

The CD147 Epitope on SARS CoV2 and the Spike in Cancer, Autoimmunity and Organ Fibrosis

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Abstract

TNF α in partnership with glycosylated CD147 conspires to create the fertile soil for de novo and recurrent cancer. CD147 is present on the spike protein S (virus or vaccine) [1], despite claims to the contrary [2,3]. These claims have been discredited [4]. Pro and con arguments for the connection between cancer and Covid-19 or its vaccines continue to rage. But the physiologic implications involving TNF α and CD147 discussed in this article are worrisome. A deep dive into the tumor microenvironment (TME) created by the high mannose high glycosylation of CD147 is undertaken.

Angiotensin II type 1 receptor antibodies and TNF α generated by the virus and/or the vaccine are biomarkers for future LC. Their presence in POTS is 70%. These activate AT1Rs and ADAM17 aka TACE, the enzyme that produces TNF α . This cytokine inhibits mannosidase and leads to the high mannose glycosylation of CD147, TNF α , IL-6, and TGF beta or their receptors, which appears to redirect their pleiotropic functions. High mannose glycosylation of CD147 drives the production of IL-17 and IFN gamma closely linked to autoimmune disease. TGF beta is linked to organ fibrosis. The TME created by these redirected cytokines spawns epithelial mesenchymal transition (EMT), cancer associated fibrosis (CAF), tumorigenesis, and metastasis. TNF α is associated with aggressive forms of colon cancer and Triple negative breast cancer (TNBC) and levels are elevated when vitamin D and magnesium are deficient.

TNBC (15% of breast cancers, but the most aggressive form) is especially prominent in the obese and in young (less than 40) African American and Hispanic women. Specific recommendations for prevention and therapy include D-mannose.

Keywords: Glycosylation, TNBC, ADAM17 aka TACE, CD147 aka EMMPRIN aka basigin, Mannosidase, TNF α

Introduction

Many oncologists and pathologists are reporting an increase in cancers, especially in those under 40, in the aftermath of COVID-19 and its vaccines. This spike and associated claims of “turbo cancers” are denied, ascribed to other considerations, or dismissed as secondary to vaccine benefits. DNA plasmid contamination, inflammatory lipid nanoparticles, or other claimed toxic elements in the vaccine are not discussed.

Follow up data to prove or not is time dependent, but a pattern may be emerging. The pandemic and its LC aftermath have driven a tsunami of relevant research. This report will tap the wealth of that research on the spike protein S. However, this is not a retrospective/prospective analysis or meta-analysis of data but a technical one investigating the relevant physiologic findings—one that is predictive in nature. This physiologic approach might contribute a

more clear cut and more timely verdict on this in the near term. Its implications pertain not only to LC but also to repeated exposure to the spike protein S. Although many claim that the benefit/risk ratio is strongly in favor of COVID-19 vaccination for the elderly and those with comorbidities, the relevant physiology suggests otherwise.

ACE2, TACE, and CD147 in SARS CoV2

SARS CoV2 can enter the cell thru both ACE2 receptors and CD147 receptors. Endocytotic invasion of the virus via ACE2 receptors with loss of ACE2 receptor bearing cells increases ACE/ACE2. This promotes Ang II accumulation and AT1R activity [5], which upregulates ADAM-17 (A Disintegrin and Metalloproteinase #17) also known as TACE (Tumor necrosis factor Alpha Converting Enzyme) (Figure 1). Synthesis of TNF α provides a robust boost to IL-6 [6].

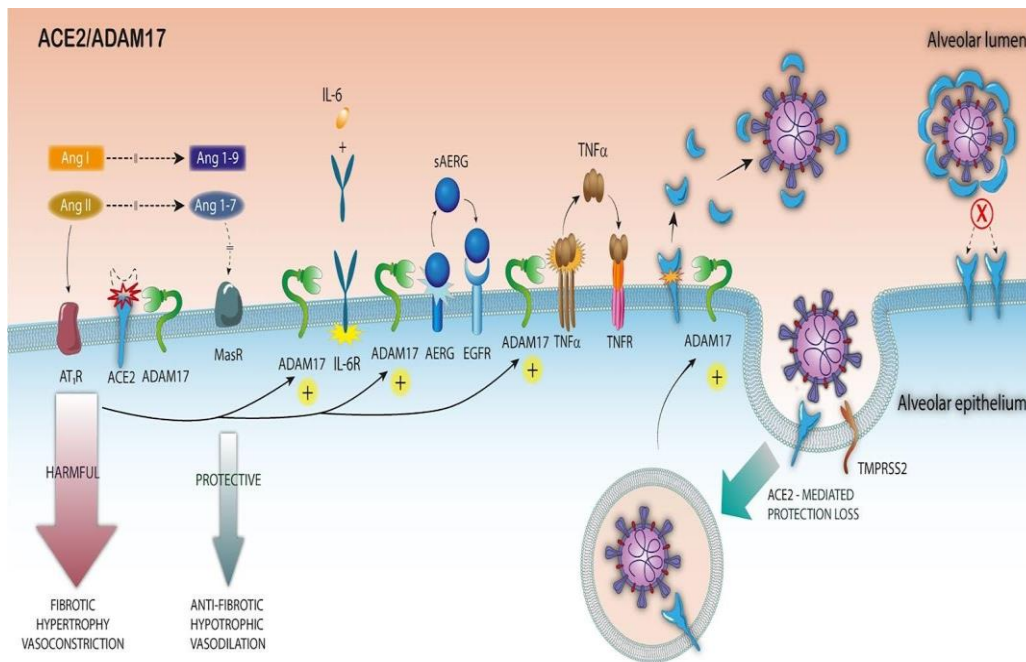


Figure 1: Angiotensin II thru AT1Rs and the invading SARS CoV2 upregulate ADAM17 aka TACE, which increases the production of TNF α and IL-6, the two most critical cytokines to COVID-19 severity [7,8]. Figure source [9].

Most studies on the cytokines induced by SARS CoV2 indicate that increasing TNF alpha and IL-6 not only determine Covid severity but are also elevated in LC [10]. Those vaccinees with LC v healthy vaccinees exhibited elevated IL-6 and AngII type 1 receptor antibodies [11]. The latter triggers AT1Rs that upregulate TACE (ADAM17)[9] and production of TNF α . TNF alpha is a potent inducer of IL-6. The majority of those with LC suffer from POTS. The majority of those with POTS (70%) have angiotensin II type 1 receptor autoantibodies that upregulate AT1Rs.

Angiotensin receptor blockers are effective in POTS [12]. ARBs may also down regulate AT1Rs signals induced by ADAM17 (activated by the spike protein S). The criticality of mannose in the pathogenesis of COVID-19 and its connection to CD147 are demonstrated by the efficacy of lectin complement pathway inhibitors [13,14].

The presence of CD147 (basigin) on the spike protein S of SARS CoV2 was initially reported in late 2020 [1]. Shortly thereafter this was challenged [2,3]. Both of these challenges have been discredited [4]. The immune dysfunction in Covid-19 cannot be explained in the absence of

CD147 on the spike protein S. ACE2 receptors are not present on PBMC, although CD147 upregulates ACE2 [15]. Every dose of the spike protein S bearing vaccine delivers ACE2 and CD147 epitopes. The CD147 epitopes have strong glycan shields (high mannose glycosylation), while the ACE2 epitopes - not so much.

Although protective against neutralizing antibodies, the CD147 glycan shield attracts mannose binding lectins (MBLs), which activates the lectin complement pathway. This in turn generates thrombosis, endothelitis with increased permeability, and inflammation with each exposure.

The CD147 bearing spike protein S, whether of viral or vaccine origin, can be found in many disparate organs including endothelial cells, sometimes long after exposure. Additional support for their presence comes from multiple studies touting the efficacy of CD147 antibodies for not only the initial strain [16] but also all subsequent variants [17]. More recent research underscores this CD147/spike connection [18]. ACE2 exhibits greater affinity than does CD147 for SARS CoV2 and may be the predominant route of entry, but ACE2 receptors are not present on T cells and only marginally so on endothelial cells, two cell types rich in CD147 receptors. T cells and endothelial cells appear to be responsible for the immune dysfunction, endothelitis, and microvascular thrombosis of Covid-19. Indeed ACE2 may potentiate the actions of CD147.

CD147 may exert its deleterious effects without actually facilitating cellular invasion [19], although CD147 can certainly cause lymphopenia [20]. The likelihood of recurrent Covid-19 is directly related to the number of boosters (see figure 2). Since CD147 upregulates ACE2 [15], perhaps repeated exposure to the CD147 bearing spike protein S in the Covid vaccines provides a more receptive ACE2 rich environment for the new variants.

