Review Article

Hyphae and Healthspan

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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.

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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.

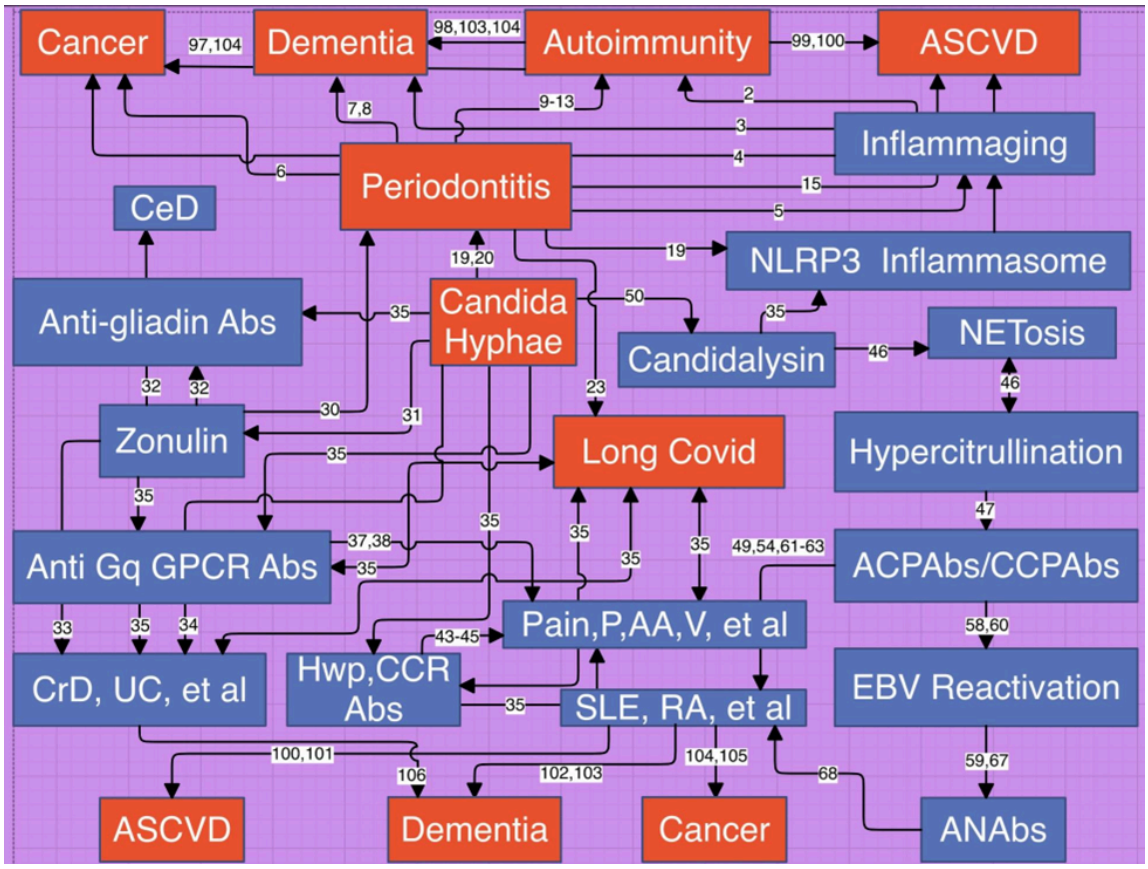

Figure 1. This is an incomplete diagrammatic representation of sections I, II, III. CeD=celiac disease, CrD=Crohn's disease, UC=ulcerative colitis, GPCR=G-protein coupled receptor, ACP=anti-citrullinated peptide, CCP=cyclic citrullinated peptide, P=psoriasis, AA=alopecia areata, V=vitiligo, Hwp=hyphal 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).

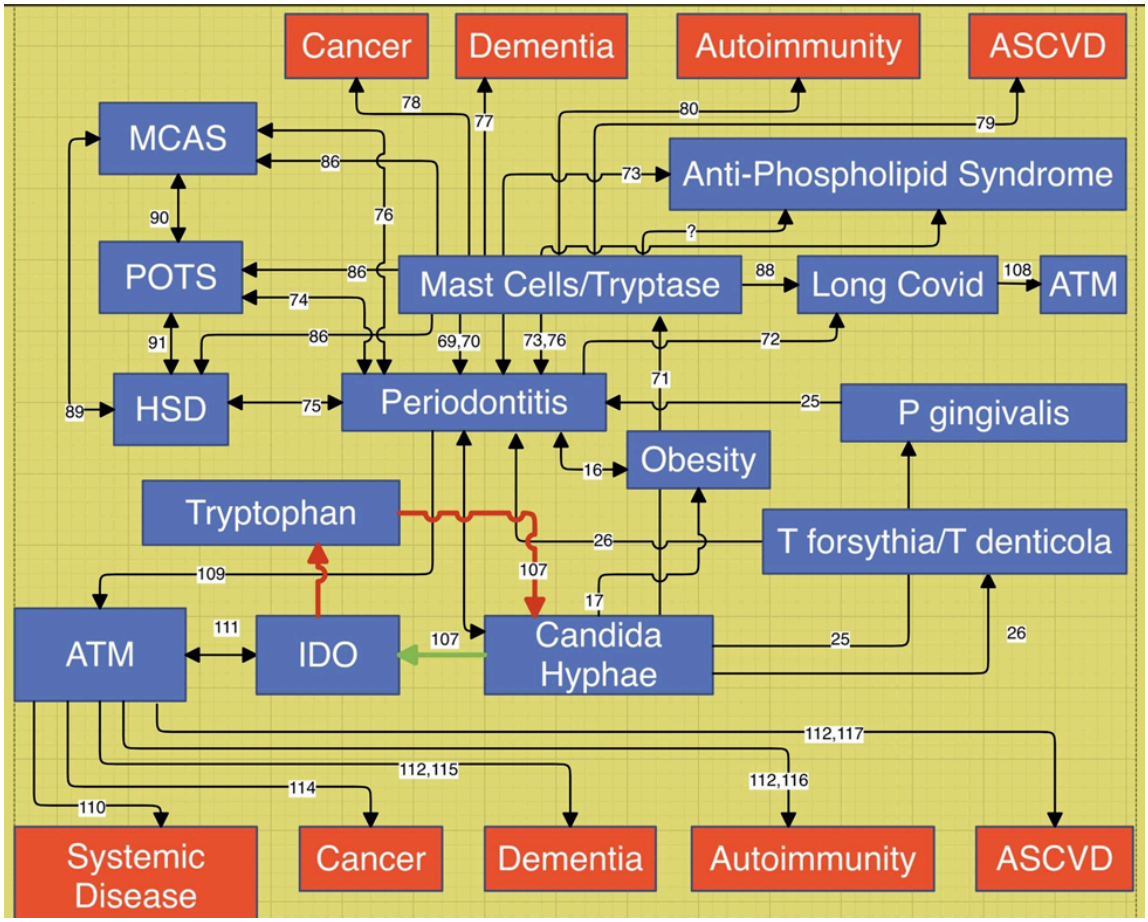

Figure 2. This is an incomplete diagrammatic representation of sections IV, V. MCAS= mast cell activation syndrome, POTS=postural, orthostatic tachycardia syndrome, ATM=altered tryptophan metabolism, IDO= indoleamine dioxygenase, numbers are references.

