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REVIEW ARTICLE

Comorbidity-associated glutamine deficiency is a predisposition to severe COVID-19

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SARS-CoV-2 vaccinations have greatly reduced COVID-19 cases, but we must continue to develop our understanding of the nature of the disease and its effects on human immunity. Previously, we suggested that a dysregulated STAT3 pathway following SARS-Co-2 infection ultimately leads to PAI-1 activation and cascades of pathologies. The major COVID-19-associated metabolic risks (old age, hypertension, cardiovascular diseases, diabetes, and obesity) share high PAI-1 levels and could predispose certain groups to severe COVID-19 complications. In this review article, we describe the common metabolic profile that is shared between all of these high-risk groups and COVID-19. This profile not only involves high levels of PAI-1 and STAT3 as previously described, but also includes low levels of glutamine and NAD^+, coupled with overproduction of hyaluronan (HA). SARS-CoV-2 infection exacerbates this metabolic imbalance and predisposes these patients to the severe pathophysiologies of COVID-19, including the involvement of NETs (neutrophil extracellular traps) and HA overproduction in the lung. While hyperinflammation due to proinflammatory cytokine overproduction has been frequently documented, it is recently recognized that the immune response is markedly suppressed in some cases by the expansion and activity of MDSCs (myeloid-derived suppressor cells) and $FoxP3^+$ Tregs (regulatory T cells). The metabolomics profiles of severe COVID-19 patients and patients with advanced cancer are similar, and in high-risk patients, SARS-CoV-2 infection leads to aberrant STAT3 activation, which promotes a cancer-like metabolism. We propose that glutamine deficiency and overproduced HA is the central metabolic characteristic of COVID-19 and its high-risk groups. We suggest the usage of glutamine supplementation and the repurposing of cancer drugs to prevent the development of severe COVID-19 pneumonia.

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FACTS

- PAI-1 is upregulated in aged individuals and in those suffering from hypertension, cardiovascular diseases, diabetes, and obesity, which are risk factors for COVID-19.
- COVID-19 associated comorbidities share not only high plasma PAI-1 levels, but also high plasma hyaluronan levels, and low NAD^+ and glutamine levels.
- Plasma glutamine and the glutamine:glutamate ratio are inversely associated with metabolic risks.
- Severe COVID-19 symptoms are characterized by an uncontrolled production of hyaluronan in the lung (hyaluronan storm), neutrophil extracellular traps (NETs), and severe immunodeficiency.
- SARS-CoV-2 infection leads to aberrant STAT3 activation, which promotes a cancer-like metabolism in the infected cells.
- There are similarities between severe COVID-19 and advanced cancer, based on the activation of STAT3.
- One commonality among many risk factors is high plasma or sputum levels of hyaluronan.

OPEN QUESTIONS

- How much do plasma levels of metabolites of interest correlate with the levels in tissues?
- Are clinical manifestations different among risk factor groups?
- Will prophylactic use of glutamine supplementation protect against the severe symptoms of COVID-19?
- Is it possible to use glutamine for treating COVID-19?
- Is HMW (high molecular weight)-hyaluronan responsible for immune suppression in COVID-19?
- Is LMW (low molecular weight)-hyaluronan responsible for hyperinflammation in COVID-19?
- Will therapeutic use of the anti-hyaluronan drug, 4-methylumbelliferone, protect high-risk people from the development of the hyaluronan storm?
- Is glutamine deficiency or hyaluronan overproduction involved in long COVID-19?
- What cells are immunosuppressed by Tregs and MDSCs?

INTRODUCTION

Globally, SARS-CoV-2 has infected hundreds of millions of people and killed over 4 million in less than two years. Perhaps the only positive aspect of the high infectivity of this virus is that it has generated large amounts of data to analyze the nature of the disease. Major risk factors for morbidity have emerged, including aging, hypertension, cardiovascular disease, diabetes, and obesity [1]. The following question thus arises: Do these conditions share

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biochemical commonalities of dysfunction with SARS-CoV-2 infection?

We previously described the involvement of dysregulated STAT1 and STAT3 pathways in COVID-19, which leads to a cascade of pathologies [2]. Subsequently, groups have observed activated STAT3 in biopsied lung specimens [3], and detected the expression of STAT3 downstream genes like PAI-1, HAS2 (hyaluronan synthase 2), and MMP9 in BALF (broncho alveolar lavage fluid) samples from severe COVID-19 patients [4]. Furthermore, increased serum PAI-1 levels were found in COVID-19 patients, as compared to those in healthy controls [5, 6]. Table 1 shows the relevant metabolic profile of COVID-19 high-risk groups. Since PAI-1 expression levels are also increased in the major COVID-19 high-risk conditions of old age, hypertension, cardiovascular disease, diabetes, and obesity [2], PAI-1 may be critical to severe COVID-19. In addition, COVID-19 associated comorbidities share not only high PAI-1 levels, but also high hyaluronan (HA: extracellular matrix glycosaminoglycan polymers) levels, and low NAD^+ (nicotinamide adenine dinucleotide) and glutamine levels (Table 1).

The low glutamine levels are particularly compelling, as seminal work by Cheng et al. identified that plasma glutamine and the glutamine:glutamate ratio are inversely associated with metabolic risks [7]. Indeed, metabolomic analyses of COVID-19 patients have shown low levels of glutamine [8–15], and Lee et al. reported that glutamine was negatively correlated with disease severity [15]. Furthermore, Paez-Franco et al. observed that the reduced levels of glutamine in severe and mild COVID-19 patients were negatively correlated with LDH (lactate dehydrogenase), CRP (C-reactive protein), and pCO_2 levels. Conversely, glutamine levels positively correlated with pO_2 [10], revealing the previously undetermined consequences of low levels of glutamine in the severe COVID-19 pathophysiologies. Consistently, Kim et al. reported that glutamine was the top candidate amongst 26,288 FDA-approved drugs tested for reversing SARS-CoV-1 associated changes in murine gene expression [16].

This review discusses the possibility that glutamine deficiency predisposes high-risk patients to severe COVID-19. Other major factors, such as low NAD^+, high HA, and high PAI-1, may be related to low glutamine levels in the high-risk groups. SARS-CoV-2 infection affects these same conditions, potentially magnifying the severe pathologies of COVID-19.

PATHOPHYSIOLOGIES

COVID-19 is characterized by a variety of clinical manifestations, including impaired type I interferon (IFN-I) production and, in severe cases, ARDS (acute respiratory distress syndrome) and extensive coagulopathy [2]. Here, we principally focus on the less characterized aspects of COVID-19 pathophysiologies: the hyaluronan storm, NETs, and immune suppression.