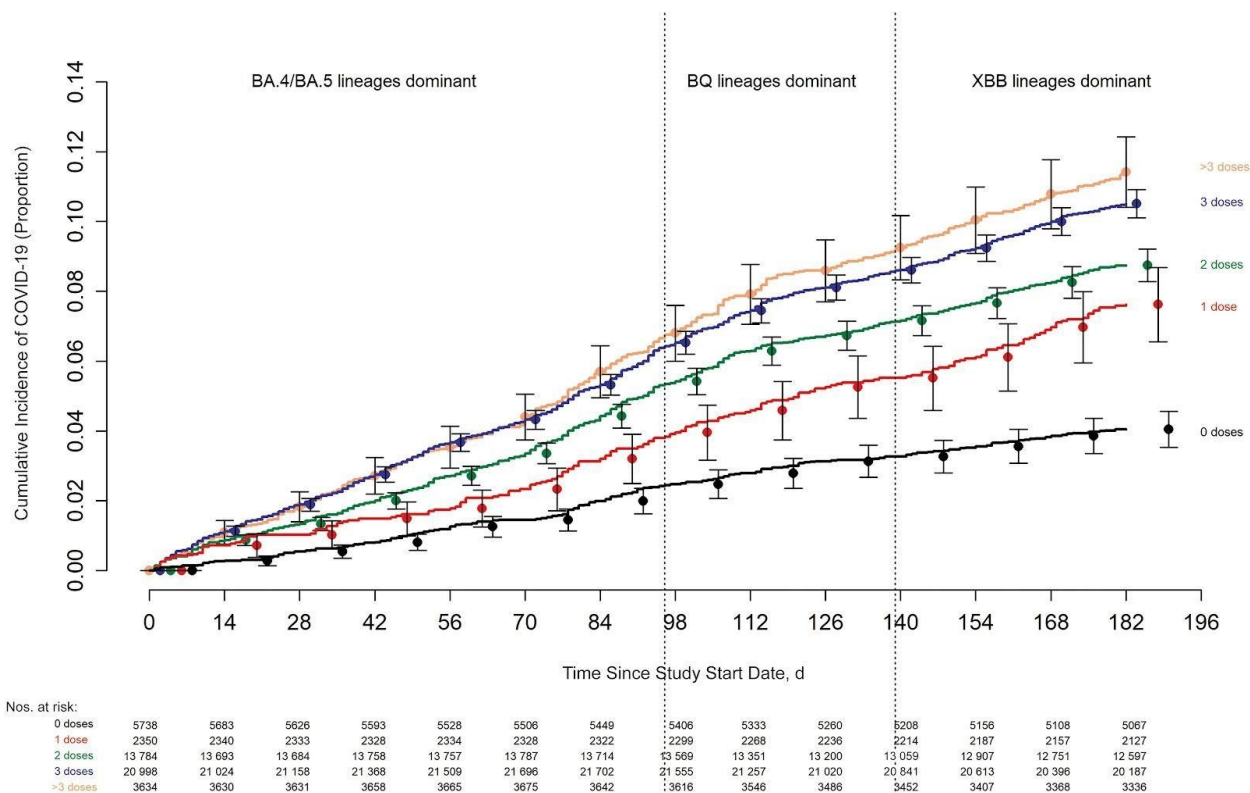


Figure 2: Number of doses is directly proportional to the number of recurrences [21].

TNF α /IL-6 and Glycosylation of TGF beta/CD147

CD147 exists in two forms: low-glycosylated CD147 (high mannose LG-CD147) and high-glycosylated CD147 (high mannose HG-CD147) [22]. TNF- α , produced by ADAM17/TACE, inhibits mannosidase and up-regulates high mannose HG-CD147. This imbalance between high mannose HG CD147 and high mannose LG CD147 appears to shift its pleiotropic preference, decreasing the physiologic and increasing the pathologic [23]. High glucose and advanced glycation end products (AGEs) potentiate this pleiotropic switch [24].

Transforming growth factor beta (TGF β) also appears to mediate CD147 glycosylation in monocytes treated with high glucose or AGEs [25]. TGF beta is another pleiotropic cytokine. Under healthy physiologic conditions it is a tumor suppressor, but when exposed to high glycosylation with elevated IL-6, TGF beta promotes fibrosis [26], immune dysfunction [27], and tumors [28]. The pleiotropic switch of TGF beta from tumor suppressor to tumor promoter may be due to the high mannose glycosylation of its receptor [29], although this is not yet clear. The switch is directly linked to Covid-19 severity [30].

The SARS-CoV-2 spike protein upregulates the RAS (ACE>ACE2) and activates AT1Rs/ADAM17 to increase TNF alpha, a potent inducer of IL-6 [6]. AT1R activation by SARS CoV2 also promotes IL-6 [31]. Glycosylated TGF beta can induce EMT de novo, where it upregulates fibrosis in the lungs, liver, kidney, heart, and other organs [32]. It can also affect the TME [33], where it works in concert with CD147 aka extracellular matrix metalloproteinase inducer (EMMPRIN) that stimulates cancer associated fibroblasts (CAFs) [34] to enhance invasion. The switch from physiologic to pathologic in pleiotropic TGF beta may also involve high glycosylation [35]. TGF beta and IFN gamma counterbalance each other under physiologic conditions [36,37]. The loss of T cell secreting IFN gamma induced by Covid-19 assures TGF beta dominance.

SARS CoV2 selectively attacks CD8+ T cells (no ACE2 receptors), causing TGF beta>IFN gamma (Figure 3) and often lymphopenia. Both of these cytokines are secreted by T cells, but TGF beta is secreted by other cell types, including stromal fibroblasts and adipocytes [38].

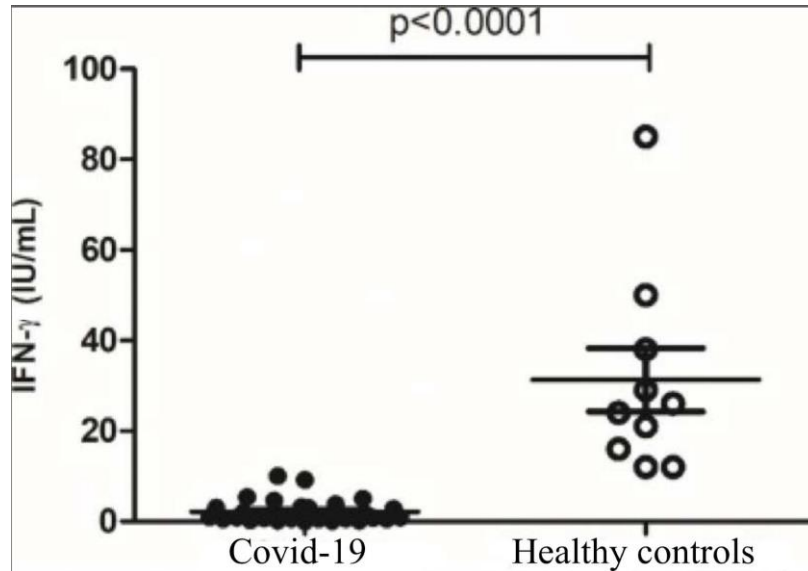


Figure 3: TGF beta counterbalances IFN gamma, but Covid-19 induces a TGF beta dominant response [39].

Loss of ACE2 bearing cells upregulates angiotensin II [40], which induces TGF- β expression via AT1Rs and ADAM17 [41]. This is treatable by angiotensin receptor blockers. Advanced glycation end products (AGEs) form when sugar interacts with proteins or fats in the bloodstream. High levels of AGEs have been linked to inflammation, oxidative stress, Alzheimer's, diabetes, heart disease, and renal failure. High glucose and AGEs increase TNF α and TGF beta [27], which enhances TGF- β induced EndMT [42]. N-glycosylation of the IL-6 receptor appears to induce the pleiotropic switch for IL-6[43]. Interestingly the tumorigenic capability of IL-6R requires cleavage by ADAM17 (TACE), at least for colon cancer [44].

Aggressive colon cancers are associated with elevated TNF α [45]. Some consider aggressive colon cancers seen post vaccination to be turbo cancers. The strong connection between autoantibody induced AT1R activity (and TNF α inducing ADAM17 stimulation) post vaccination in those that developed CFS [11] and the elevated TNF α seen in aggressive colon cancer adds legitimacy to the claim (see section 5). This is further supported by the ADAM17 dependent cleavage of IL-6R that enhances its tumorigenic capability in colon cancer [46]. IL-6 also upregulates CD147 [46].

CD147, TGF Beta and Fibrosis

Recurrent exposure to the CD147 containing spike protein S on either the virus or boosters in an environment characterized by high glucose and AGEs appears to create a predisposition to not only autoimmune disease/cancer but also fibrosis.

TNF α and IL-6 are the primary cytokines in mild to severe Covid as well as LC. TNF α is a potent stimulator of IL-6 [6] and CD147 signaling to TGF beta can initiate EMT[CD147 signaling to TGF-beta can facilitate pulmonary fibrosis via either EMT [47] or endothelial mesenchymal transition (EndMT) [48]. Not

surprisingly LC has seen a surge in pulmonary fibrosis [49,50]. TGF beta appears to be a major player in this process mediated by IL-6 [51]. CD147 also appears to be critical in the appearance of pulmonary fibrosis in LC [52]. Parallels with IPF are easily drawn. IPF is linked to TGF beta and IL-6[53]. The extracellular matrix in IPF is defective. Glycosylated EMMPRIN (CD147) may be involved via secretion of MMPs [54].

Acute exacerbations of idiopathic pulmonary fibrosis (IPF) in a selected cohort occurred in 4 of 10 patients a few days after COVID-19 vaccination. Ironically this group was granted priority access to vaccination because of the fear of SARS posed by Covid-19 in such compromised individuals [55]. Furthermore, CD147 is the primary determinant of atherosclerotic cardiovascular disease [56]. Not surprisingly ASCVD is exacerbated in LC [57]. The mechanism appears to be a CD147 dependent increase in TNF α [58]. Those with LC are also at increased risk of hepatic fibrosis (5%) [58]. TGF beta is the principal cytokine associated with hepatic fibrosis [59] and renal fibrosis [60]. Early elevation of TGF beta in Covid-19 portends greater risk of subsequent cardiac fibrosis [61]. TGF beta also plays a pivotal role in cardiac fibrosis as well [62].