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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.

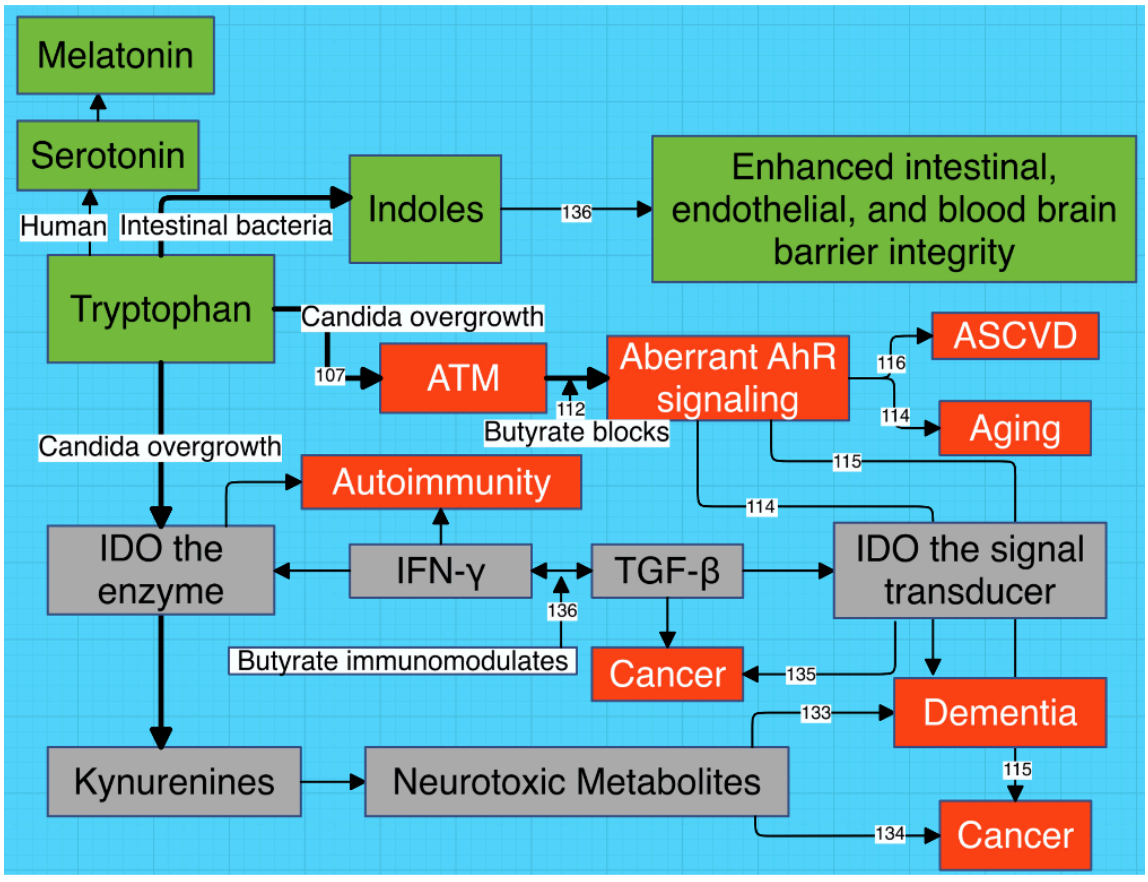

Figure 3. ATM characterizes LC (autoimmunity), cancer, dementia, and many other diseases. IFN-γ (interferon gamma) and TGF-β (transforming growth factor beta) counterbalance each other. TGF-β oversees tolerogenesis - too much and cancer antigens are tolerated, too little and host antigens are not. Candida 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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References

1. ^ *Li, X., Li, C., Zhang, W. et al. Inflammation and aging: signaling pathways and intervention therapies. Sig Transduct Target Ther 8, 239 (2023) https://doi.org/10.1038/s41392-023-01502-8*
2. ^ *Santos-Moreno P, Burgos-Angulo G, Martinez-Ceballos MA, Pizano A, Echeverri D, Bautista-Niño P K, et al. Inflammaging as a link between autoimmunity and cardiovascular disease: the case of rheumat oid arthritis. RMD Open. 2021 Jan;7(1):e001470 https://doi.org/10.1136/rmdopen-2020-001470*
3. ^ *Mekli K, Lophatananon A, Maharani A, Nazroo JY, Muir KR (2023) Association between an inflammat ory biomarker score and future dementia diagnosis in the population-based UK Biobank cohort of 500, 000 people. PLoS ONE 18(7): e0288045. https://doi.org/10.1371/journal.pone.0288045*
4. ^ *Berben L, Floris G, Wildiers H, Hatse S. Cancer and Aging: Two Tightly Interconnected Biological Proces ses. Cancers (Basel). 2021 Mar 19;13(6):1400. https://doi.org/10.3390/cancers13061400*
5. ^ *Zhu, L.; Tang, Z.; Hu, R.; Gu, M.; Yang, Y. Ageing and Inflammation in Periodontium (2024). Encyclope dia. Available online: https://encyclopedia.pub/entry/51981*
6. ^ *Kim EH, Nam S, Park CH, Kim Y, Lee M, Ahn JB, Shin SJ, Park YR, Jung HI, Kim BI, Jung I, Kim HS. Perio dontal disease and cancer risk: A nationwide population-based cohort study. Front Oncol. 2022 Aug 23; 12:901098. https://doi.org/10.3389/fonc.2022.901098*
7. ^ *Guo H, Chang S, Pi X, Hua F, Jiang H, Liu C, Du M. The Effect of Periodontitis on Dementia and Cognitiv e Impairment: A Meta-Analysis. Int J Environ Res Public Health. 2021 Jun 25;18(13):6823. https://doi.or g/10.3390/ijerph18136823*
8. ^ *Lundergan W, Parthasarathy K, Knight N. Periodontitis and Alzheimer's Disease: Is There a Connectio n? Oral. 2024; 4(1):61-73. https://doi.org/10.3390/oral4010006*
9. ^ *Rutter-Locher Z, Smith TO, Giles I, Sofat N. Association between Systemic Lupus Erythematosus and P eriodontitis: A Systematic Review and Meta-analysis. Front Immunol. 2017 Oct 17;8:1295. https://doi.or g/10.3389/fimmu.2017.01295*
10. ^ *Hussain SB, Leira Y, Zehra SA, Botelho J, Machado V, Ciurtin C, D'Aiuto F, Orlandi M. Periodontitis and Systemic Lupus Erythematosus: A systematic review and meta-analysis. J Periodontal Res. 2022 Jan;57 (1):1-10. https://doi.org/10.1111/jre.12936*
11. ^ *Stanomir A, Micu IC, Picoș A, Roman A, Soancă A, Onet D, Onea TN, Rednic S, Ciurea A, Pamfil C. Perio dontitis Burden in Diffuse Versus Limited Systemic Sclerosis Subtypes: A Pilot Study. Curr Health Sci J. 20 23 Apr-Jun;49(2):280-287. https://doi.org/10.12865/CHSJ.49.02.280*