CT scans of severe SARS-CoV-2 patients revealed characteristic multiple round white patches called “ground-glass opacities”, containing fluid in the lungs [17]. In almost all cases of SARS-CoV-2, the main pathological finding is diffuse alveolar damage (DAD) [18]. DAD is characterized by damage to the alveolar lining and endothelial cells, leading to pulmonary edema and hyaline membrane formation (the exudative phase), and later by proliferative changes involving alveolar and bronchial lining cells and interstitial cells (the proliferative phase) [19]. To analyze the nature of hyaline membranes in COVID-19, Hellman et al. performed hyaluronan (HA) histochemistry using a direct and specific HA staining method [20] as overproduced HA was suggested to be a fatal cause of COVID-19 [17]. They reported that HA-positive-exudate and alveolar plugs filled the alveolar spaces [20]. They also showed that in the proliferative phase, HA is localized in the thickened perialveolar interstitium. Similar findings were reported by Kaber et al., in which COVID-19 autopsies revealed the extensive occlusion of airway spaces filled with poorly organized polymeric material that stained robustly for HA [21]. They also observed that sputum HA, particularly low-molecular weight HA (LMW-HA), was increased ~20-fold in COVID-19 samples as compared to healthy control samples. Consistently, the critical group of COVID-19 cases had significantly higher serum levels of HA [22] and patients infected with SARS-CoV-2 had higher levels of HA in plasma and lung tissue [23]. One systematic study of COVID-19 autopsies revealed that the average lung weight was ~3.2 times normal and, in an extreme case, 4.6 times normal [24]. These “heavy lungs” may be a direct result of the overproduction of HA and its ability to absorb 1000 times its molecular weight in water [17]. Mechanistically, over-produced HA may quickly induce an accumulation of water in the airspace and perialveolar interstitium, causing sudden fatal hypoxia and death in critical COVID-19 [24]. Together, the over-production of HA and subsequent absorption of water are referred to as an induced-hyaluronan storm [24]. We will hereafter use the term hyaluronan storm to describe this phenomenon.

Another significant pathologic change of ARDS in COVID-19 is the formation of dysregulated neutrophil extracellular traps (NETs) in the blood and lower respiratory tract of critically ill patients [25]. NETs are a recently identified neutrophil effector mechanism in which neutrophils contain and kill microbial organisms through the externalization of a meshwork of chromatin fibers, together with granule-derived antimicrobial proteins [26]. In severe COVID-19, neutrophil infiltration of the lungs leads to increased NETs formation and contributes to microthrombosis/coagulopathy and COVID-19-related ARDS [18, 27].

A prevailing concept is that a primary cause of death from COVID-19 is due to a hyperactive inflammatory response, characterized by the overproduction of proinflammatory cytokines such as TNF, IL-6, IL-1β, IL-18, IL-12/IL-23p40, IL-10, and IL-8 [28]. A presumed cytokine storm evokes the consideration of anti-cytokine therapy; specifically, IL-6 receptor (IL-6R) antagonists, in clinical trials for COVID-19. However, a comparison of COVID-19 with other severe diseases demonstrated that the levels of IL-6 were far less than those seen in other inflammatory syndromes, such as sepsis [29]. The nature of the immune dysfunction in severe COVID-19 does not resemble a standard cytokine storm response, as compared to other diseases [29]. Recent reports have indicated that the levels of proinflammatory cytokines seen in COVID-19 are usually no higher, and often lower, than those in other inflammatory states [30, 31]. Finally, the lack of convincing clinical benefits from COVID-19 clinical trials of anti-IL6R inhibitor monoclonal antibodies [32, 33] indicated a minor role for IL-6, a critical cytokine typically associated with a cytokine storm. However, IL-6, together with IL-8, and TNF-α are good biomarkers for severe COVID-19 [28, 34]. In particular, IL-8 seems to serve as a more accurate COVID-19 disease biomarker than IL-6 [28, 35]. While it is not as high as in sepsis [30], the levels of IL-8 are significantly higher in the sera of COVID-19 patients, as compared to sera from healthy people [36–39] or those infected with influenza [28]. Furthermore, the prognostic value of IL-8 for COVID-19 fatalities was suggested by two different groups [40, 41]. Finally, IL-8 is a major chemoattractant for neutrophils and seems to be involved in NETs formation as described later.

On the other hand, indications of immunosuppression are becoming evident in COVID-19 patients. Remy et al. performed ELISpot functional assays to evaluate the innate and acquired immunities in COVID-19 cases and found that the major immunologic abnormality in COVID-19 is a profound defect in host immunity. They detected a decrease in the number of functional T-cells and the lower expression of critical cytokines from mononuclear cells, thus indicating a decrease in both the quality and quantity of the immune response in severe COVID-19 [42]. Moreover, poor outcomes in COVID-19 patients are correlated with increases in both Treg proportions and intracellular levels of

Table 1. Metabolic profiles of COVID-19 high-risk groups.

	Aging	Hypertension	Cardio-vascular disease	Diabetes	Obesity	COVID-19
Glutamine	Opposing results [166–168] from blood metabolomic studies. Positive effect of supplementation into the elderly [169]	Plasma glutamine and glutamine-to-glutamate ratio were inversely related to hypertension [7, 170]	Plasma glutamine and glutamine-to-glutamate ratio were inversely related to risk of cardiovascular mortality [170]	Decreased from plasma metabolomic analysis, and inversely associated with diabetes [7, 171]. Positive effect of supplementation in diabetes [120]	Decreased in white adipose tissues, but not in the plasma [70]. Supplementation reduces obesity [172]	Decreased from plasma metabolomic analysis [8–12, 15]
NAD^+	Plasma NAD + was significantly and negatively correlated with age from 20 to 87 years [173]	Positive effect of NAD^+ booster in controlling hypertension [174]. No data available about the plasma levels.	Significantly reduced in the human DCM-heart samples compared to NF controls [175]. No data available about the plasma levels.	Intracellular NAD^+ levels of endothelial progenitor cells were reduced in T2D patients [176]. No data available about the plasma levels.	Longer-term overfeeding with HFD resulted in reduced NAD^+ levels in skeletal muscle [177]. No data available about the plasma levels.	Combined metabolic activator including NAD^+ booster had a positive effects on COVID-19 cases [178]. No data available about the plasma levels.
Hyaluronan	Serum levels continued to increase with age [179]	Little data available about the serum levels [180]	Serum levels correlated significantly with the risk for coronary heart disease over the next 10 years [181]	Serum levels correlate with poor blood glucose control and diabetic angiopathy [182]	Circulating HA negatively correlated with BMI and triglycerides [183]	Significant increase in the serum of critical cases [22, 184], prominent hyaluronan exudates in the COVID-19 lungs [20, 21]
PAI-1	Increase with aging-associated thrombosis [185]	Positive associations between PAI-1 and hypertension [186]	Elevated plasma levels are associated with MACE [187]	Elevated concentrations in blood from patients with T2D [188]	Increased in morbid obesity [189]	Increased in the plasma [5, 6]

HFD indicates high-fat diet, *DCM* dilated cardiomyopathy, *NF controls* non-failing controls, *T2D*type 2 diabetes,*BMI*body mass index, *MACE*major adverse cardiovascular events.

the lineage-defining transcription factor FoxP3, as detected in cytometric and transcriptomic profiling analyses by Galván-Peña et al. [43]. These Tregs over-expressed a range of suppressive effectors, reminiscent of tumor-infiltrating Tregs that suppress anti-tumor T cell responses [43]. Vick et al. also reported that in the most critical COVID-19 clinical disease states, patients had an altered Treg signature including increased frequency, activation status, and migration markers [44].