Glycosylation and Autoimmune Disease

Long Covid (LC) has now been declared an autoimmune disease by the Autoimmune Registry [63]. Some consider autoimmune disease to be the long term sequelae of a viral infection. Others have shown a distinct link with CD8+ T cell deficiency [64]. So the low CD8+ T cell count (CD4/CD8 is increased) in SARS2 [65] is worrisome. Both HIV infection (CD4+) and Covid-19 (CD8+) target T cells. CD4+ T cell loss (CD4+/CD8+ is decreased) has long been thought the primary culprit in autoimmune disease. However, recently the involvement of CD8+ T cells has been revealed [66].

CD147 receptors on CD4+ T cells inhibit Th17 responses. Anti-CD147 antibodies stimulate CD147 to enhance suppression of Th17. But as glycosylation of CD147 proceeds, production of IFN-gamma and IL-17 by Th17 helper T cells is triggered [67]. HG (high glycosylated) CD147 stimulates secretion of IL-17 and IFN gamma from Th17 cells [68]. IL-17 is tightly linked to autoimmune disease. LG CD147 on CD4+ T memory cells inhibits human Th17 responses, i.e., it opposes the path to autoimmune disease [68]. Anti-CD147 not only protects against autoimmune disease but also protects against all variants of SARS CoV2 [17]. CD147 promoted the differentiation of Th17 cells by regulation of cytokine production [69]. The importance of TGF beta in this area has also recently been recognized [70,71].

The mechanism for the pleiotropic switch for IFN gamma appears to resemble that for TGF beta. High mannose glycosylation of the cytokine receptor may enhance sensitivity for both [72] Th17 T cells not only secrete IL-17 but also IFN-gamma [73], both of which are tightly linked to autoimmune disease [74]. Females exhibit more robust T cell activation than males [75] and have higher levels of type I IFN alpha and beta [76]. T cell production of IFN gamma (IFN type II) is triggered by IFN alpha and beta (IFN type I). It is a secondary release, STAT dependent IFN. This mechanism supports the greater incidence of autoimmune disease in females. A study on US Marines documents this gender generated difference in IFN [77].

The increase in post vaccination autoimmunity suggests that the CD147 receptors on CD8+ T cells may be at risk [78]. The cause of autoimmune disease is multifactorial but appears to involve Th17 [79]. Vitamin D deficiency is clearly contributory. Many with LC suffer low flow POTS. Many have not only angiotensin II type 1 receptor or beta adrenergic receptor autoantibodies [80] but also ANA, antiphospholipid, and Sjogren autoantibodies [81]. A more complete list associated with the severity of COVID-19 includes alopecia totalis, psoriasis, vitiligo, vasculitis, Crohn disease, ulcerative colitis, rheumatoid arthritis, adult-onset Still disease, ankylosing spondylitis, and sarcoidosis [82].

The Spike Protein S, Mannose, and Cancer

TNF α , the signature cytokine for Covid-19, inhibits alpha mannosidase [83], decreasing mannose trimming in the Golgi with more high mannose HG CD147 in the ER. N-glycosylation of CD147 involves three asparagine sites (Asn 44,152,186). The high mannose glycosylation appears to primarily involve the Asn152 site. This induces an increase in MMP activity and fibrosis in normal otherwise healthy cells as well as dysplastic cells (EMT, EndMT, CAFs) [84]. High mannose glycosylation of Asn152 on the CD147 receptor on the cell membranes of tumor cells is specifically associated with invasion and metastasis [85]. High-mannose N-glycans are tumor progression markers and are more frequently elevated in metastases than other types of glycans in breast [86] and other cancers [87-89].

This ultimately increases circulating soluble high mannose glycosylated cytokines and/or their membrane bound receptors. This activates mannose binding lectins (MBLs) and the lectin complement pathway (LCP) with its associated complement/clotting cascade and inflammation [90].

This portends a poor outcome in Covid-19 [91]. Exposure to CD147 on the spike protein S, whether via infection or vaccination, poses significant long term risks [92]. Its overexpression is linked to tumorigenesis [93,34], tumor progression, and predicts a poor prognosis [94].

With respect to vaccination the spike protein S is not limited to the site of injection, but can circulate [95]. According to analysis of a Japanese biodistribution study of the Pfizer mRNA vaccine, the S1 subunit could be found in spleen, bone marrow, liver, lungs, lymph nodes, heart, brain and spinal cord, eyes, kidneys, adipose tissue, adrenal glands, ovaries and uterus, testes, pancreas, prostate, stomach and intestines, thyroid, thymus, muscle, and salivary glands [96], although S1 reportedly disappeared after 14 days. LC with persistent spike protein S (see figure 4) can potentiate EMT/EndMT in the TME with subsequent tumor invasion/metastasis in many organs distant to the injection site, bypassing the blood-gas barrier.

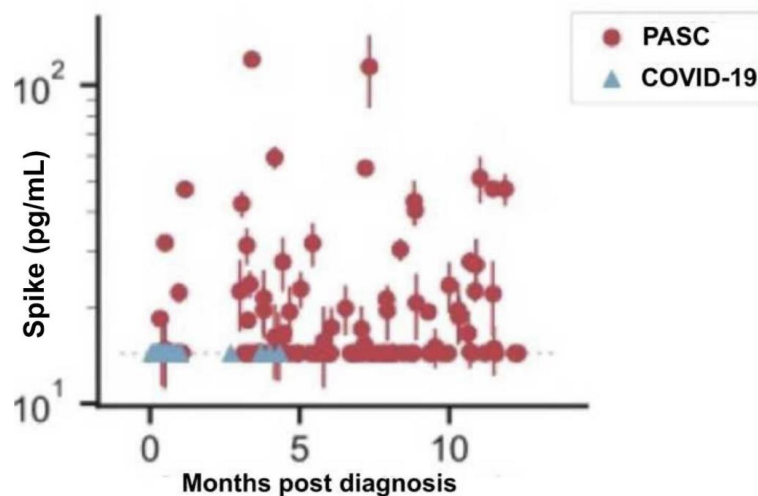


Figure 4: In LC residual spike protein S, containing CD147, can be demonstrated [97].

The S1 spike protein promotes NF-κB activation [98]. The activation of ADAM17 by the AngII-ATR1 axis promotes NF-κB activation [99]. TNF-α, IL-1β, and IL-6 can activate NF-κB and NF-κB can activate TNF-α, IL-1β, and IL-6 levels [100]. Vitamin D down regulates NF-κB [101]. This suggests that the high IL-1β, IL-6, and TNF-α levels found in LC [102] are mediated through both ADAM17 and NF-κB directly. The prominence of IL-6 and autoantibodies post vaccination LC [11] and the sudden appearance of autoimmunity post vaccination [79] suggests a correlation between the viral spike protein S and that of its vaccine. TNF-α, elevated in those most susceptible to Covid-19, i.e., an overactive RAS, has been directly linked to triple negative breast cancer (TNBC) [103]. Breast tumors negative for estrogen, progesterone, and HER2 receptors are classified as triple negative. Repeated doses of the Covid vaccine and/or recurrent Covid-19 are continually stoking the production of TNF-α and increasing the risk of this more aggressive TNBC. According to the American Cancer Society, TNBC is more frequent in African-Americans, Hispanics and the obese [104]. TNBC is linked to vitamin D [105] and magnesium deficiencies [106]. This is noteworthy, as the term “turbo cancer” may be applicable to this group [107]. Upon exposure to the CD147 bearing spike protein S cancer risk can increase not only via a mechanism involving high mannose glycosylation of CD147 but also via loss of CD147 bearing T cells invaded and consumed by the virus.

CD147 receptors are expressed on CD4+ (T helper) and CD8+

(T cytotoxic) cells. CD8+ T cells are selectively but not solely reduced by SARS CoV2, increasing CD4+/CD8+ [108]. This is the inverse of HIV where the ratio decreased [109]. Both viruses present highly glycosylated CD147 membrane epitopes. Loss of CD8+ T cells translates to loss of control over progression of CA (growth, metastasis) [110-113].

Most cancer cells feature cell membrane CD147 antigens [115]. Presence of cytotoxic CD8+ T cells expressing CD147 receptors limits cancers expressing CD147 antigens [113-116]. They are present on cell membranes of 31 different types of cancer [116]. CD4+ T cells monitor premalignant cells, i.e., dysplasia and carcinoma in situ. CD8+ T cells suppress those that actually invade (loss of p53 function) [112]. In short, loss of CD4+ T cells renders an individual susceptible to opportunistic infections. Loss of CD8+ T cells renders an individual susceptible to cancer, both de novo and recurrent [117].

Prevention and Therapy

The active form of vitamin D can retard the development of autoimmune disease and cancer in several ways. It may oppose the ill effects of AGEs by reducing expression of their receptors and by opposing AGE signaling pathways [118-120]. Vitamin D is inversely associated with diabetes, obesity, and age. Many studies have shown a strong correlation between vitamin D deficiency and cancer/autoimmune/disease (Figure 5) [121].