12. ^ *Patil BS, Patil S, Gururaj TR. Probable autoimmune causal relationship between periodontitis and Has himotos thyroidits: a systemic review. Niger J Clin Pract. 2011 Jul-Sep;14(3):253-61. https://doi.org/10.4 103/1119-3077.86763*

13. ^ *Tsimpiris A, Tsolianos I, Grigoriadis A, Tsimtsiou Z, Goulis DG, Grigoriadis N. Association of chronic per iodontitis with multiple sclerosis: A systematic review and meta-analysis. Mult Scler Relat Disord. 2023 Sep;77:104874. https://doi.org/10.1016/j.msard.2023.104874*

14. ^ *de Molon RS, Rossa C Jr, Thurlings RM, Cirelli JA, Koenders MI. Linkage of Periodontitis and Rheumato id Arthritis: Current Evidence and Potential Biological Interactions. Int J Mol Sci. 2019 Sep 13;20(18):454 1. https://doi.org/10.3390/ijms20184541*

15. ^ *Skipina TM, Elhawary MM, Soliman EZ. Periodontal disease is associated with elevated atherosclerotic cardiovascular disease risk score. Am J Med Sci. 2022 Sep;364(3):327-332. https://doi.org/10.1016/j.amj ms.2022.04.002*

16. ^ *Kim CM, Lee S, Hwang W, Son E, Kim TW, Kim K, et al. Obesity and periodontitis: A systematic review a nd updated meta-analysis. Front Endocrinol (Lausanne). 2022 Oct 24;13:999455. https://doi.org/10.338 9/fendo.2022.999455*

17. ^ *Shoukat M, Ullah F, Tariq MN, Din G, Khadija B, Faryal R. Profiling of potential pathogenic candida sp ecies in obesity. Microb Pathog. 2023 Jan;174:105894. https://doi.org/10.1016/j.micpath.2022.105894*

18. ^ *Bhuyan R, Bhuyan SK, Mohanty JN, Das S, Juliana N, Juliana IF. Periodontitis and Its Inflammatory Ch anges Linked to Various Systemic Diseases: A Review of Its Underlying Mechanisms. Biomedicines. 202 2; 10(10):2659. https://doi.org/10.3390/biomedicines10102659*

19. ^ *Isola G, Polizzi A, Santonocito S, Alibrandi A, Williams RC. Periodontitis activates the NLRP3 inflamma some in serum and saliva. J Periodontol. 2022 Jan;93(1):135-145. https://doi.org/10.1002/JPER.21-0049*

20. ^ *Matarese G, Currò M, Isola G, Caccamo D, Vecchio M, Giunta ML, et al. Transglutaminase 2 up-regulati on is associated with RANKL/OPG pathway in cultured HPDL cells and THP-1-differentiated macropha ges. Amino Acids. 2015 Nov;47(11):2447-55. https://doi.org/10.1007/s00726-015-2039-5*

21. ^ *Reyna-Beltrán E, Iranzo M, Calderón-González KG, Mondragón-Flores R, Labra-Barrios ML, Morme neo S, et al. The Candida albicans ENO1 gene encodes a transglutaminase involved in growth, cell divisi on, morphogenesis, and osmotic protection. J Biol Chem. 2018 Mar 23;293(12):4304-4323. https://doi.o rg/10.1074/jbc.M117.810440*

22. ^ *Gupta S, Mohindra R, Singla M, Khera S, Sahni V, Kanta P, et al. The clinical association between Perio dontitis and COVID-19. Clin Oral Investig. 2022 Feb;26(2):1361-1374. https://doi.org/10.1007/s00784-0*

21-04111-3

23. ^*Lloyd-Jones, G., Pontes, C.C., Molayem, S. et al. The Oral-Vascular-Pulmonary Infection Route: a Pathogenic Mechanism Linking Oral Health Status to Acute and Post-Acute COVID-19.Curr Oral Health Rep 10, 163-174 (2023). https://doi.org/10.1007/s40496-023-00354-z*

24. ^*Suresh Unniachan A, Krishnavilasom Jayakumari N, Sethuraman S. Association between Candidaspecies and periodontal disease: A systematic review. Curr Med Mycol. 2020 Jun;6(2):63-68. https://doi.org/10.18502/CMM.6.2.3420*

25. ^*Bartnicka D, Gonzalez-Gonzalez M, Sykut J, Koziel J, Ciaston I, Adamowicz K, et al. Candida albicans Shields the Periodontal Killer Porphyromonas gingivalis from Recognition by the Host Immune System and Supports the Bacterial Infection of Gingival Tissue. Int J Mol Sci. 2020 Mar 14;21(6):1984. https://doi.org/10.3390/ijms21061984*

26. ^*Shigeishi H, Nakamura M, Oka I, Su CY, Yano K, Ishikawa M, et al. The Associations of Periodontopathic Bacteria and Oral Candida with Periodontal Inflamed Surface Area in Older Adults Receiving Supportive Periodontal Therapy. Diagnostics (Basel). 2021 Aug 2;11(8):1397. https://doi.org/10.3390/diagnostics11081397*