Agrati et al. reported another type of immunosuppression in severe COVID-19 [38]. They found the expansion of MDSCs (myeloid-derived suppressor cells) in the blood, associated with disease severity, as well as suppressed T-cell functions. Of the three subsets of MDSCs, increased proportions of G-MDSCs [37, 38], M-MDSCs [45], or both [46, 47] were closely associated with the disease severity.

COVID-19 appears to be a combination of a hyperinflammatory response due to the overproduction of inflammatory cytokines, immunosuppression due to the increased levels of Tregs and MDSCs, and respiratory distress produced by a hyaluronan storm and NETs. In the following sections, we describe how a comorbidity-associated glutamine deficiency worsens these conditions in severe COVID-19.

PLEIOTROPIC ACTIVITIES OF GLUTAMINE

Glutamine

L-Glutamine is the most abundant amino acid in the blood, and is released mainly from skeletal muscles and transported to a variety of tissues [48]. Although most tissues can synthesize glutamine, during periods of stress the demand outpaces the supply, and the expression levels of glutamine transporters on plasma membranes become critical [48]. Two principal enzymes regulate intracellular glutamine metabolism. Glutamine synthetase (GS) catalyzes the synthesis of glutamine from glutamate and ammonia, while glutaminase (GLS) catalyzes glutaminolysis, the hydrolysis of glutamine to glutamate [49]. In contrast to glutamate, glutamine has a gamma-amide nitrogen that is essential for the biosynthesis of nucleotides and hexosamine [49] (Fig. 1). As described later, HA is the product of the hexosamine biosynthesis pathway (HBP). In nucleotide biosynthesis, glutamine and glutamate either directly or indirectly serve as the nitrogen donors for all nitrogen atoms in purines and pyrimidines [49] (Fig. 1). For rapidly dividing cells such as cancers, enterocytes, and lymphocytes, glutamine consumption corresponds to an urgent need for nucleotide biosynthesis. Growing cells also use glutamine to maintain energy from mitochondria through anaplerosis, a replenishment process of TCA cycle intermediates [50]. Cancer cells create a more demanding situation and utilize glutamine metabolism through TCA cycle anaplerosis to synthesize a majority of the non-essential amino acids in proteins [50]. α-Ketoglutarate (α-KG), one of the TCA cycle intermediates, is produced through glutamate dehydrogenase 1 (GLUD1) or by several mitochondrial aminotransferases, including alanine aminotransferase (ALT) and asparagine aminotransferase (AST) [48] (Fig. 1). α-KG is also implicated in $CD4^+$ T cell differentiation, possibly through the epigenetic regulation of cellular histone and DNA methylation levels [51].

Glutamine is also used for the synthesis of glutathione (GSH), the major endogenous antioxidant molecule in mitochondria [52] and the nucleus [53], which consists of glutamine-derived glutamate, cysteine, and glycine (Fig. 1). Cells are exposed to oxidative stress not only during nutrient starvation and catabolic stresses after trauma, surgery, sepsis, or infection, but also during active cell proliferation [54]. As glutamate represents the first important step in the synthesis of GSH intermediate compounds, intracellular glutamine availability is the key to GSH synthesis