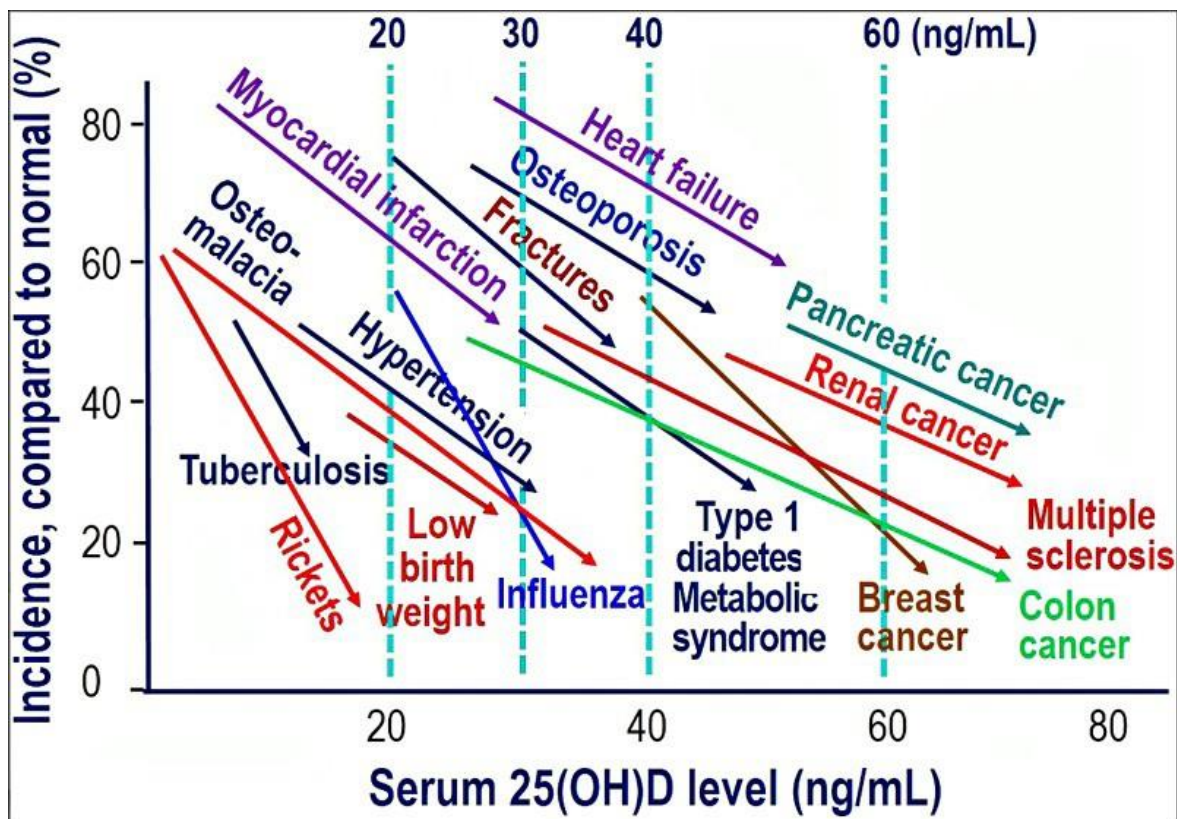


Figure 5: The spectrum of disease repressed by vitamin D is wide [121].

Many articles denigrating or claiming no benefit from vitamin D supplementation are improperly structured [122]. Vitamin D loses its efficacy as the calcium: magnesium ratio rises. A high ratio can increase the risk for cardiovascular disease (CVD), metabolic syndrome, colorectal cancer, prostate cancer, survival following breast cancer, and cancer mortality [123]. The Ca:Mg ratio exceeded 4.0 for those hospitalized with Covid-19 and approached 5.0 for those that died [124]. The target ratio in Western society should be as close to 2.0 as possible. According to

the NHANES II in 1977, the American mean was 2.6. According to NHANES (1999-2000), the mean for the US population Ca:Mg for 2000 was 3.0 with a mean ratio as high as 3.7 in women supplementing with calcium. Vitamin D downregulates renin and NF-kB and AT1R activity [125]. Vitamin D also downregulates many proinflammatory cytokines triggered by HG CD147. There are numerous commercial anti-cytokines earmarked for specific autoimmune diseases (see figure 6). Vitamin D sufficiency accomplishes much the same (Figure 7).

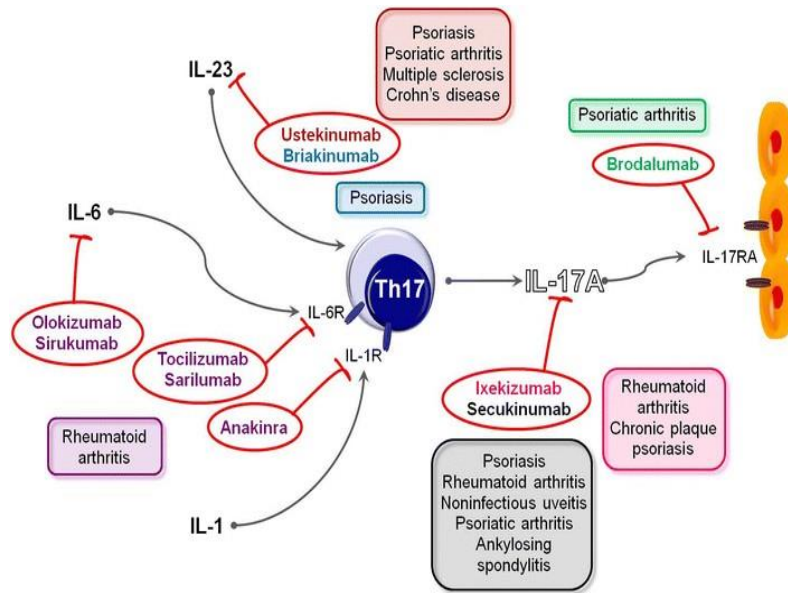


Figure 6: Figure discloses a wide range of commercial products targeting receptors and cytokines [126].

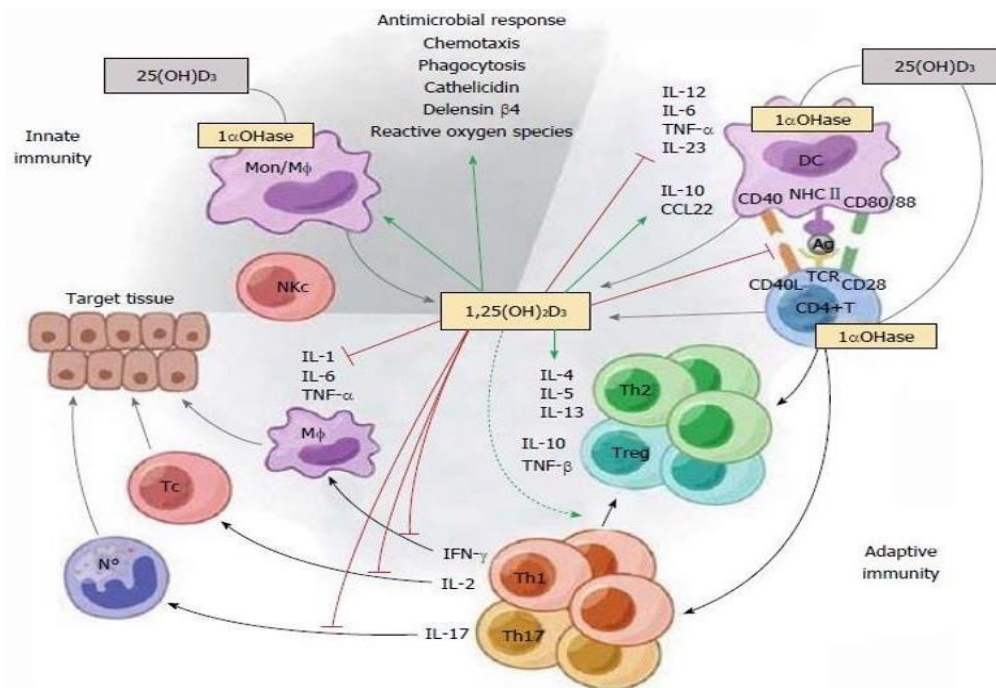


Figure 7: Figure discloses that all commercially targeted receptors and cytokines in figure 6 and more are covered by vitamin D [127].

Vitamin B6 as pyridoxal phosphate [128] and some polyphenols [129] oppose the formation of AGEs. The mannose in cranberries may add to the efficacy of their polyphenols. Mannose has emerged as a new approach for thwarting cancer and autoimmunity. By blocking TNF α [130], the primary culprit in Covid-19 and LC, oral D-mannose might offer benefits for cancer [131], diabetes, obesity, lung disease [132] and depression [133].

