ASCVD

These diseases all conspire to limit both healthspan and lifespan. Their pathogenesis is complex, but they appear to be linked to each other. Autoimmunity is linked to cancer[97], dementia[98], and ASCVD[99]. SLE and RA are specifically linked with ASCVD[100][101], dementia[102][103], and cancer[104][105]. IBD is also linked with dementia[106].

Candida may actively participate in this linkage not only via hyphae and candidalysin induced autoantibodies but also via

yeast/hyphae release of indoleamine dioxygenase (IDO) and D3 deficiency. CO is a growing problem due to the growing prominence of a 1) more sedentary lifestyle with decreased exposure to sunlight and 2) nutritional deterioration of the Western diet (alcohol, refined sugar, processed meats). This is important because Candida can produce indoleamine dioxygenase (IDO), the enzyme that degrades tryptophan. IDO expression has been detected in both the yeast and hyphal forms of Candida[107] and tryptophan opposes the commensal yeast to pathogenic hyphal transition[107].

Pathogenesis appears to proceed via ATM. ATM is a physiologic abnormality central to many diseases, including LC[108]. ATM has been reported in periodontitis[109] and is a feature of most chronic inflammatory diseases[110]. The IDO releasing potential of CO{m/107/} may not only induce ATM but ATM may also potentiate CO[111]. SCFAs

produced by gut bacteria activate this receptor[112], inhibit Candida hyphal invasion, and prevent ATM[113].

Recently the vital role of aryl hydrocarbon receptor (AhR) in aging[114], dementia, autoimmune disease, cancer[115], and ASCVD[116] has been recognized. AhR activity is dependent on its ligands. For example, NF-κB (mediates NLRP3) and kynurenines are AhR ligands that accelerate aging and neurodegeneration, while indoles of intestinal bacterial origin are ligands that oppose this[114]. ATM inactivates the immune response dependent function of AhR[117]. Elevated IDO and aberrant AhR signaling have been reported in Alzheimer's disease[114]. AhR plays a protective role in periodontitis[118]. These reports suggest that any long term increase in IDO release by Candida hyphae and the consequent decrease in indoles/SCFAs and increase in kynurenines, NF-κB,..., may leave unopposed detrimental AhR ligands that largely determine healthspan.

This biochemical relationship between Candida, tryptophan, IDO, AhR, and SCFAs, e.g., butyrate, may link Candida with any disease characterized by ATM, e.g., cancer, dementia, autoimmunity, and ASCVD. Furthermore, it may link Candida to any disease characterized by a gut microbiome low in biodiversity and SCFAs, e.g., LC, ME/CFS, and fibromyalgia. The association between Candida and butyrate, a GLP-1 agonist like semaglutide (Ozempic), further implicates Candida as a villain in dementia[119][120], cancer[121] and obesity.

It is not generally appreciated that in addition to tryptophan D3 also opposes the yeast to hyphae morphogenesis. This effect of D3 is neither endocrine, intracrine, autocrine, nor paracrine, but intraluminal within the intestine[122]. The magnitude of this greatly underappreciated benefit of D3 might be easily underestimated. The dietary addition of a prebiotic, probiotic, and postbiotic should oppose CO. The subsequent increase in SCFAs, especially butyrate, should ameliorate any imbalance in IFN-γ and TGF-β, which are cytokine reciprocals (see figure 3). A Ca:Mg ratio exceeding 2.0 is also characteristic of cancer, autoimmune disease[123], and ASCVD[124]. If this ratio exceeds 2.0, magnesium deficiency is also associated with dementia[125]. Furthermore, magnesium deficiency enhances immune evasion by Candida[126].

Conclusion

The described linkages are provocative but do not constitute cause and effect. Furthermore, the magnitude of any such

input is unknown. However, since a decrease in dietary refined carbohydrates and alcohol is healthful in many other ways, the therapeutic approach seems clear. D3 and tryptophan both oppose the yeast to hyphae transition (see figure 2). Although the addition of sun exposure and/or supplemental D3[122] to one's routine should be unequivocally beneficial, the addition of tryptophan is less clear[127], if CO is well established in the gut microbiome. If there is an improvement in mood and sleep, this concern might be lessened (see figure 3). Most on a Western diet are long on calcium and short on magnesium, up-regulating zonulin[128] and immune evasion by Candida. Obesity Is directly connected to ATM in both children and adults[129][130] and is the leading culprit that might illuminate the otherwise inexplicable recent rise in early onset cancer. Ultimately Candida must be recognized as the great facilitator of not only other pathogens but also many autoantibodies, e.g., anti-gliadin Abs, anti-Gq coupled GPCRAbs, anti-CCRAbs, ACPAbs, anti-CCPAbs, and ANAs, that interconnect cancer, dementia, ASCVD, and systemic disease. Although the conclusions are conceptual and not empiric, they conform to the 2400 year old adage of Hippocrates. Although not all disease begins in the gut, the gut microbiome appears to start or potentiate most diseases, even those driven by epigenetic abnormalities. Diet and exercise[131] and their impact on the gut microbiome are clearly within our purview.