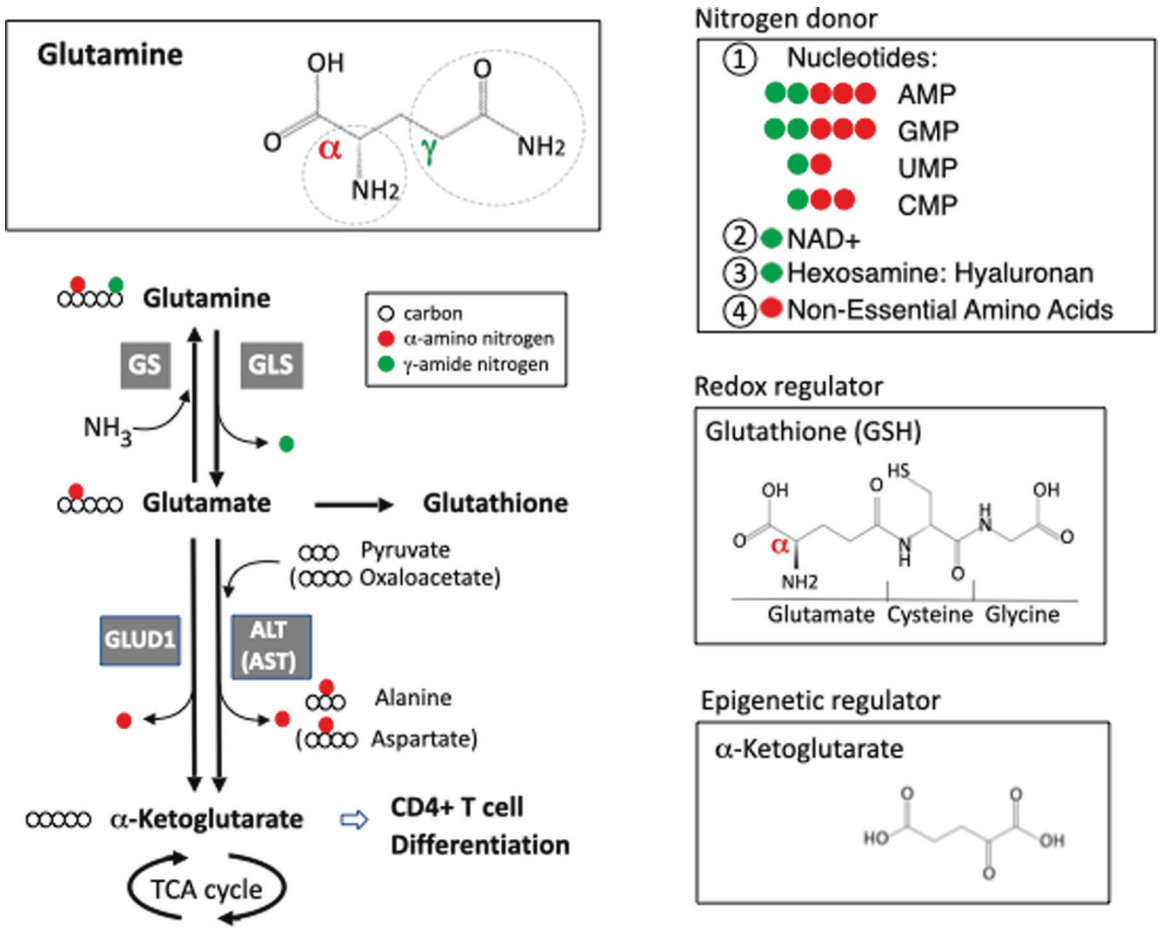

Fig. 1 Roles of glutamine. The pleiotropic roles of glutamine as a nitrogen donor, in the formation of a redox regulator (glutathione), and as an epigenetic regulator for $CD4^+$ T cell differentiation (α-Ketoglutarate). Nitrogen donor legends are modified from Zhang et al. [49]. GS glutamine synthetase, GLS glutaminase, GLUD1 Glutamate dehydrogenase 1, ALT alanine aminotransferase, AST aspartate aminotransferase.

[52]. In turn, glutamine deprivation results in increased reactive oxygen species (ROS) levels through decreased GSH [55].

NAD^+

Glutamine is an important nitrogen donor for the production of NAD^+, in the last steps of both the *de novo* (from dietary tryptophan) and Preiss-Handler (from dietary niacin) pathways [56] (Fig. 2). NAD^+ is an essential coenzyme and substrate for metabolism. Although NAD^+ is also produced through salvage pathways from nicotinamide (NAM) and nicotinamide riboside (NR) precursors [56], people with ultra-rare inborn errors in the glutamine synthetase gene exhibit severe secondary NAD^+ deficiency [57], indicating that the glutamine supply for both the *de novo* synthesis and Preiss-Handler pathways is indispensable for NAD^+ synthesis (Fig. 2).

In addition, the age-associated dysfunction of enzymes in NAD^+ production, such as QPRT (quinolinate phosphoribosyl transferase) [58] in the de novo pathway, may be a reason why elderly persons are more susceptible to severe COVID-19. Minhas et al. reported that aged human macrophages had lower QPRT expression that was associated with an induction of upstream KP (kynurenine pathway) metabolites culminating in the accumulation of QA (quinolinic acid), but decreased production of the downstream metabolites NAMN (nicotinic acid mononucleotide), NAAD (nicotinic acid dinucleotide), and NAD^+ [58] (Fig. 2). Reduced expression of QPRT was found in several lung cell lines infected with SARS-CoV-2 [59], suggesting that the dysfunction of QPRT expression and reduction of NAD^+ may be exacerbated in COVID-19. Other mechanisms for the age-related reduction of NAD^+ could result from increases in NAD^+-consuming enzymes (NADases). NADases include SIRTs (sirtuins) and CD38, and in particular, CD38 is activated in the elderly population [60]. NAD^+ deficiency is shared amongst the comorbidities of COVID-19 (Table 1) and thus potentially represents a critical component of the disease.

HBP AND HYALURONAN

HA is a glycosaminoglycan component of the ECM and presents at high concentrations in the lung. It has important roles in water homeostasis, cell-matrix signaling, tissue healing, inflammation, angiogenesis, and cell migration [61]. As HA is exclusively produced through the hexosamine biosynthetic pathway (HBP) [62] (Fig. 3), understanding this pathway is crucial for treating the hyaluronan storm in severe COVID-19. The HBP utilizes 2–5% of the glucose that enters cells, and after the first two steps of glycolysis, the resultant fructose-6-phosphate (F6P) is catabolized with the rate-limiting enzyme glutamine-fructose-6-phosphate amidotransferase (GFAT), which transfers the amino group from glutamine to produce glucosamine-6-phosphate (GlcN-6P) and glutamate [62]. The HBP is regarded as a nutrient sensor since the end product is UDP-GlcNAc, which is composed of substrates derived from the metabolism of amino acids (glutamine), nucleotides (uridine), carbohydrates (glucose), and fatty acids (acetyl-CoA) [62]. The UDP-GlcNAc substrate is used in a wide variety of cellular processes, such as N-glycosylation, N-glycan

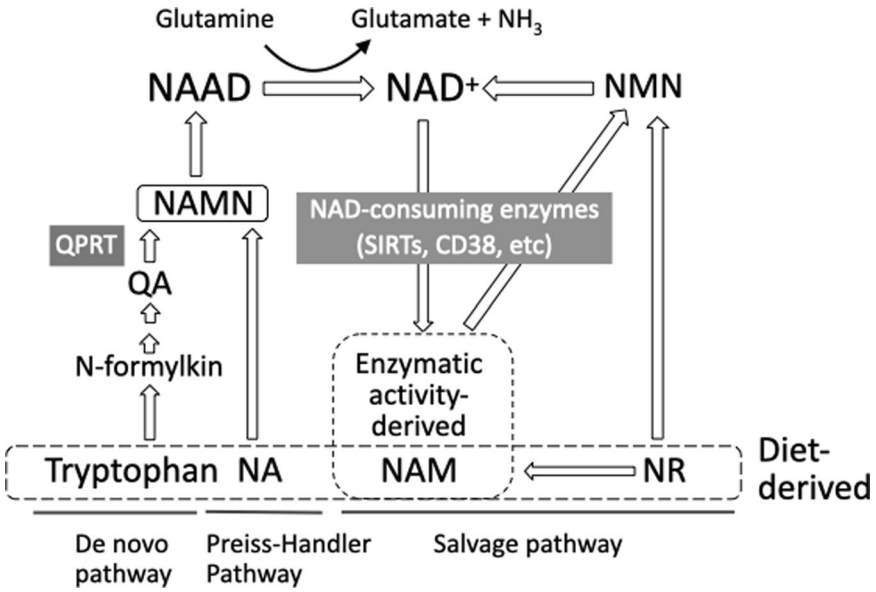

Fig. 2 NAD$^+$ biosynthetic pathways. NAD$^+$ is produced through three independent pathways: the *de novo* synthesis, Preiss-Handler, and salvage pathways. The QPRT and CD38 enzymes are responsible for the decline in NAD$^+$ levels with age. The de novo synthesis pathway from diet-derived tryptophan occurs through the kynurenine pathway. The first step in this pathway is the conversion of tryptophan to N-formylkin. After two more reaction steps, N-formylkin is transformed into QA, which is then converted into NAMN by the rate-limiting enzyme, QPRT. NAMN is a shared metabolite with the Preiss-Handler pathway, which uses NA from a dietary source. NAMN is then transformed into NAAD. The final step of both the de novo and Preiss-Handler pathways requires glutamine as a gamma-amide nitrogen donor to transform NAAD into NAD$^+$ with NADS. The NAD$^+$ salvage pathway uses NAM, which is either generated as a by-product of the enzymatic activities of NAD$^+$-consuming enzymes such as SIRTs and CD38, or derived from food. NAM is transformed into NMN to make NAD$^+$. NR is also a precursor of NMN. NR and NMN are potent NAD$^+$ boosters in vivo. N-formylkin N-formylkynurenine, QA quinolinic acid, QPRT Quinolinate phosphoribosyl transferase, NAMN nicotinic acid mononucleotide, NA nicotinic acid, NAAD nicotinic acid adenine dinucleotide, NAM nicotinamide, NR nicotinamide riboside, NMN nicotinamide mononucleotide.