Mannose can also enhance chemotherapy [134]. D-mannose is also efficacious in TNBC (negative estrogen progesterone, and HER2 receptors) [135], a more aggressive form seen more frequently in women under 40. Efficacy for D-mannose has also been reported for pancreatic cancer [136], aggressive colon cancers [137], and clear cell carcinoma of the kidney (also linked to TNF α) [138]. These four cancers are at the top of the list for those claiming Covid vaccine related turbo cancers [139]. A recent article [140] reported that serum mannose in colorectal cancer (CRC) is more sensitive than CEA in screening for early diagnosis or for LNM staging. Elevated levels are associated with a poor prognosis in CRC. Perhaps the elevated mannose in these patients is bound to the high mannose glycosylated surfaces of cytokines, glycoproteins, tumor cells, and other CD147 bearing elements. Serum mannose might compete with his-CRP as a general screen. Since TNF α inhibits mannosidase, any strategy that suppresses TNF alpha might increase mannose trimming in the Golgi, lower the high mannose glycoproteins, and relieve the aberrant protein folding and related ER stress.

In general a storage vitamin D or 25(OH)D3 level above 50ng/mL, a Ca:Mg<3.5, a BMI near 25, a diet rich in antioxidants, blood pressure and HA1c within normal limits, and avoidance of Covid vaccines, if possible should decrease the risks of Covid-19 in all its forms and complications, including autoimmunity, organ fibrosis, and cancer. A diet rich accentuating apples, oranges, peaches, cranberries, and blueberries, all rich in mannose, is a good start.

Summary

- TNF α is the signature cytokine of Covid-19 and LC
- TNF α is a potent inducer of IL-6 and together are hallmarks of both Covid severity and LC
- High glucose and AGEs upregulate TNF α and TGF beta
- SARS CoV2 invades and removes T cells that produce IFN gamma (C1INH), causing TGF beta>IFN gamma
- Invasion by SARS CoV2 via ACE2 receptors activates ADAM17 aka TACE, the converting enzyme that releases TNF α
- Angiotensin II type 1 receptor antibodies, predictive of LC post Covid and CFS post Covid vaccination (present in 70% of POTS) activate AT1Rs
- Activation of AT1Rs by any means activates ADAM17, increasing TNF α
- CD147 increases TNF α in atherosclerosis
- Covid worsens cardiovascular disease
- TNF α inhibits mannosidase
- This high mannose glycosylation of these pleiotropic cytokines or their receptors appears to constitute their “switch”, e.g., anti-

inflammatory to proinflammatory, tumor suppressor to tumor promoter

- High mannose glycosylation of CD147 aka EMMPRIN upregulates its MMP activity and is a marker for EMT, CAF, tumor invasion, and metastasis
- IL-6 and TGF beta are associated not only with malignancy, but also with autoimmunity and organ fibrosis, e.g., idiopathic pulmonary fibrosis
- CD147 aka basigin aka EMMPRIN is present on the spike protein S of both the virus and its vaccines
- Booster doses and recurrent infections repeatedly stoke the production of TNF α , associated with the spike in the aggressive triple negative form of breast cancer
- Vitamin D, magnesium, and D-mannose oppose TNF α and/or NF-kB, integral to preventing TNBC, colon cancer, and pancreatic cancer

Conclusion

TNF α appears to be the primary cytokine in the pathogenesis of Covid-19 in all its forms and the associated risks of cancer, autoimmunity, and fibrosis. It promotes the high mannose glycosylation of CD147. Overexpression of CD147 is linked with tumorigenesis and tumor progression, i.e., local spread, metastasis, poor prognosis, and resistance to chemotherapy. TNF α promotes the high mannose glycosylation of the TGF beta receptor. This in concert with EMMPRIN aka CD147 facilitates EMT, EndMT, and CAF, affiliated with both organ fibrosis and tumor spread. CD147 in concert with Th17 triggers the secretion of IL17 and IFN gamma, tightly linked to autoimmune disease.

TNF α , produced by TACE aka ADAM17, is upregulated when SARS CoV2 enters the cell endocytotically or when AT1Rs are activated by any means (Figure 1).

Elevated TNF α is linked with aggressive TNBC and aggressive colon cancers. The former is more commonly encountered in women under 40, African Americans, Hispanics, the obese, the vitamin D deficient, and the magnesium deficient. Both are claimed to be vaccine induced turbo cancers. If the presented scenario based on the most recent physiologic findings is correct, then the repeated doses of the vaccine and the recurrent infections they enable (Figure 2) both stoke repeated exposures to elevated TNF α . In those susceptible, as described, these exposures carry great risk.

References

1. Wang K, Chen W, Zhang Z, Deng Y. et al. (2020) CD147-Spike Protein Is a Novel Route for SARS-CoV-2 Infection to Host Cells. *Signal Transduction and Targeted Ther* 5: 283.
2. Ragotte RJ, Pulido D, Donnellan FR, Hill ML, Gorini G, et al. (2021) Human Basigin (CD147) Does Not Directly Interact with SARS-CoV-2 Spike Glycoprotein. *MSphere* 6:e00647-21.
3. Shilts J, Crozier TWM, Greenwood EJD, Lerner P, Wright GJ (2021) No Evidence for Basigin/CD147 as a Direct SARS-

- CoV-2 Spike Binding or Receptor. *Scientific Reports*, 11, Article No. 413.
4. Chambers PW (2021) Basigin Binds Spike S on SARS-CoV2. *Open Access Library J* 8:e8064.
 5. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, et al. (2020) Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. *Circ Res* 126(10):1456-1474.
 6. Benihoud K, Esselin S, Descamps D, et al. (2007) Respective roles of TNF- α and IL-6 in the immune response-elicited by adenovirus-mediated gene transfer in mice. *Gene Ther* 14:533-544.
 7. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, et al. (2020) An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 26(10):1636-1643.
 8. Aziz M, Fatima R, Assaly R (2020) Elevated interleukin-6 and severe COVID-19: A meta-analysis. *J Med Virol* 92(11):2283-2285.
 9. Zipeto D, Palmeira JDF, Argañaraz GA, Argañaraz ER (2020) ACE2/ADAM17/TMPRSS2 Interplay May Be the Main Risk Factor for COVID-19. *Front Immunol* 11:576745.
 10. Low RN, Low RJ, Akrami A (2023) A review of cytokine-based pathophysiology of Long COVID symptoms. *Front Med (Lausanne)* 10:1011936.
 11. Semmler A, Mundorf AK, Kuechler AS, Schulze-Bosse K, Heidecke H, et al. (2023) Chronic Fatigue and Dysautonomia following COVID-19 Vaccination Is Distinguished from Normal Vaccination Response by Altered Blood Markers. *Vaccines* 11(11):1642.
 12. Yu X, Li H, Murphy TA, Nuss Z, Liles J, et al. (2018) Angiotensin II Type 1 Receptor Autoantibodies in Postural Tachycardia Syndrome. *J Am Heart Assoc* 7(8):e008351.
 13. Rambaldi A, Gritti G, Micò MC, Frigeni M, Borleri G, et al. (2020) Endothelial injury and thrombotic microangiopathy in COVID-19: Treatment with the lectin-pathway inhibitor narsoplimab. *Immunobiology* 225(6):152001.
 14. Knierman et al. (2021) Severe SARS-CoV-2 infection treated with the mannose binding lectin associated serine protease 2 (MASP2) inhibitor Narsoplimab *J Allergy Infect Dis* 2(1):24-28.
 15. Fenizia C, Galbiati S, Vanetti C, Vago R, Clerici M, et al. (2021) SARS-CoV-2 Entry: At the Crossroads of CD147 and ACE2. *Cells* 10(6):1434.
 16. Bian H, Zheng ZH, Wei D, et al. (2021) Safety and efficacy of meplazumab in healthy volunteers and COVID-19 patients: a randomized phase 1 and an exploratory phase 2 trial. *Signal Transduct Target Ther* 6(1):194.
 17. Geng J, Chen L, Yuan Y, et al. (2021) CD147 antibody specifically and effectively inhibits infection and cytokine storm of SARS-CoV-2 and its variants delta, alpha, beta, and gamma. *Sig Transduct Target Ther* 6:347.
 18. Behl T, Kaur I, Aleya L, Sehgal A, Singh S, et al. (2022) CD147-spike protein interaction in COVID-19: Get the ball rolling with a novel receptor and therapeutic target. *Sci Total Environ* 808:152072.
 19. Elisa Avolio, Michele Carrabba, Rachel Milligan, Maia Kavanagh Williamson, et al. (2021) The SARS-CoV-2 Spike protein disrupts human cardiac pericytes function through CD147 receptor-mediated signaling: a potential non-infective mechanism of COVID-19 microvascular disease. *Clin Sci (Lond)* 135(24):2667-2689.
 20. Mohamed A. Helal, Shaimaa Shouman, Ahmad Abdelwaly, Ahmed O. Elmehrath, Mohamed Essawy, et al. (2022) Molecular basis of the potential interaction of SARS-CoV-2 spike protein to CD147 in COVID-19 associated-lymphopenia. *J Biomolecular Structure and Dynamics* 3:1109-1119.
 21. Nabin K Shrestha, Patrick C Burke, Amy S Nowacki, James F Simon, Amanda Hagen, et al. (2023) Effectiveness of the Coronavirus Disease 2019 Bivalent Vaccine. *Open Forum Infectious Diseases* 10:ofad209.
 22. Asgari R, Vaisi-Raygani A, Alegha MSE, Mohammadi P, Bakhtiari M, et al. (2023) CD147 and MMPs as key factors in physiological and pathological processes. *Biomed Pharmacother* 157:113983.
 23. Zhong FY, Zhao YC, Zhao CX, Gu ZC, Lu XY, et al. (2022) The Role of CD147 in Pathological Cardiac Hypertrophy Is Regulated by Glycosylation. *Oxid Med Cell Longev* 2022:6603296.
 24. Mahmoud AM, Ali MM (2021) High Glucose and Advanced Glycation End Products Induce CD147-Mediated MMP Activity in Human Adipocytes. *Cells* 10(8):2098.
 25. Bao W, Min D, Twigg SM, Shackel NA, Warner FJ, et al. (2010) Monocyte CD147 is induced by advanced glycation end products and high glucose concentration: possible role in diabetic complications. *Am J Physiol Cell Physiol* 299(5):C1212-9.
 26. Meng Xm, Nikolic-Paterson D, Lan H (2016) TGF- β : the master regulator of fibrosis. *Nat Rev Nephrol* 12:325-338.
 27. Larson C, Oronsky B, Carter CA, Oronsky A, Knox SJ, et al. (2020) TGF-beta: a master immune regulator. *Expert Opin Ther Targets* 24(5):427-438.
 28. Baba AB, Rah B, Bhat GR, Mushtaq I, Parveen S, et al. (2022) Transforming Growth Factor-Beta (TGF- β) Signaling in Cancer-A Betrayal Within. *Front Pharmacol* 13:791272.
 29. Kim YW, Park J, Lee HJ, Lee SY, Kim SJ (2012) TGF- β sensitivity is determined by N-linked glycosylation of the type II TGF- β receptor. *Biochem J* 445(3):403-11.
 30. Ferreira-Gomes M, Kruglov A, Durek P, et al. (2021) SARS-CoV-2 in severe COVID-19 induces a TGF- β -dominated chronic immune response that does not target itself. *Nat Commun* 12:1961.
 31. Patra T, Meyer K, Geerling L, Isbell TS, Hoft DF, et al. (2020) SARS-CoV-2 spike protein promotes IL-6 trans-signaling by activation of angiotensin II receptor signaling in epithelial cells. *PLoS Pathog* 16(12):e1009128.
 32. Budi EH, Schaub JR, Decaris M, Turner S, Derynck R (2021) TGF- β as a driver of fibrosis: physiological roles and therapeutic opportunities. *J Pathol* 254(4):358-373.