27. ^*Wenjun Liu, Wei Zhang, Mingfu Ye, Association between carbohydrate-to-fiber ratio and the risk of periodontitis, Journal of Dental Sciences (2024) 19(1):246-253 https://doi.org/10.1016/j.jds.2023.04.012*

28. ^*Molek, M., Florenly, F., Lister, I. et al. Xerostomia and hyposalivation in association with oral candidiasis: a systematic review and meta-analysis. Evid Based Dent (2022). https://doi.org/10.1038/s41432-021-0210-2*

29. ^*Patel, D., Louca, C. & Machuca Vargas, C. Oral manifestations of long COVID and the views of healthcare professionals. Br Dent J 236, 111-116 (2024). https://doi.org/10.1038/s41415-023-6715-7*

30. ^*Wright, Casey D., "Zonulin as a Mediator of Psychological Stress and Periodontal Disease" (2022). Graduate Theses, Dissertations, and Problem Reports. 11331. https://researchrepository.wvu.edu/etd/11331*

31. ^*Abigail, E., & Haytham, E. (2018). Assessment of the relevance of intestinal Zonulin test for inflammatory conditions in an integrated clinical setting. https://api.semanticscholar.org/CorpusID:53624540*

32. ^*DaFonte TM, Valitutti F, Kenyon V, Locascio JJ, Montuori M, Francavilla R, et al; CD-GEMM Study Group. Zonulin as a Biomarker for the Development of Celiac Disease. Pediatrics. 2024 Jan 1;153(1):e2023063050. https://doi.org/10.1542/peds.2023-063050*

33. ^*Caviglia GP, Dughera F, Ribaldone DG, Rosso C, Abate ML, Pellicano R, Bresso F, Smedile A, Saracco GM, Astegiano M. Serum zonulin in patients with inflammatory bowel disease: a pilot study. Minerva Me*

d. 2019 Apr;110(2):95-100. https://doi.org/10.23736/S0026-4806.18.05787-7

34. ^*Jangi S, Hsia K, Zhao N, Kumamoto CA, Friedman S, Singh S, Michaud DS. Dynamics of the Gut Mycobiome in Patients With Ulcerative Colitis. Clin Gastroenterol Hepatol. 2024 Apr;22(4):821-830.e7. https://doi.org/10.1016/j.cgh.2023.09.023*

35. ^*Chambers, P. (2024). Candida and Long Covid: Mannan Not from Heaven. Qeios. https://doi.org/10.32388/JE31EO.5*

36. ^*Riemekasten G, Petersen F, Heidecke H. What Makes Antibodies Against G Protein-Coupled Receptors so Special? A Novel Concept to Understand Chronic Diseases. Front Immunol. 2020 Dec 15;11:564526. https://doi.org/10.3389/fimmu.2020.564526*

37. ^*Xie, A.X., Madayag, A., Minton, S.K. et al. Sensory satellite glial Gq-GPCR activation alleviates inflammatory pain via peripheral adenosine 1 receptor activation. Sci Rep 10, 14181 (2020). https://doi.org/10.1038/s41598-020-71073-z*

38. ^*Li H, Wang R, Lu Y, Xu X, Ni J. Targeting G protein-coupled receptor for pain management. Brain Circ. 2017 Apr-Jun;3(2):109-113. https://doi.org/10.4103%2Fbc.bc_3_17*

39. ^*An SS, Liggett SB. Taste and smell GPCRs in the lung: Evidence for a previously unrecognized widespread chemosensory system. Cell Signal. 2018 Jan;41:82-88. https://doi.org/10.1016/j.cellsig.2017.02.002*

40. ^*Chan CK, Liao SY, Zhang YL, Xu A, Tse HF, Vanhoutte PM. Protective effects of histamine on Gq-mediated relaxation in regenerated endothelium. Am J Physiol Heart Circ Physiol. 2014 Jan 15;306(2):H286-90. https://doi.org/10.1152/ajpheart.00733.2013*

41. ^*Shen J, Zhang D, Fu Y, Chen A, Yang X, Zhang H. Cryo-EM structures of human bradykinin receptor-Gq proteins complexes. Nat Commun. 2022 Feb 7;13(1):714. https://doi.org/10.1038/s41467-022-28399-1*

42. ^*Aloyouny AY, Bepari A, Rahman I. Evaluating the Role of CXCR3 in Pain Modulation: A Literature Review. J Pain Res. 2020 Aug 6;13:1987-2001. https://doi.org/10.2147/JPR.S254276*

43. ^*Hedrick MN, Lonsdorf AS, Hwang ST, Farber JM. CCR6 as a possible therapeutic target in psoriasis. Expert Opin Ther Targets. 2010 Sep;14(9):911-22. https://doi.org/10.1517/14728222.2010.504716*

44. ^*Ito T, Kageyama R, Nakazawa S, Honda T. Understanding the significance of cytokines and chemokines in the pathogenesis of alopecia areata. Exp Dermatol. 2020 Aug;29(8):726-732. https://doi.org/10.1111/exd.14129*

45. ^*He, Q., Yuan, Q., Shan, H. et al. Mechanisms of ligand recognition and activation of melanin-concentrating hormone receptors. Cell Discov 10, 48 (2024). https://doi.org/10.1038/s41421-024-00679-8*

46. ^Unger L, Skoluda S, Backman E, Amulic B, Ponce-Garcia FM, Etiaba CN, et al. Candida albicans induces neutrophil extracellular traps and leucotoxic hypercitrullination via candidalysin. EMBO Rep. 2023 Nov 6;24(11):e57571. https://doi.org/10.15252/embr.202357571

47. a, bCiesielski O, Biesiekierska M, Panthu B, Soszyński M, Pirola L, Balcerczyk A. Citrullination in the pathology of inflammatory and autoimmune disorders: recent advances and future perspectives. Cell Mol Life Sci. 2022 Jan 25;79(2):94. https://doi.org/10.1007/s00018-022-04126-3

48. ^Martos R, Tar I, Nagy AC, Csősz É, Kiss C, Márton I. Hypercitrullination and anti-citrullinated protein antibodies in chronic apical periodontitis, a laboratory investigation. Does autoimmunity contribute to the pathogenesis? Int Endod J. 2023 May;56(5):584-592. https://doi.org/10.1111/iej.13903

49. ^Alghamdi M, Alasmari D, Assiri A, Mattar E, Aljaddawi AA, Alattas SG, Redwan EM. An Overview of the Intrinsic Role of Citrullination in Autoimmune Disorders. J Immunol Res. 2019 Nov 25;2019:7592851. https://doi.org/10.1155/2019/7592851