branching, O-GlcNAcylation, and HA synthesis in the ER, Golgi, cytosol or nucleus, and plasma membrane, respectively. UDP-GlcNAc is also produced through the salvage pathway of GlcNAc by NAGK (N-acetylglucosamine kinase) [63]. Intracellular GlcNAc is generated by the removal of O-GlcNAc protein modifications from substrates and the lysosomal degradation of glycoconjugates and extracellular matrix components [63]. Protein modification by O-GlcNAcylation is similar to phosphorylation, in terms of its dynamic and reversible kinetics [64]. The modification regulates distinct cellular processes and occurs on a wide spectrum of intracellular proteins. The human O-GlcNAcome is composed of over 5,000 proteins and 7,000 modification sites [64].

HA is produced primarily by HAS2 from its precursors UDP-glucuronic acid (UDP-GlcUA) and UDP-GlcNAc [62]. The HAS2 gene is transcriptionally induced by viral infections [61], and the protein is regulated by O-GlcNAc modification (O-GlcNAcylation). O-GlcNAcylation transfers a single O-GlcNAc moiety from UDP-GlcNAc to serine/threonine residues of proteins. The HAS2 protein is stabilized in the plasma membrane by the O-GlcNAc modification at serine-221, resulting in increased HA production [65]. Conversely, HAS2 activity is inhibited by phosphorylation at threonine-110 by AMP-activated protein kinase (AMPK), a master metabolic regulator [65].

HAS2 expression is regulated by another important energy sensor, SIRT1 (sirtuin 1) [62]. SIRT1 inhibits the activity of HAS2 in an NAD$^+$-dependent manner. Therefore, NAD$^+$ deficiencies caused by comorbidities such as aging, diabetes, obesity, and cardiovascular disease (Table 1) will impede SIRT1's anti-HAS2 activity and lead to increased HA production.

The most common physiological size of the HA polymer in tissues is about 0.5–2 MDa [66], corresponding to high molecular weight HA (HMW-HA). HMW-HA has viscoelastic and anti-inflammatory properties and is a ligand of CD44. Smaller HA polymers of less than 0.5 MDa are known as low molecular weight HA (LMW-HA), and are usually generated during HA turnover but can also accumulate at sites of inflammation with hyaluronidase, oxidative stress, and/or hypoxia [67]. Generally, LMW-HA is regarded as a proinflammatory factor. Numerous studies have demonstrated the pathological function of LMW-HA in human respiratory diseases, including ARDS [67].

CONSEQUENCES OF GLUTAMINE DEFICIENCY AND COVID-19

COVID-19 high-risk groups, such as the elderly, diabetics, obese people, and those with cardiovascular disease, share a background of low glutamine and enhanced HBP activation [68–71]. As mentioned previously, GFAT is a rate-limiting enzyme for HBP (Fig. 3), and a direct transcriptional target of ATF4 (the activating transcription factor 4) [72], which is activated by glutamine deprivation [73]. In addition, the high risk groups tend to show glucose intolerance [74–76], which will cause high glucose flux to the uronic acid pathway as well as HBP (Fig. 3), producing the substrates UDP-GlcUA and UDP-GlcNAc, respectively, for HA synthesis. Therefore, the combination of low glutamine and high glucose levels could predispose the high-risk groups to produce pathological amounts of HA.

As the role of glutamine in the immune system is broad, here we focus on its functions in neutrophils for NETs formation (NETosis), the development of myeloid-derived suppressor cells (MDSCs), and the differentiation into FoxP3$^+$ Treg cells, which are all involved in the pathogenesis of severe COVID-19.

NETosis

Neutrophilia is common in COVID-19, and the neutrophil/lymphocyte ratio (NLR) is higher in critical patients as compared to moderately ill or healthy persons [36]. In fact, neutrophilia is

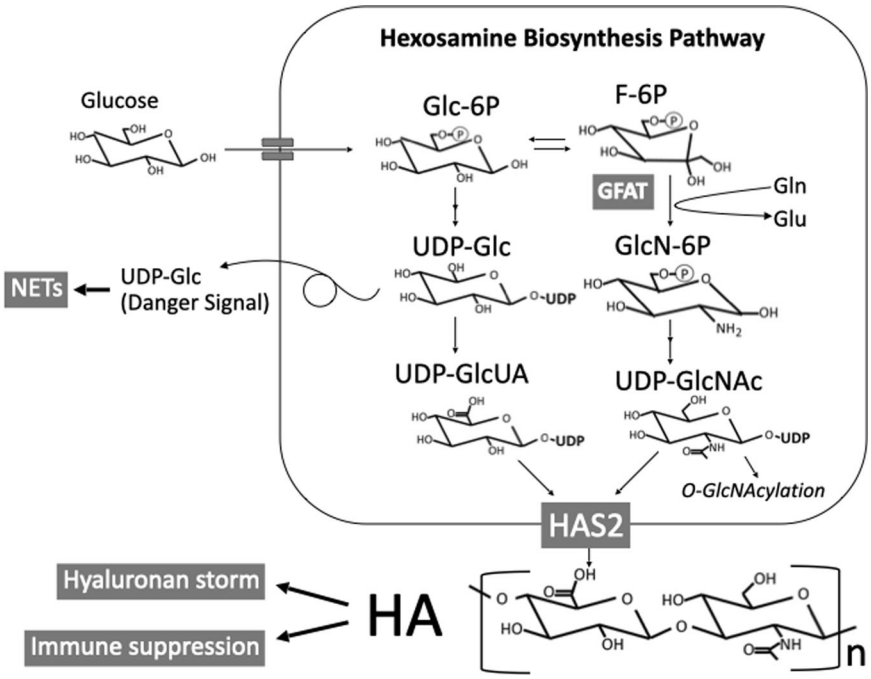

Fig. 3 HBP and hyaluronan. Schematic representation of metabolic pathways that lead to the production of substrates for the HAS2 enzyme, UDP-GlcUA and UDP-GlcNAc. The monomer unit of HA is shown. LMW-HA activates PAI-1 and promotes a hyaluronan storm. HMW-HA contributes to immunosuppression. UDP-Glc is released from the infected cells and serves as a danger signal to neighboring cells, resulting in NETs formation. Glc-6P glucose-6 phosphate, UDP-Glc uridine diphosphate glucose, UDP-GlcUA uridine diphosphate glucuronic acid, F-6P fructose-6 phosphate, GlcN-6p glucosamine 6-phosphate, UDP-GlcNAc uridine 5′-diphospho-N-acetylglucosamine, GFAT glutamine-fructose-6-phosphate transaminase, HAS2 hyaluronan synthase 2, HA hyaluronan.