33. Zhang J, ten Dijke P, Wuhler M, et al. (2021) Role of glycosylation in TGF- β signaling and epithelial-to-mesenchymal transition in cancer. *Protein Cell* 12:89-106.
34. Huang Defa, Rao Dingyu, Jin Qing, Lai Mi, Zhang Jiali, et al. (2023) Role of CD147 in the development and diagnosis of hepatocellular carcinoma. *Frontiers in Immunology* 14:2023.
35. Chen Z, Yu H, Chen X, Chen W, Song W, et al. (2023) Mutual regulation between glycosylation and transforming growth factor- β isoforms signaling pathway. *Int J Biol Macromol* 236:123818.
36. Delvig AA, Lee JJ, Chrzanowska-Lightowlers ZM, Robinson JH (2002) TGF-beta1 and IFN-gamma cross-regulate antigen presentation to CD4 T cells by macrophages. *J Leukoc Biol* 72(1):163-166.
37. Sobral LM, Montan PF, Martelli-Junior H, Graner E, Coletta RD (2007) Opposite effects of TGF-beta1 and IFN-gamma on transdifferentiation of myofibroblast in human gingival cell cultures. *J Clin Periodontol* 34(5):397-406.
38. Lee MJ (2018) Transforming growth factor beta superfamily regulation of adipose tissue biology in obesity. *Biochim Biophys Acta Mol Basis Dis* 1864(4 PtA):1160-1171.
39. Dhanda AD, Felmler D, Boeira P, Moodley P, Tan H, et al. (2022) Patients with moderate to severe COVID-19 have an impaired cytokine response with an exhausted and senescent immune phenotype. *Immunobiology* 227(2):152185.
40. Mahmudpour M, Roozbeh J, Keshavarz M, Farrokhi S, Nabipour I (2020) COVID-19 Cytokine Storm: The Anger of Inflammation. *Cytokine* 133:155151.
41. Ehanire T, Ren L, Bond J, Medina M, Li G, et al. (2015) Angiotensin II Stimulates Canonical TGF- β Signaling Pathway through Angiotensin Type 1 Receptor to Induce Granulation Tissue Contraction. *J Molecular Medicine* 93:289-302.
42. Yoshimatsu Y, Wakabayashi I, Kimuro S, Takahashi N, Takahashi K, et al. (2020) TNF- α enhances TGF- β -induced endothelial-to-mesenchymal transition via TGF- β signal augmentation. *Cancer Sci* 111(7):2385-2399.
43. Riethmueller S, Somasundaram P, Ehlers JC, Hung CW, Flynn CM, et al. (2017) Proteolytic Origin of the Soluble Human IL-6R In Vivo and a Decisive Role of N-Glycosylation. *PLoS Biol* 15(1):e2000080.
44. Schumacher N, Rose-John S (2019) ADAM17 Activity and IL-6 Trans-Signaling in Inflammation and Cancer. *Cancers (Basel)* 11(11):1736.
45. Al Obeid OA, Alkhayal KA, Al Sheikh A, Zubaidi AM, Vaali-Mohammed MA, et al. (2014) Increased expression of tumor necrosis factor- α is associated with advanced colorectal cancer stages. *World J Gastroenterol* 20(48):18390-18396.
46. Hu J, Lei L, Wang Y, Wang K, Hu X, et al. (2016) Interleukin-6 Drives Multiple Myeloma Progression by Up-Regulating of CD147/Emmprin Expression. *Blood* 128:5632.
47. Wu J, Ru NY, Zhang Y, Li Y, Wei D, et al. (2011) HAB18G/CD147 promotes epithelial-mesenchymal transition through TGF- β signaling and is transcriptionally regulated by Slug. *Oncogene* 30(43):4410-27.
48. Inui N, Sakai S, Kitagawa M (2021) Molecular Pathogenesis of Pulmonary Fibrosis, with Focus on Pathways Related to TGF- β and the Ubiquitin-Proteasome Pathway. *Int J Mol Sci* 22(11):6107.
49. Mohammadi A, Balan I, Yadav S, Matos WF, Kharawala A, et al. (2022) Post-COVID-19 Pulmonary Fibrosis. *Cureus* 14(3):e22770.
50. Ambardar SR, Hightower SL, Huprikar NA, Chung KK, Singhal A, et al. (2021) Post-COVID-19 Pulmonary Fibrosis: Novel Sequelae of the Current Pandemic. *J Clin Med* 10(11):2452.
51. Epstein Shochet G, Brook E, Bardenstein-Wald B, Shitrit D (2020) TGF- β pathway activation by idiopathic pulmonary fibrosis (IPF) fibroblast derived soluble factors is mediated by IL-6 trans-signaling. *Respir Res* 21(1):56.
52. Wu J, Chen L, Qin C, Huo F, Liang X, et al. (2022) CD147 contributes to SARS-CoV-2-induced pulmonary fibrosis. *Signal Transduct Target Ther* 7(1):382.
53. Luo H, Yan J, Zhou X (2023) Constructing an extracellular matrix-related prognostic model for idiopathic pulmonary fibrosis based on machine learning. *BMC Pulm Med* 23:397.
54. Sgalla G, Magri T, Lerede M, Comes A, Richeldi L (2022) COVID-19 Vaccine in Patients with Exacerbation of Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* 206(2):219-221.
55. Benihoud, Jin R, Zhu X, Yan J, Li G (2015) Function of CD147 in atherosclerosis and atherothrombosis. *J Cardiovasc Transl Res* 8(1):59-66.
56. Vilaplana-Carnerero C, Giner-Soriano M, Dominguez A, Morros R, Pericas C, et al. (2023) Atherosclerosis, Cardiovascular Disease, and COVID-19: A Narrative Review. *Biomedicines* 11(4):1206.
57. Engelen SE, Robinson AJB, Zurke YX, et al. (2022) Therapeutic strategies targeting inflammation and immunity in atherosclerosis: how to proceed?. *Nat Rev Cardiol* 19:22-542.
58. Kolesova O, Vanaga I, Laivacuma S, Derovs A, Kolesova A, et al. (2021) Storozenko J, Rozentale B, Viksna L. Intriguing findings of liver fibrosis following COVID-19. *BMC Gastroenterol* 21(1):370.
59. Xu F, Liu C, Zhou D, Zhang L (2016) TGF- β /SMAD Pathway and Its Regulation in Hepatic Fibrosis. *J Histochem Cytochem* 64(3):157-67.
60. Park CH, Yoo TH (2022) TGF- β Inhibitors for Therapeutic Management of Kidney Fibrosis. *Pharmaceuticals (Basel)* 15(12):1485.
61. Mustroph J, Hupf J, Baier MJ, Evert K, Brochhausen C, et al. (2021) Cardiac Fibrosis Is a Risk Factor for Severe COVID-19. *Front Immunol* 12:740260.
62. Saadat S, Nouredini M, Mahjoubin-Tehran M, Nazemi S, Shojaie L, et al. (2021) Pivotal Role of TGF- β /Smad Signaling in Cardiac Fibrosis: Non-coding RNAs as Effectual Players. *Front Cardiovasc Med* 7:588347.
63. COVID-19 Added to the list of Autoimmune Diseases <https://www.autoimmuneregistry.org/long-covid-announcement>