50. ^Liu J, Gao J, Wu Z, Mi L, Li N, Wang Y, Peng X, Xu K, Wu F, Zhang L. Anti-citrullinated Protein Antibody Generation, Pathogenesis, Clinical Application, and Prospects. Front Med (Lausanne). 2022 Jan 12;8:802934. https://doi.org/10.3389/fmed.2021.802934

51. ^Roghani SA, Dastbaz M, Lotfi R, Shamsi A, Abdan Z, Rostampour R, et al. The development of anti-cyclic citrullinated peptide (anti-CCP) antibody following severe COVID-19. Immun Inflamm Dis. 2024 May;12(5):e1276. https://doi.org/10.1002/iid3.1276

52. ^Payet J, Belkhir R, Gottenberg JE, Bergé E, Desmoulins F, Meyer O, Mariette X, Seror R. ACPA-positive primary Sjögren's syndrome: true primary or rheumatoid arthritis-associated Sjögren's syndrome? RMD Open. 2015 Apr 30;1(1):e000066. https://doi.org/10.1136/rmdopen-2015-000066

53. ^Paksoy T, Ustaoglu G, Tasci M, Demirci M, Unlu O, Yasar MF. Assessment of Epstein-Barr virus, Candida albicans, and some periodontal pathogens in rheumatoid arthritis patients with periodontitis. North Clin Istanb. 2023 Aug 9;10(4):490-500. https://doi.org/10.14744/nci.2023.58998

54. ^Ceccarelli, F., Perricone, C., Colasanti, T. et al. Anti-carbamylated protein antibodies as a new biomarker of erosive joint damage in systemic lupus erythematosus. Arthritis Res Ther 20, 126 (2018). https://doi.org/10.1186/s13075-018-1622-z

55. ^Lammers KM, Lu R, Brownley J, Lu B, Gerard C, Thomas K, et al. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. Gastroenterology. 2008 Jul;135(1):194-204.e3. https://doi.org/10.1053/j.gastro.2008.03.023

56. ^Rork JF, Rashighi M, Harris JE. Understanding autoimmunity of vitiligo and alopecia areata. Curr Opin Pediatr. 2016 Aug;28(4):463-9. https://doi.org/10.1097/MOP.0000000000000375

57. ^Ho J, Camilli G, Griffiths JS, Richardson JP, Kichik N, Naglik JR. Candida albicans and candidalysin in in flammatory disorders and cancer. Immunology. 2021 Jan;162(1):11-16. https://doi.org/10.1111/imm.13255

58. ^Yamada H, Ozawa T, Kishi H, Okada S, Nakashima Y, Muraguchi A, Yoshikai Y. Cutting Edge: B Cells Expressing Cyclic Citrullinated Peptide-Specific Antigen Receptor Are Tolerized in Normal Conditions. J Immunol. 2018 Dec 15;201(12):3492-3496. https://doi.org/10.4049/jimmunol.1800826

59. a, bHouen G, Trier NH. Epstein-Barr Virus and Systemic Autoimmune Diseases. Front Immunol. 2021 Jan 7;11:587380. https://doi.org/10.3389/fimmu.2020.587380

60. ^Cuomo L, Cirone M, Di Gregorio AO, Vitillo M, Cattivelli M, Magliocca V, et al. Elevated antinuclear antibodies and altered anti-Epstein-Barr virus immune responses. Virus Res. 2015 Jan 2;195:95-9. https://doi.org/10.1016/j.virusres.2014.09.014

61. ^Pratesi, F., Tommasi, C., Anzilotti, C., Chimenti, D. and Migliorini, P. (2006), Deiminated Epstein-Barr virus nuclear antigen 1 is a target of anti–citrullinated protein antibodies in rheumatoid arthritis. Arthritis & Rheumatism, 54: 733-741. https://doi.org/10.1002/art.21629

62. ^Skare TL, Nisihara R, Barbosa BB, da Luz A, Utiyama S, Picceli V. Anti-CCP in systemic lupus erythematosus patients: a cross sectional study in Brazilian patients. Clin Rheumatol. 2013 Jul;32(7):1065-70. https://doi.org/10.1007/s10067-013-2213-7

63. ^Draborg AH, Duus K, Houen G. Epstein-Barr virus and systemic lupus erythematosus. Clin Dev Immunol. 2012;2012:370516. https://doi.org/10.1155/2012/370516

64. ^Ashangari, C, Asghar, SF, Syed, S, Sulema, A. Abstract 116: Antinuclear Antibody levels Study in Postural Orthostatic Tachycardia Syndrome, Circulation: Cardiovascular Quality and Outcomes (2016) https://www.ahajournals.org/doi/10.1161/circoutcomes.9.suppl_2.116

65. ^Bernal KDE, Whitehurst CB. Incidence of Epstein-Barr virus reactivation is elevated in COVID-19 patients. Virus Res. 2023 Sep;334:199157. https://doi.org/10.1016/j.virusres.2023.199157

66. ^Gold JE, Okyay RA, Licht WE, Hurley DJ. Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation. Pathogens. 2021 Jun 17;10(6):763. https://doi.org/10.3390/pathogens10060763

67. ^Harley JB, Chen X, Pujato M, Miller D, Maddox A, Forney C, et al. Transcription factors operate across disease loci, with EBNA2 implicated in autoimmunity. Nat Genet. 2018 May;50(5):699-707. https://doi.o

rg/10.1038/s41588-018-0102-3

68. ^*James JA, Harley JB, Scofield RH. Epstein-Barr virus and systemic lupus erythematosus. Curr Opin Rheu matol (2006) 18(5):462-7. https://doi.org/10.1097/01.bor.0000240355.37927.94*

69. ^*Trimarchi M, Lauritano D, Ronconi G, Caraffa A, Gallenga CE, Frydas I, Kritas SK, Calvisi V, Conti P. Ma st Cell Cytokines in Acute and Chronic Gingival Tissue Inflammation: Role of IL-33 and IL-37. Internati onal Journal of Molecular Sciences. 2022; 23(21):13242. https://doi.org/10.3390/ijms232113242*

70. ^*Lagdive SS, Lagdive SB, Mani A, Anarthe R, Pendyala G, Pawar B, Marawar PP. Correlation of mast cell s in periodontal diseases. J Indian Soc Periodontol. 2013 Jan;17(1):63-7. https://doi.org/10.4103/0972-1 24X.107500*