intimately associated with NETosis [41]. The major chemoattractant of neutrophils, IL-8, is clearly involved not only in the recruitment of neutrophils but also in the induction of NETosis [77]. One of the stimuli for IL-8 secretion from lung cells is possibly UDP-glucose, a product of the glucuronic pathway (Fig. 3) and a type of danger signal [78] released from the infected cells. Adjacent lung cells are then stimulated through P2RY14 to secrete IL-8, which acts as a chemo-attractant for neutrophils [79]. It is also possible that UDP-glucose directly stimulates the P2RY14 expressed on neutrophils to attract them to the site of infection [79, 80]. Recruited neutrophils sometimes control infection by the production of NETs. Ouwendijk et al. suggested that regulated NETs formation may defend hosts against SARS-CoV-2 infection in asymptomatic or mild cases, but additional factors may lead to excessive NETs production and lung obstruction [25]. Comorbidity-associated glutamine deficiency may be one of the factors contributing to pathologic NETs production, as glutamine impaired the chemotactic migration of neutrophils to infection sites in an animal model [81], and glutamine deprivation induced the expression of IL-8 [82, 83].

MDSCs

As noted previously, MDSCs are expanded in COVID-19 [38, 45, 46], and the increased proportions of G-MDSCs [37, 38], M-MDSCs [45], or both [46, 47] were closely associated with the disease severity. Low glutamine levels may affect the differentiation of MDSCs and contribute to these expanded populations in severe COVID-19, but the experimental results are inconsistent. Some studies reported that low glutamine inhibited the differentiation of MDSCs [84, 85], while others revealed that glutamine deprivation promoted the generation of MDSCs [86]. In a murine arthritis model, the inhibition of glutaminolysis suppressed the differentiation of M-MDSCs, but promoted the expansion of G-MDSCs [87]. In other studies, CRP enhanced the production of MDSCs [88, 89], and clinically, glutamine was shown to inhibit CRP levels [90]. Therefore, it is possible that glutamine limits the production of MDSCs indirectly, through inhibiting CRP production.

Tregs

Glutamine also contributes to $CD4^+$T cell differentiation. Upon glutamine restriction, $CD4^+$T cells differentiated into $FoxP3^+$ Treg cells despite the presence of Th1-directing cytokines [51, 91]. A decrease in the intracellular amount of glutamine-derived α-KG shifted the balance of Th1 and Treg cells toward that of a Treg phenotype [51]. The altered profile of Tregs in severe COVID-19 [43, 44] may result from low glutamine levels and the resultant α-KG deficiency. The consequences of this immunosuppression are thus widespread, and some of the likely targets may be the tissue-resident immune cells, such as alveolar macrophages, MAIT (Mucosal associated invariant T) cells and γδ T cells [92–95].

COVID-19 exhibits a wide range of the combination of hyperinflammation and immunosuppression. As these immunological perturbations can be explained as consequences of glutamine deficiency, it is advantageous to maintain appropriate glutamine levels for COVID-19 prevention and treatment. Interestingly, malnutrition is linked to higher serum HA levels [96]. Furthermore, the long-term effects of malnutrition predispose patients to severe COVID-19 in an age-dependent manner [97], and are associated with hyperinflammation and immunosuppression [98]. How malnutrition affects glutamine levels remains to be determined.

GLUTAMINE DEFICIENCY AT THE CROSSROADS OF COVID-19 AND ITS COMORBIDITIES

Based on the above considerations, we now provide an overview of the pathophysiologies of COVID-19 in terms of comorbidity-associated glutamine deficiency (Fig. 4).