64. Gravano DM, Hoyer KK (2013) Promotion and prevention of autoimmune disease by CD8+ T cells. *J Autoimmun* 45:68-79.
65. De Zuani M, Laznicková P, Tomasková V, Dvoncová M, Forte G, et al. (2021) High CD4-To-CD8 Ratio Identifies an At-Risk Population Susceptible to Lethal COVID-19. *Scandinavian J Immunology* Article ID: e13125.
66. Deng Q, Luo Y, Chang C, Wu H, Ding Y, et al. (2019) The Emerging Epigenetic Role of CD8+T Cells in Autoimmune Diseases: A Systematic Review. *Front Immunol* 10:856.
67. Pata S, Surinkaew S, Takheaw N, Laopajon W, Chuensirikulchai K, et al. (2021) Differential CD147 Functional Epitopes on Distinct Leukocyte Subsets. *Front Immunol* 12:704309.
68. Miao J, Zhang K, Zheng Z, Zhang R, Lv M, et al. (2020) CD147 Expressed on Memory CD4+ T Cells Limits Th17 Responses in Patients With Rheumatoid Arthritis. *Front Immunol* 11:545980.
69. Yang H, Wang J, Li Y, Yin ZJ, Lv TT, et al. (2017) CD147 modulates the differentiation of T-helper 17 cells in patients with rheumatoid arthritis. *APMIS* 125(1):24-31.
70. Wu B, Zhang S, Guo Z, Bi Y, Zhou M, et al. (2021) The TGF- β superfamily cytokine Activin-A is induced during autoimmune neuroinflammation and drives pathogenic Th17 cell differentiation. *Immunity* 54(2):308-323.e6.
71. Kardalas E, Maraka S, Papagianni M, Paltoglou G, Siristatidis C, et al. (2021) TGF- β Physiology as a Novel Therapeutic Target Regarding Autoimmune Thyroid Diseases: Where Do We Stand and What to Expect. *Medicina* 57(6):621.
72. Krug J, Rodrian G, Petter K, Yang H, Khoziainova S, et al. (2023) N-glycosylation Regulates Intrinsic IFN- γ Resistance in Colorectal Cancer: Implications for Immunotherapy. *Gastroenterology* 164(3):392-406.e5.
73. Xu W, Li R, Sun Y (2019) Increased IFN- γ -producing Th17/Th1 cells and their association with lung function and current smoking status in patients with chronic obstructive pulmonary disease. *BMC Pulm Med* 19:137.
74. Han L, Yang J, Wang X, Li D, Lv L, et al. (2015) Th17 cells in autoimmune diseases. *Front Med* 9(1):10-9.
75. Takahashi T, et al. (2020) Sex differences in immune responses that underlie COVID-19 disease outcomes *Nature* 588:315-320.
76. Pujantell M, Altfeld M (2022) Consequences of sex differences in Type I IFN responses for the regulation of antiviral immunity. *Front Immunol* 13:986840.
77. Sauerwald N, Zhang Z, Ramos I, Nair VD, Soares-Schanoski A, et al. (2022) Pre-infection antiviral innate immunity contributes to sex differences in SARS-CoV-2 infection. *Cell Syst* 13(11):924-931.
78. Ricke DO (2023) Immediate onset signatures of autoimmune diseases after vaccination (2023). *Global Translational Medicine* 2(3):1455.
79. Henderson LA, Hoyt KJ, Lee PY, Rao DA, et al. (2020) Th17 Reprogramming of T Cells in Systemic Juvenile Idiopathic Arthritis. *JCI Insight* 5, Article ID:e132508.
80. Badiudeen T, et al. (2019) A functional cell-based bioassay for assessing adrenergic autoantibody activity in postural tachycardia syndrome. *J Transl Autoimmun* 20(2):100006.
81. Fedorowski A (2019) Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management. *J Intern Med* 285(4):352-366.
82. Lim SH, Ju HJ, Han JH, Lee JH, Lee WS, et al. (2023) Autoimmune and Autoinflammatory Connective Tissue Disorders Following COVID-19. *JAMA Netw Open* 6(10):e2336120.
83. Regal-McDonald K, Patel RP (2020) Selective Recruitment of Monocyte Subsets by Endothelial N-Glycans. *Am J Pathol* 190(5):947-957.
84. Huang W, Luo WJ, Zhu P, Tang J, Yu XL, et al. (2013) Modulation of CD147-induced matrix metalloproteinase activity: role of CD147 N-glycosylation. *Biochem J* 449(2):437-448.
85. Li W, Wang D, Ge Y, Zhang L, Wu J, et al. (2021) Discovery and Biological Evaluation of CD147 N-Glycan Inhibitors: A New Direction in the Treatment of Tumor Metastasis. *Molecules* 26(1):33.
86. Ščupáková K, Adelaja OT, Balluff B, Ayyappan V, Tressler CM, et al. (2021) Clinical importance of high-mannose, fucosylated, and complex N-glycans in breast cancer metastasis. *JCI Insight* 6(24):e146945.
87. Li JH, Huang W, Lin P, Wu B, Fu ZG, et al. (2016) N-linked glycosylation at Asn152 on CD147 affects protein folding and stability: Promoting tumor metastasis in hepatocellular carcinoma. *Sci Rep* 6:35210.
88. Park DD, Phoomak C, Xu G, Olney LP, Tran KA, et al. (2020) Metastasis of cholangiocarcinoma is promoted by extended high-mannose glycans. *Proc Natl Acad Sci USA* 117(14):7633-7644.
89. Boyaval F, Dalebout H, Van Zeijl R, Wang W, Fariña-Sarasqueta A, et al. (2022) High-Mannose N-Glycans as Malignant Progression Markers in Early-Stage Colorectal Cancer. *Cancers* 14(6):1552.
90. Heindel DW, Koppolu S, Zhang Y, Kasper B, Meche L, et al. (2020) Glycomic analysis of host response reveals high mannose as a key mediator of influenza severity. *Proc Natl Acad Sci USA* 117(43):26926-26935.
91. Federica Defendi F, Leroy C, Epaulard O, Clavarino G, Vilotitch A, et al. (2021) Complement Alternative and Mannose-Binding Lectin Pathway Activation Is Associated with COVID-19 Mortality. *Frontiers in Immunol* 10, Article No. 742446.
92. Parry PI, Lefringhausen A, Turni C, Neil CJ, Cosford R, et al. (2023) 'Spikeopathy': COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA. *Biomedicines* 11(8):2287.
93. Fahs A, Hussein N, Zalzali H, Ramadan F, Ghamloush F, et al. (2022) CD147 Promotes Tumorigenesis via Exosome-Mediated Signaling in Rhabdomyosarcoma. *Cells* 11(15):2267.
94. Xin X, Zeng X, Gu H, Li M, Tan H, et al. (2016) CD147/EMMPRIN overexpression and prognosis in cancer: A systematic review and meta-analysis. *Sci Rep* 6:32804.
95. Yonker LM, Swank Z, Bartsch YC, Burns MD, Kane A, et al.