71. ^*Yu M, Song XT, Liu B, Luan TT, Liao SL, Zhao ZT. The Emerging Role of Mast Cells in Response to Fung al Infection. Front Immunol. 2021 Jun 3;12:688659. https://doi.org/10.3389/fimmu.2021.688659*

72. ^*Louisa, M., Amalina, A., Putranto, R. A., Komala, O. N., & Anggraini, W. (2024). Periodontal disease sev erity in patients with long COVID and non-COVID-19. Dental Journal, 57(1), 50-55. https://doi.org/10.2 0473/j.djmkg.v57.i1.p50-55*

73. ^*Schenkein HA, Berry CR, Burmeister JA, Brooks CN, Barbour SE, Best AM, Tew JG. Anti-cardiolipin anti bodies in sera from patients with periodontitis. J Dent Res. 2003 Nov;82(11):919-22. https://doi.org/10.1 177/154405910308201114*

74. ^*Brooks JK, Francis LA. Postural orthostatic tachycardia syndrome: Dental treatment considerations. J A m Dent Assoc. 2006 Apr;137(4):488-93. https://doi.org/10.14219/jada.archive.2006.0221*

75. ^*Kapferer-Seebacher I, Pepin M, Werner R, Aitman TJ, Nordgren A, Stoiber H, et al. Periodontal Ehlers-Danlos Syndrome Is Caused by Mutations in C1R and C1S, which Encode Subcomponents C1r and C1s of Complement. Am J Hum Genet. 2016 Nov 3;99(5):1005-1014. https://doi.org/10.1016/j.ajhg.2016.08.019*

76. ^*Kak, M. M., Bharali, J., Rastogi, P., & Chaubey, K. K. (2021). Role of mast cells in periodontal health and disease: A comparative study. International Journal of Applied Dental Sciences, 7(4), 113-116. https://do i.org/10.22271/ORAL.2021.V7.I4B.1361*

77. ^*Jones MK, Nair A, Gupta M. Mast Cells in Neurodegenerative Disease. Front Cell Neurosci. 2019 Apr 30; 13:171. https://doi.org/10.3389/fncel.2019.00171*

78. ^*Guo X, Sun M, Yang P, Meng X, Liu R. Role of mast cells activation in the tumor immune microenviron ment and immunotherapy of cancers. Eur J Pharmacol. 2023 Dec 5;960:176103. https://doi.org/10.1016/ j.ejphar.2023.176103*

79. ^Kovanen PT, Bot I. Mast cells in atherosclerotic cardiovascular disease - Activators and actions. Eur J P harmacol. 2017 Dec 5;816:37-46. https://doi.org/10.1016/j.ejphar.2017.10.013

80. ^Kaczmarczyk-Sekuła, K., Dyduch, G., Kostański, M., Wielowieyska-Szybińska, D., Szpor, J., Białas, M., & Okoń, K. (2015). Mast cells in systemic and cutaneous lupus erythematosus. Polish Journal of Patholog y, 66(4), 397-402 https://doi.org/10.5114/pjp.2015.57253

81. ^Suurmond, J, Dorjee, AL, Boon, MR, Knol, EF, Huizinga, TW, Toes, RE, et al. Mast cells are the main int erleukin 17-positive cells in anticitrullinated protein anti-body-positive and -negative rheumatoid art hritis and osteoarthritis synovium. Arthritis Res. Ther. 2011, 13, R150. https://doi.org/10.1186/s13075-01 5-0847-3

82. ^Nakae, S.; Suto, H.; Berry, G.J.; Galli, S.J. Mast cell-derived TNF can promote Th17 cell-dependent neutr ophil recruitment in oval-bumin-challenged OTII mice. Blood 2007, 109, 3640-3648 https://doi.org/1 0.1182/blood-2006-09-046128

83. ^Kenna, T.; A Brown, M. The role of IL-17-secreting mast cells in inflammatory joint disease. Nat. Rev. Rheumatol. 2012, 9, 375-379 https://doi.org/10.1038/nrrheum.2012.205

84. ^De Zuani M, Dal Secco C, Frossi B. Mast cells at the crossroads of microbiota and IBD. Eur J Immunol. 2 018 Dec;48(12):1929-1937 https://doi.org/10.1002/eji.201847504

85. ^Kempuraj, D, Tagen, M, Iliopoulou, BP, Clemons, A, Vasiadi, M, Boucher, W, et al. Luteolin inhibits mye lin basic protein-induced human mast cell activation and mast cell-dependent stimulation of Jurkat T c ells. J. Cereb. Blood Flow Metab. 2008, 155, 1076-1084 https://doi.org/10.1038/bjp.2008.356

86. ^Schofield JR. Persistent Antiphospholipid Antibodies, Mast Cell Activation Syndrome, Postural Orthosta tic Tachycardia Syndrome and Post-COVID Syndrome: 1 Year On. Eur J Case Rep Intern Med. 2021;8(3):0 02378. Published 2021 Mar 22. https://doi.org/10.12890/2021_002378

87. ^Gutowski Ł, Kanikowski S, Formanowicz D. Mast Cell Involvement in the Pathogenesis of Selected Mus culoskeletal Diseases. Life (Basel). 2023 Aug 5;13(8):1690. https://doi.org/10.3390/life13081690

88. ^Sumantri S, Rengganis I. Immunological dysfunction and mast cell activation syndrome in long COVID. Asia Pac Allergy. 2023 Mar;13(1):50-53. https://doi.org/10.5415/apallergy.0000000000000022

89. ^Monaco A, Choi D, Uzun S, Maitland A, Riley B. Association of mast-cell-related conditions with hyper mobile syndromes: a review of the literature. Immunol Res. 2022 Aug;70(4):419-431. https://doi.org/10. 1007/s12026-022-09280-1

90. ^Kohno R, Cannom DS, Olshansky B, Xi SC, Krishnappa D, Adkisson WO, et al. Mast Cell Activation Disor der and Postural Orthostatic Tachycardia Syndrome: A Clinical Association. J Am Heart Assoc. 2021 Sep

7;10(17):e021002. https://doi.org/10.1161/JAHA.121.021002

91. ^Gazit Y, Nahir AM, Grahame R, Jacob G. Dysautonomia in the joint hypermobility syndrome. Am J Med. 2003;115:33-40. https://doi.org/10.1016/S0002-9343(03)00235-3