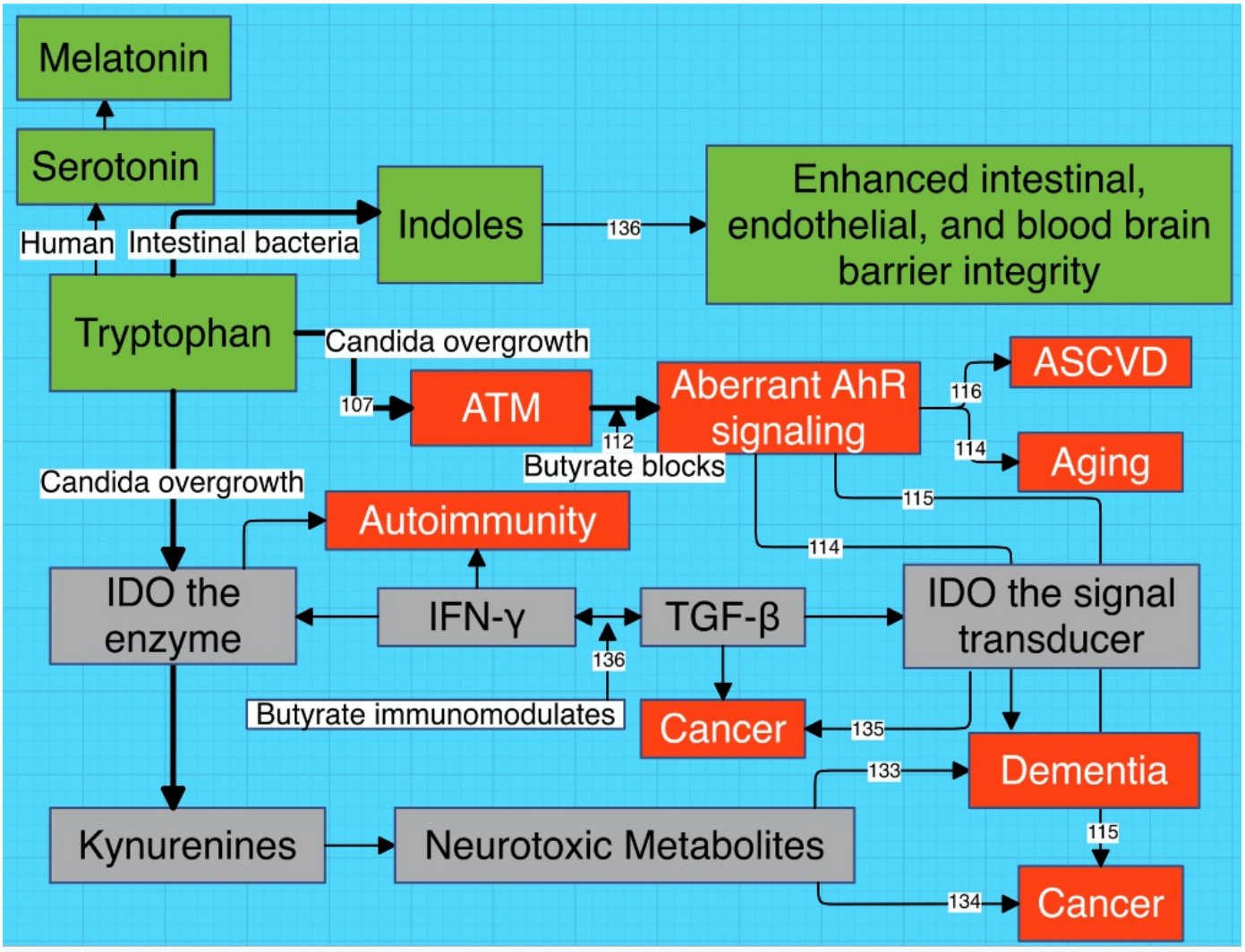

Figure 3. ATM characterizes LC (autoimmunity), cancer, dementia, and many other diseases. IFN-γ (interferon gamma) and TGF-β (transforming growth factor beta) counterbalance each other. TGF-β oversees tolerogenesis - too much and cancer antigens are tolerated, too little and host antigens are not. Candida can release its own IDO, creating ATM and potentiating cancer/dementia; AhR=aryl hydrocarbon receptor; numbers are

references [132][133][134][135][136].

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