- (2023) Circulating Spike Protein Detected in Post-COVID-19 mRNA Vaccine Myocarditis. *Circulation* 147(11):867-876.
96. Japanese Government (n.d.) SARS-CoV-2 MRNA Vaccine (BNT162, PF-07302048). In: Pfizer Report, Japanese Government, Tokyo, 6.
97. Swank Z, Senussi Y, Manickas-Hill Z, Yu XG, Li JZ, et al. (2023) Persistent Circulating Severe Acute Respiratory Syndrome Coronavirus 2 Spike Is Associated With Post-acute Coronavirus Disease 2019 Sequelae. *Clin Infect Dis* 76(3):e487-e490.
98. Forsyth CB, Zhang L, Bhushan A, Swanson B, Zhang L, et al. (2022) The SARS-CoV-2 S1 Spike Protein Promotes MAPK and NF- κ B Activation in Human Lung Cells and Inflammatory Cytokine Production in Human Lung and Intestinal Epithelial Cells. *Microorganisms* 10(10):1996.
99. Rattis BAC, Ramos SG, Celes MRN (2021) Curcumin as a Potential Treatment for COVID-19. *Front Pharmacol* 12:675287.
100. Zhou Q, Zhang L, Dong Y, et al. (2023) The role of SARS-CoV-2-mediated NF- κ B activation in COVID-19 patients. *Hypertens Res* (2023).
101. Mazanova A, Shymanskyi I, Lisakovska O, Labudzynski D, Khomenko A, et al. (2022) The link between vitamin D status and NF- κ B-associated renal dysfunction in experimental diabetes mellitus. *Biochim Biophys Acta Gen Subj* 1866(7):130136.
102. Schultheiß, Christoph, Edith Willscher, Lisa Paschold, Cornelia Gottschick, et al. (2022) The IL-1 β , IL-6, and TNF Cytokine Triad Is Associated with Post-Acute Sequelae of COVID-19. *Cell Reports Medicine* 3 (6):100663.
103. Narasimhan H, Ferraro F, Bleilevens A, Weiskirchen R, Stickeler E, et al. (2022) Tumor Necrosis Factor- α (TNF α) Stimulates Triple-Negative Breast Cancer Stem Cells to Promote Intratumoral Invasion and Neovascrogenesis in the Liver of a Xenograft Model. *Biology* 11(10):1481.
104. Harborg S, Zachariae R, Olsen J, Johannsen M, Cronin-Fenton D, et al. (2021) Overweight and prognosis in triple-negative breast cancer patients: a systematic review and meta-analysis. *NPJ Breast Cancer* 7(1):119.
105. Blasiak J, Pawlowska E, Chojnacki J, Szczepanska J, Fila M, et al. (2020) Vitamin D in Triple-Negative and BRCA1-Deficient Breast Cancer-Implications for Pathogenesis and Therapy. *Int J Mol Sci* 21(10):3670.
106. Rodriguez-Morán M, Guerrero-Romero F (2004) Elevated concentrations of TNF- α are related to low serum magnesium levels in obese subjects. *Magnes Res* 17(3):189-196.
107. Cathcart-Rake EJ, Ruddy KJ, Bleyer A, Johnson RH (2021) Breast Cancer in Adolescent and Young Adult Women Under the Age of 40 Years. *JCO Oncol Pract* 17(6):305-313.
108. Urra JM, Cabrera CM, Porras L, Rodenas I (2020) Selective CD8 Cell Reduction by SARS-CoV-2 Is Associated with a Worse Prognosis and Systemic Inflammation in COVID-19 Patients. *Clinical Immunol* 217:08486.
109. Serrano-Villar S, Sainz T, Lee SA, Hunt PW, Sinclair E, et al. (2014) HIV-Infected Individuals with Low CD4/CD8 Ratio Despite Effective Antiretroviral Therapy Exhibit Altered T Cell Subsets, Heightened CD8+ T Cell Activation, and Increased Risk of Non-AIDS Morbidity and Mortality. *PLoS Pathogens* 10: e1004078.
110. Ostroumov D, Fekete-Drimusz N, Saborowski M, Kühnel F, Woller N (2018) CD4 and CD8 T Lymphocyte Interplay in Controlling Tumor Growth. *Cellular and Molecular Life Sciences* 75:689-713.
111. Knutti N, Huber O, Friedrich K (2019) CD147 (EMMPRIN) Controls Malignant Properties of Breast Cancer Cells by Interdependent Signaling of WNT and JAK/STAT Pathways. *Molecular and Cellular Biochemistry* 451:197-209.
112. Chen Y, Xu J, Wu X, Yao H, Yan Z, et al. (2020) CD147 Regulates Antitumor CD8+ T-Cell Responses to Facilitate Tumor-Immune Escape. *Cellular & Molecular Immunol* 18:1995-2009.
113. Zheng H, Gong B (2017) CD147 Expression Was Positively Linked to Aggressiveness and Worse Prognosis of Gastric Cancer: A Meta and Bioinformatics Analysis. *Oncotarget* 8:90358-90370.
114. Nabeshima K, Iwasaki H, Koga K, Hojo H, Suzumiya J, et al. (2006) Emmprin (Basigin/CD147): Matrix Metalloproteinase Modulator and Multifunctional Cell Recognition Molecule That Plays a Critical Role in Cancer Progression. *Pathology Int* 56:359-367.
115. Landras A, Reger de Moura C, Jouenne F, Lebbe C, Menashi S, et al. (2019) CD147 Is a Promising Target of Tumor Progression and a Prognostic Biomarker. *Cancers* 11(11):1803.
116. hang J, Wang Z, Zhang X, Dai Z, Zhi-Peng W, et al. (2022) Large-Scale Single-Cell and Bulk Sequencing Analyses Reveal the Prognostic Value and Immune Aspects of CD147 in Pan-Cancer. *Front Immunol* 13:810471.
117. Giles JR, Globig AM, Kaech SM, Wherry EJ (2023) CD8+T cells in the cancer-immunity cycle. *Immunity* 56(10):2231-2253.
118. Kheirouri S, Alizadeh M (2020) Vitamin D and advanced glycation end products and their receptors. *Pharmacol Res* 158:104879.
119. Omidian M, Djalali M, Javanbakht MH, Eshraghian MR, Abshirini M, et al. (2019) Mahmoudi M. Effects of vitamin D supplementation on advanced glycation end products signaling pathway in T2DM patients: a randomized, placebo-controlled, double blind clinical trial. *Diabetol Metab Syndr* 11:86.
120. Chen J, van der Duin D, Campos-Obando N, Ikram MA, Nijsten TEC, et al. (2019) Serum 25-hydroxyvitamin D3 is associated with advanced glycation end products (AGEs) measured as skin autofluorescence: The Rotterdam Study. *Eur J Epidemiol* 34(1):67-77.
121. Wimalawansa SJ (2018) Non-musculoskeletal benefits of vitamin D. *J Steroid Biochem Mol Biol* 175:60-81.
122. Chambers P (2022) Comment on Huțanu et al. Low Serum Vitamin D in COVID-19 Patients Is Not Related to Inflammatory Markers and Patients' Outcomes-A Single-

- Center Experience and a Brief Review of the Literature. *Nutrients* 2022, 14, 1998. *Nutrients* 14(16):3387.
123. Costello RB, Rosanoff A, Dai Q, Saldanha LG, Potischman NA (2021) Perspective: Characterization of Dietary Supplements Containing Calcium and Magnesium and Their Respective Ratio-Is a Rising Ratio a Cause for Concern? *Adv Nutr* 12(2):291-297.
124. Guerrero-Romero F, Mercado M, Rodriguez-Moran M, Ramirez-Renteria C, Martinez-Aguilar G, et al. (2022) Magnesium-to-Calcium Ratio and Mortality from COVID-19. *Nutrients* 14(9):1686.
125. Yosuke Nakayama, Seiji Ueda, Seiya Okuda (2014) Molecular Mechanism Underlying the Renoprotective Action of Vitamin D. *Circulation J* 78(3):599-600.
126. Tabarkiewicz J, Pogoda K, Karczmarczyk A, et al. (2015) The Role of IL-17 and Th17 Lymphocytes in Autoimmune Diseases. *Arch Immunol Ther Exp* 63:435-449.
127. Miguel Cervero Jiménez, Victoria Alcazar Lázaro, Jose Luis Agud Aparicio, Concepción García-Lacalle (2015) Chapter 10-Vitamin D and HIV Infection: Immunomodulatory and Extraskelatal Effects. Prevalence, Risk Factors, and Effects of Antiretroviral Therapy. *Health of HIV Infected People*, Academic Press 2015:157-173.
128. Mascolo E, Verni F (2020) Vitamin B6 and Diabetes: Relationship and Molecular Mechanisms. *Int J Mol Sci* 21(10):3669.
129. Chang H, Johnson E, Khoo C, Wang W, Gu L (2022) Cranberry Juice Polyphenols Inhibited the Formation of Advanced Glycation End Products in Collagens, Inhibited Advanced Glycation End Product-Induced Collagen Crosslinking, and Cleaved the Formed Crosslinks. *J Agric Food Chem* 70(49):15560-15569.
130. Xiao P, Hu Z, Lang J, et al. (2023) Mannose metabolism normalizes gut homeostasis by blocking the TNF- α -mediated proinflammatory circuit. *Cell Mol Immunol* 20:119-130.
131. Nan F, Sun Y, Liang H, Zhou J, Ma X, et al. (2022) Mannose: A Sweet Option in the Treatment of Cancer and Inflammation. *Front Pharmacol* 13:877543.
132. Dhanalakshmi M, Sruthi D, Jinuraj KR, Das K, Dave S, et al. (2023) Mannose: a potential saccharide candidate in disease management. *Med Chem Res* 32(3):391-408.
133. Chen N, Zhao M, Guo Y, et al. (2023) D-mannose is a rapid inducer of ACS2 to trigger rapid and long-lasting antidepressant responses through augmenting BDNF and TPH2 levels. *Transl Psychiatry* 13:338.
134. Gonzalez PS, O'Prey J, Cardaci S, et al. (2018) Mannose impairs tumour growth and enhances chemotherapy. *Nature* 563:719-723.
135. Zhang R, Yang Y, Dong W, Lin M, He J, et al. (2022) D-mannose facilitates immunotherapy and radiotherapy of triple-negative breast cancer via degradation of PD-L1. *Proc Natl Acad Sci USA* 119(8):e2114851119.
136. Xie J, Wu S, Liao W, Ning J, Ding K (2023) Src is a target molecule of mannose against pancreatic cancer cells growth in vitro & in vivo. *Glycobiology* cwad070.
137. Zhao P, Zhang Z (2018) TNF- α promotes colon cancer cell migration and invasion by upregulating TROP-2. *Oncol Lett* 15(3):3820-3827.
138. Zhang W, Li C, Wu F, Li N, Wang Y, et al. (2021) Analyzing and Validating the Prognostic Value of a TNF-Related Signature in Kidney Renal Clear Cell Carcinoma. *Front Mol Biosci* 8:689037.
139. Koh B, Tan DJH, Ng CH, Fu CE, Lim WH, et al. (2023) Patterns in Cancer Incidence Among People Younger Than 50 Years in the US, 2010 to 2019. *JAMA Netw Open* 6(8):e2328171.
140. Wang X, Li H, Chang X, Tian Z (2023) High serum mannose in colorectal cancer: a novel biomarker of lymph node metastasis and poor prognosis. *Front Oncol* 13:1213952.

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