92. ^Wang Y, Wang T, Cai M, Zhu S, Song L, Wang Q. Expression and existence forms of mast cell activating molecules and their antibodies in systemic lupus erythematosus. Immun Inflamm Dis. 2022 Feb;10(2):235-240. https://doi.org/10.1002/iid3.567

93. ^Gumà M, Olivé A, Roca J, et al Association of systemic lupus erythematosus and hypermobility Annals of the Rheumatic Diseases 2002;61:1024-1026 https://doi.org/10.1136/ard.61.11.1024

94. a, bShaw BH, Stiles LE, Bourne K, Green EA, Shibao CA, Okamoto LE, et al. The face of postural tachycardia syndrome - insights from a large cross-sectional online community-based survey. J Intern Med. 2019 Oct;286(4):438-448. https://doi.org/10.1111/joim.12895

95. ^Abu-Shakra M, Gladman DD, Urowitz MB, Farewell V. Anticardiolipin antibodies in systemic lupus erythematosus: clinical and laboratory correlations. Am J Med. 1995 Dec;99(6):624-8. https://doi.org/10.1016/s0002-9343(99)80249-6

96. ^Meroni PL, Tsokos GC. Editorial: Systemic Lupus Erythematosus and Antiphospholipid Syndrome. Front Immunol. 2019 Feb 25;10:199. https://doi.org/10.3389/fimmu.2019.00199

97. ^Mangani D, Yang D, Anderson AC. Learning from the nexus of autoimmunity and cancer. Immunity. 2023 Feb 14;56(2):256-271 https://doi.org/10.1016/j.immuni.2023.01.022

98. ^Weaver DF. Alzheimer's disease as an innate autoimmune disease (AD2): A new molecular paradigm. Alzheimers Dement. 2022 Sep 27. https://doi.org/10.1002/alz.12789

99. ^Mortensen, MB, Jensen, JM, Sand, NPR, Kragholm, K, Blaha, MJ, Grove, EL, et al. Association of Autoimmune Diseases With Coronary Atherosclerosis Severity and Ischemic Events, JACC (2024) 83(25):2643-54 https://doi.org/10.1016/j.jacc.2024.04.030

100. ^Keyes, E, Grinnell, M, Jacoby, D, Vazquez, T, Diaz, D, Werth, VP, et al. Assessment and management of the heightened risk for atherosclerotic cardiovascular events in patients with lupus erythematosus or dermatomyositis (2021) IJWD 7(5A):560-75 https://doi.org/10.1016/j.ijwd.2021.08.015

101. ^Popescu D, Rezus E, Badescu MC, Dima N, Seritean Isac PN, Dragoi I-T, et al. Cardiovascular Risk Assessment in Rheumatoid Arthritis: Accelerated Atherosclerosis, New Biomarkers, and the Effects of Biological Therapy. Life. 2023; 13(2):319. https://doi.org/10.3390/life13020319

102. ^Jin T, Huang W, Cao F, Yu X, Guo S, Ying Z, et al. Causal association between systemic lupus erythematosus and the risk of dementia: A Mendelian randomization study. Front Immunol. 2022 Dec 8;13:106311

o https://doi.org/10.3389/fimmu.2022.1063110

103. ^*Kodishala, C, Hulshizer, CA, Kronzer, VL, Davis III, JM, Ramanan, VK, Vassilaki, M, et al. Risk Factors fo r Dementia in Patients With Incident Rheumatoid Arthritis: A Population-Based Cohort Study The Journ al of Rheumatology January 2023, 50 (1) 48-55; https://doi.org/10.3899/jrheum.220200*

104. ^*Song, L., Wang, Y., Zhang, J. et al. The risks of cancer development in systemic lupus erythematosus (SL E) patients: a systematic review and meta-analysis. Arthritis Res Ther 20, 270 (2018). https://doi.org/1 0.1186/s13075-018-1760-3*

105. ^*Beydon M, Pinto S, De Rycke Y, Fautrel B, Mariette X, Seror R, et al. Risk of cancer for patients with rhe umatoid arthritis versus general population: a national claims database cohort study. Lancet Reg Healt h Eur. 2023 Oct 30;35:100768. https://doi.org/10.1016/j.lanepe.2023.100768*

106. ^*Zamani M, Ebrahimtabar F, Alizadeh-Tabari S, et al. Risk of common neurological disorders in adult p atients with inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis. (2024) https://do.org/10.1093/ibd/izae012*

107. a, b*Bozza, S, Fallarino, F, Pitzurra, L, Zelante, T, Montagnoli, C, Bellocchio, S, et al; A Crucial Role for Try ptophan Catabolism at the Host/Candida albicans Interface. J Immunol 1 March 2005; 174 (5): 2910-29 18. https://doi.org/10.4049/jimmunol.174.5.2910*

108. ^*Eroğlu İ, Eroğlu BÇ, Güven GS. Altered tryptophan absorption and metabolism could underlie long-ter m symptoms in survivors of coronavirus disease 2019 (COVID-19). Nutrition. 2021 Oct;90:111308 http s://doi.org/10.1016/j.nut.2021.111308*

109. ^*Kurgan Ş, Önder C, Balcı N, Akdoğan N, Altıngöz SM, Serdar MA, Günhan M. Influence of periodontal i nflammation on tryptophan-kynurenine metabolism: a cross-sectional study. Clin Oral Investig. 2022 S ep;26(9):5721-5732. https://doi.org/10.1007/s00784-022-04528-4*

110. ^*Harris DMM, Szymczak S, Schuchardt S, Labrenz J, Tran F, Welz L, et al. Tryptophan degradation as a s ystems phenomenon in inflammation - an analysis across 13 chronic inflammatory diseases. EBioMedic ine. 2024 Apr;102:105056. https://doi.org/10.1016/j.ebiom.2024.105056*

111. ^*Brown AJ, Brown GD, Netea MG, Gow NA. Metabolism impacts upon Candida immunogenicity and pat hogenicity at multiple levels. Trends Microbiol. 2014 Nov;22(11):614-22. https://doi.org/10.1016/j.tim.2 014.07.001*

112. ^*Modoux M, Rolhion N, Lefevre JH, Oeuvray C, Nádvorník P, Illes P, et al. Butyrate acts through HDAC in hibition to enhance aryl hydrocarbon receptor activation by gut microbiota-derived ligands. Gut Microb es. 2022 Jan-Dec;14(1):2105637. https://doi.org/10.1080/19490976.2022.2105637*

113. ^McCrory C, Lenardon M, Traven A. Bacteria-derived short-chain fatty acids as potential regulators of fungal commensalism and pathogenesis. Trends Microbiol. 2024 May 9:S0966-842X (24)00089-1. https://doi.org/10.1016/j.tim.2024.04.004