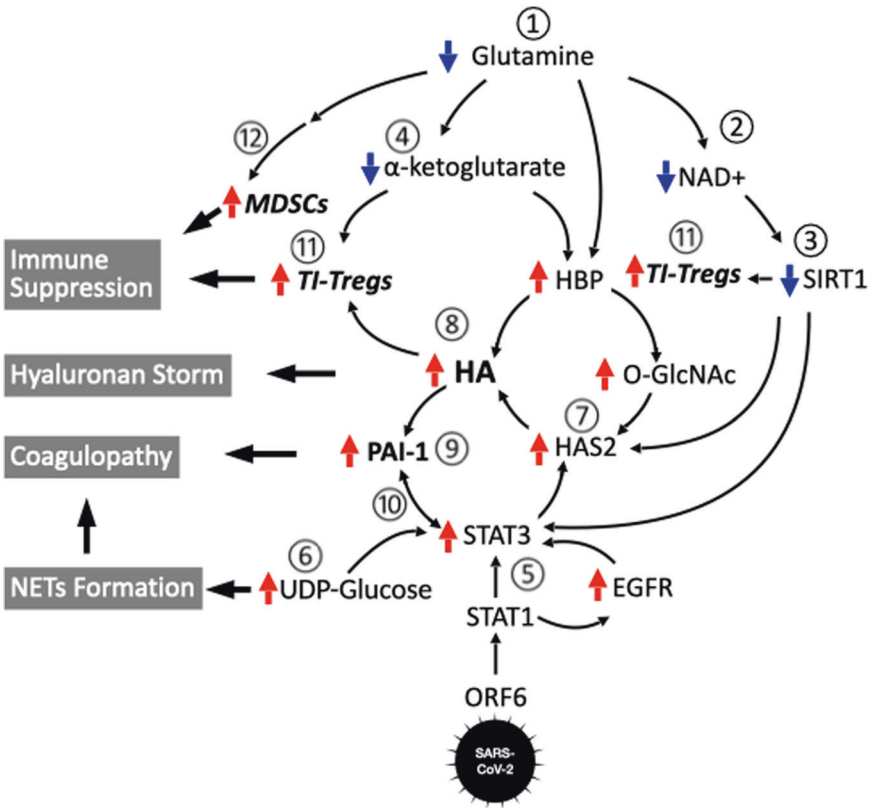

Fig. 4 Synergistic metabolic pathways that lead to a hyaluronan storm, NETosis, coagulopathy, and immune suppression. Before the SARS-CoV-2 infection, comorbidity-associated glutamine deficiency (1) and comorbidity-associated NAD^+ deficiency (2) lead to low α-KG (4) and impaired SIRT1 activity (3), respectively. This results in the hyperproduction of HA and PAI-1, and immunodeficiency. After SARS-CoV-2 infection, STAT3 is activated through the EGFR pathway (5) and the extracellular UDP-Glucose-stimulated P2RY14 pathway (6). Activated STAT3 can induce the transcription of *HAS2* (7). The HAS2 enzyme is stabilized by O-GlcNAcylation, and HA is produced (8). In addition, a critical HAS2 negative regulator, SIRT1 (3), is neutralized by SARS-CoV-2 infection and low NAD^+ levels. This results in increased HAS2 activity and higher HA levels, and contributes to a hyaluronan storm. LMW-HA derived from excess HA production stimulates the production of PAI-1 (9), and PAI-1 indirectly activates STAT3 (10) leading to coagulopathy. Danger signals, such as UDP-glucose, activate the innate immune responses and the formation of NETS (NETosis), thus exacerbating the coagulopathy. Glutamine deficiency during the infection leads to immunosuppression through the increase in the populations of systemic TI-Tregs (tumor-infiltrating-like Tregs) (11) and MDSCs (12). TI-Tregs are increased by the over-production of HMW-HA. Details of these events are described in the main text.

Before the infection, comorbidity-associated glutamine deficiency (1, Fig. 4) leads to low α-KG (4, Fig. 4), and comorbidity-associated NAD^+ deficiency (2, Fig. 4) results in impaired SIRT1 activity (3, Fig. 4). These metabolic changes initiate the hyperproduction of HA and PAI-1, and the expansion of Tregs and MDSC populations. Therefore, glutamine deficiency in the high-risk groups may have previously established low levels of immune dysfunction and HA overproduction prior to infection.

After SARS-CoV-2 infection, the cells are exposed to intense oxidative stress, which consumes intracellular glutamine for the production of the antioxidant, glutathione [99]. This would further exacerbate the glutamine deficiency, potentially leading to grave metabolic dysfunction in the high-risk populations.

SARS-CoV-2 ORF6 binds the nuclear pore complex, NUP98/Rae1, and inhibits STAT1 translocation to the nucleus [100]. SARS-CoV-2 NSP1 protein blocks STAT1 phosphorylation and nuclear translocation but also efficiently blocks IFN-I induction [101]. STAT3 is compensatorily activated through the EGFR pathway [2] (5, Fig. 4). In addition, P2RY14 can activate STAT3 by the extracellular UDP-Glucose released from damaged cells [102] (6, Fig. 4).

Activated STAT3 induces the transcription of *HAS2* (7, Fig. 4) [2, 102], and the membrane-bound HAS2 enzyme is stabilized by O-GlcNAcylation as it produces HA (8, Fig. 4). In addition, SIRT1, a critical negative regulator of the HAS2 gene, is disabled (3, Fig. 4) due to low levels of its substrate NAD^+ under conditions of low glutamine and aging. Furthermore, SARS-CoV-2 significantly decreased the *SIRT1* expression in the PBMCs and lung tissue of infected patients [39, 103]. Therefore, SIRT1's anti-HAS2 activity is neutralized in two distinct manners, leading to increased HAS2 activity and higher HA levels.

The LMW-HA derived from excessive HA stimulates the production of PAI-1 (9, Fig. 4), which indirectly activates STAT3 (10, Fig. 4) [2]. Consequently, a positive feedback loop between activated STAT3 and PAI-1 is established. A hyaluronan storm is evoked by the combination of decreased negative regulation by SIRT1 and activation of HAS2 by STAT3 and O-GlcNacylation.

Another complication in severe COVID-19 is coagulopathy, in which PAI-1, as well as NETs formation (NETosis), are involved. Neutrophils are recruited to the site of infection through the innate immune response to danger signals like UDP-glucose, and they use NETosis as a tactic to combat infection. Aggregated NETs-induced vessel occlusion was observed in the lungs, glomeruli, and hepatic periportal fields in the autopsied specimens, implicating NETs aggregation in the multi-organ damage by COVID-19 [104].

SARS-CoV-2 infection exacerbates the glutamine deficiency that leads to immunosuppression through increases in the systemic $FoxP3^+$ Treg (11, Fig. 4) and MDSC populations (12, Fig. 4). Consistent with these findings, considerable associations with co-infections (other infections upon the diagnosis of COVID-19) and/or superinfection (other infections following COVID-19) have been reported in severe COVID-19 [105, 106]. Galvan-Pena et al. found

Table 2. Similarities between COVID-19 and advanced cancer.

	COVID-19	Advanced cancer
STAT3	Activated STAT3 in the infected lungs [3]	Well known for its role in tumor cell proliferation, survival, invasion and immunosuppression. STAT3 signaling also has its role in mitochondria and epigenetic regulation [190]
Glutamine levels	Decreased from plasma metabolomic analysis [8–12, 15]	In colorectal cancer, low levels were associated with an advanced cancer stage and with poor cancer-specific survival [115].
Warburg effect	Increased aerobic glycolysis in vitro [112], incidental detection of PET/CT positive infected lesions in cancer patients [113]	Well established in a variety of cancers [111]
PAI-1	Increased in the plasma [5, 6]	PAI-1 increase in the plasma and tissue of various type of human cancers [191]
Hyaluronan	Significant increase in the serum of critical cases [22, 184], prominent hyaluronan exudates in the COVID-19 lungs [20, 21]	Increase in the serum of advanced cancers [192], the degree of HA accumulation is strongly correlated with a poor prognosis in advanced cancer patients [193]
Tregs	FoxP3$^+$ Tregs with tumor-infiltration Treg signature [43]	High FoxP3$^+$ Tregs infiltration was significantly associated with shorter overall survival in the majority of solid tumors [194]
EGFR	Activated EGFR in mouse model of SARS-CoV-1 [195], in vitro model of SARS-CoV-2 [150]	A driver of tumorigenesis mostly in lung and breast cancer and in glioblastoma [196]

that FoxP3$^+$ Tregs from COVID-19 patients had a similar gene expression pattern to tumor-infiltrating Tregs (11, Fig. 4), which are known to suppress local antitumor responses [43]. Interestingly, in a murine model, tumor-infiltrating FoxP3$^+$ Tregs acquired elevated levels of CD44, an HA receptor expressed on activated and memory Tregs [107]. CD44 is stimulated by HMW-HA to promote Treg persistence and function [108]. Therefore, in the presence of HA overproduction, HMW-HA stimulates FoxP3$^+$ Tregs. Conversely, LMW-HA has proinflammatory effects, including the induction of PAI-1. In this regard, MDSCs are possibly involved in the production of LMW-HA. One report stated that tumor-infiltrating M-MDSCs express hyaluronidase 2, which degrades HMW-HA in the ECM to generate proinflammatory LMW-HA [109]. The distinct immunological natures of COVID-19-associated MDSCs and tumor-infiltrating MDSCs continue to be examined.