114. a, b, cOjo ES, Tischkau SA. The Role of AhR in the Hallmarks of Brain Aging: Friend and Foe. Cells. 2021 Oct 13;10(10):2729. https://doi.org/10.3390/cells10102729

115. ^Wang Z, Snyder M, Kenison JE, Yang K, Lara B, Lydell E, et al. How the AhR Became Important in Cancer: The Role of Chronically Active AhR in Cancer Aggression. Int J Mol Sci. 2020 Dec 31;22(1):387. https://doi.org/10.3390/ijms22010387

116. ^Zhu K, Meng Q, Zhang Z, Yi T, He Y, Zheng J, Lei W. Aryl hydrocarbon receptor pathway: Role, regulation and intervention in atherosclerosis therapy (Review). Mol Med Rep. 2019 Dec;20(6):4763-4773. https://doi.org/10.3892/mmr.2019.10748

117. ^Seo, SK., Kwon, B. Immune regulation through tryptophan metabolism.Exp Mol Med 55, 1371–1379 (2023). https://doi.org/10.1038/s12276-023-01028-7

118. ^Zeng X, Feng M, Lu J, Wang R, Deng L, Yang Y, Luo L. Beyond transcription, aryl hydrocarbon receptor plays a protective role in periodontitis by interacting with CaMKII. J Periodontol. 2024 Jul 5. https://doi.org/10.1002/JPER.24-0021

119. ^Meissner WG, Remy P, Giordana C, Maltête D, Derkinderen P, Houéto JL, et al; LIXIPARK Study Group. Trial of Lixisenatide in Early Parkinson's Disease. N Engl J Med. 2024 Apr 4;390(13):1176-1185. https://doi.org/10.1056/NEJMoa2312323

120. ^Edison, P., et al. GLP-1 Drug Liraglutide May Protect Against Dementia, Alzheimer's Association International Conference® (AAIC®) July 2024, Philadelphia https://aaic.alz.org/downloads2024/AAIC-2024-GLP-1-Ph2-trial.pdf

121. ^Wang L, Xu R, Kaelber DC, Berger NA. Glucagon-Like Peptide 1 Receptor Agonists and 13 Obesity-Associated Cancers in Patients With Type 2 Diabetes. JAMA Netw Open. 2024;7(7):e2421305. https://doi.org/10.1001/jamanetworkopen.2024.21305

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

123. ^Ashique S, Kumar S, Hussain A, Mishra N, Garg A, Gowda BHJ, et al. A narrative review on the role of magnesium in immune regulation, inflammation, infectious diseases, and cancer. J Health Popul Nutr. 2023 Jul 27;42(1):74. https://doi.org/10.1186/s41043-023-00423-0

124. ^Yang Z, Zhang Y, Gao J, Yang Q, Qu H, Shi J. Association between dietary magnesium and 10-year risk of a first hard atherosclerotic cardiovascular disease event. Am J Med Sci. 2024 May 26:S0002-9629(24)01261-8. https://doi.org/10.1016/j.amjms.2024.05.014

125. ^Du K, Zheng X, Ma ZT, Lv JY, Jiang WJ, Liu MY. Association of Circulating Magnesium Levels in Patients With Alzheimer's Disease From 1991 to 2021: A Systematic Review and Meta-Analysis. Front Aging Neurosci. 2022 Jan 10;13:799824. https://doi.org/10.3389/fnagi.2021.799824

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

127. ^Hu D, Liu J, Yu W, Li C, Huang L, Mao W, Lu Z. Tryptophan intake, not always the more the better. Front Nutr. 2023 Apr 11;10:1140054. https://doi.org/10.3389/fnut.2023.1140054

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

129. ^Lischka J, Schanzer A, Baumgartner M, de Gier C, Greber-Platzer S, Zeyda M. Tryptophan Metabolism Is Associated with BMI and Adipose Tissue Mass and Linked to Metabolic Disease in Pediatric Obesity. Nutrients. 2022 Jan 11;14(2):286. https://doi.org/10.3390/nu14020286

130. ^Cussotto S, Delgado I, Anesi A, Dexpert S, Aubert A, Beau C, et al. Tryptophan Metabolic Pathways Are Altered in Obesity and Are Associated With Systemic Inflammation. Front Immunol. 2020 Apr 15;11:557. https://doi.org/10.3389/fimmu.2020.00557

131. ^Mailing LJ, Allen JM, Buford TW, Fields CJ, Woods JA. Exercise and the Gut Microbiome: A Review of the Evidence, Potential Mechanisms, and Implications for Human Health. Exerc Sport Sci Rev. 2019 Apr;47(2):75-85. https://doi.org/10.1249/JES.0000000000000183

132. ^Rogiers O, Frising UC, Kucharíková S, Jabra-Rizk MA, van Loo G, Van Dijck P, et al. Candidalysin Crucially Contributes to Nlrp3 Inflammasome Activation by Candida albicans Hyphae. mBio. 2019 Jan 8;10(1):e02221-18. https://doi.org/10.1128/mBio.02221-18

133. ^Gouasmi R, Ferraro-Peyret C, Nancey S, Coste I, Renno T, Chaveroux C, Aznar N, Ansieau S. The Kynurenine Pathway and Cancer: Why Keep It Simple When You Can Make It Complicated. Cancers (Basel). 2022 Jun 4;14(11):2793. https://doi.org/10.3390/cancers14112793

134. ^Fernandes BS, Inam ME, Enduru N, Quevedo J, Zhao Z. The kynurenine pathway in Alzheimer's disease: a meta-analysis of central and peripheral levels. Braz J Psychiatry. 2023 May-Jun;45(3):286-297. htt

ps://doi.org/10.47626/1516-4446-2022-2962

135. ^*Pallotta MT, Rossini S, Suvieri C, Coletti A, Orabona C, Macchiarulo A, Volpi C, Grohmann U. Indoleamine 2,3-dioxygenase 1 (IDO1): an up-to-date overview of an eclectic immunoregulatory enzyme. FEBS J. 2022 Oct;289(20):6099-6118. https://doi.org/10.1111/febs.16086*

136. ^*Aburto, M.R., Cryan, J.F. Gastrointestinal and brain barriers: unlocking gates of communication across the microbiota–gut–brain axis. Nat Rev Gastroenterol Hepatol 21, 222–247 (2024). https://doi.org/10.1038/s41575-023-00890-0*

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