The metabolic environment of low glutamine is present in both comorbidities and upon SARS-CoV-2 infection itself. The enhanced metabolic dysfunction occurs in a background of immunosuppression that exacerbates the pathologies of NETosis, coagulopathy, and the hyaluronan storm.

SIMILARITIES BETWEEN SEVERE COVID-19 AND ADVANCED CANCER

Severe COVID-19 and advanced cancer share common aspects of their pathologies. Recently, Nan et al. performed a protein-protein network analysis between COVID-19 and lung cancer databases and identified 10 common hub genes associated with both diseases. The genes encoding proteins that potentially share a common hub of biological activity were *ALB (albumin), IL-8, FGF2, IL-6, INS (insulin), MMP2, MMP9, PTGS2 (Prostaglandin-Endoperoxide Synthase 2), VEGFA and STAT3* [110]. Significantly, half of these genes are downstream targets (*IL-8, MMP2, MMP9, PTGS2*, and *VEGFA)*, and three are upstream regulators (*FGF2, INS*, and *IL-6)* of STAT3. These results are consistent with our proposal that STAT3 plays a central role in the severe pathologies of COVID-19 and that commonalities exist in the pathogenesis of advanced cancer and COVID-19 [2]. One of the hallmarks in cancer is the Warburg effect, or aerobic glycolysis. It is well established in a variety of cancers [111] and recently identified in SARS-CoV-2-infected cells [112]. The widely-applied cancer detection method, the PET (positron emission tomography) scan, was developed based on the Warburg effect, and incidental detections of PET/CT positive SARS-CoV-2-infected lesions in cancer patients have been reported [113], indicating the increased glycolysis in infected cells. This Warburg effect in COVID-19 may be the result of activated STAT3, as STAT3 is involved in the Warburg effect [114] and activated in infected alveolar epithelial cells [3]. The cited similarities of COVID-19 with cancer-related biological signatures such as the Warburg effect and the involvement of PAI-1, HA, Tregs, and EGFR, are shown in Table 2. Glutamine levels linked to COVID-19 and cancer are also listed, although the range of effects are limited. However, in colorectal cancer, low levels of serum glutamine and other amino acids abnormalities were associated with advanced cancer stages and poor prognosis [115].

From these similarities, we can envisage that severe COVID-19 is a cancer-like metabolic disorder, but one that develops immediately after SARS-CoV-2 infection in high-risk individuals who suffer from at least one of multiple metabolic disorders with low glutamine levels. We propose repurposing the following drugs, which are mostly used in cancer therapy, because of the similarities in the pathophysiologies of COVID-19 and advanced cancer. As described later, serum/plasma HA is upregulated in all high-risk groups analyzed, including cancer. Here, we primarily focus on the drugs that regulate HA production. As such, the proposed drugs are categorized into two targets: I. Drugs targeting hyaluronan, II: Drugs targeting STAT3.

I. DRUGS TARGETING HYALURONAN

Anti-diabetic measures

To prevent and treat severe COVID-19, the first priority is to control glucose levels. Chen et al. reported that severe COVID-19 was associated with higher blood glucose (WMD 2.21, 95% CI:1.30–3.13, $P < 0.001$) [116], and elevated glucose levels favor SARS-CoV-2 infection in vitro [117]. Logetti et al. found evidence linking elevated glucose to each major step of the life-cycle of the virus, progression of the disease, and presentation of symptoms, after systematically retraced the steps of the SARS-CoV-2 infection [118]. However, an extreme reduction of glucose levels that leads to compensatorily activated HBP [119] should be avoided, and consultations with diabetes-specialized doctors are required.

Glutamine

Glutamine has anti-diabetic activities that help to reduce the glucose input into the uronic acid pathway and HBP. Studies have revealed that glutamine supplementation can lead to a decrease in the levels of fasting blood glucose and postprandial glucose, and an increase in insulin production [120]. Glutamine

supplementation also resulted in higher levels of glucagon-like peptide-1 (GLP-1), a gut hormone known to increase insulin levels [120].

Prophylactic glutamine supplementation is recommended to those in high-risk groups; however, glutamine supplementation after the infection should be carefully considered. Glutamine supplementation may favor SARS-CoV-2 proliferation [121], although metabolomic analyses revealed that glutamine levels are relatively low [8–12]. In addition, small clinical trials showed that glutamine reduced the severity after infection in standard risk COVID-19 patients [122, 123]; however, these preliminary findings need to be expanded to confidently assess glutamine supplementation in treating COVID-19. Compared to the beneficial effects of glutamine, its adverse side effects are minimal. Risk assessments of glutamine supplements indicated that they are safe for healthy individuals in amounts up to 14 g per day [124]. There are rare contraindications to glutamine supplementation and caution should be exercised with patients with high plasma glutamine levels or acute hepatic insufficiency, and/or renal failure [125, 126]. However, in 2013, a randomized clinical trial study, REDOXS, showed that glutamine use in critically ill patients was associated with increased mortality, with no beneficial effects [127]. Although the authors used higher doses of glutamine (giving around 1 gram/kg/day) than recommended and included patients that fulfilled the contraindication criteria for its supplementation [126, 128], these results shifted the guidelines to downgrade the use of glutamine in critically ill patients. However, glutamine supplementation has been widely used in critical care situations [126, 128]. Clearly, the effects of long term use of high-dose glutamine supplementation need to be carefully determined.

Dexamethasone

Dexamethasone showed some success in treating COVID-19 [129]. This empirical effect can be attributed to its glutamine synthetase promoting activity [130], and/or inhibition of HAS2 [131]. However, its significant immunosuppressive activity could compound the already existing immunosuppressed state in severe COVID-19, thus posing a higher risk of secondary infections and/or reactivation of quiescent infections such as tuberculosis [132].

4-MU (4-Methylumbelliferone)

Besides dexamethasone, 4-MU also has anti-HAS2 activity [133, 134] and therefore inhibits the production of HA. Last year, Shi et al. proposed the application of 4-MU to treat the hyaluronan storm in COVID-19 [17]. Similar proposals were made by other groups after identifying abundant HA in the infected alveoli of severe COVID-19 cases [20, 21]. 4-MU has been used for more than 20 years in humans to treat biliary spasms in France, Germany, Japan, and other countries [135]. Recently, the involvement of HA in cancer progression has become increasingly appreciated (Table 2) and 4-MU has become a promising anti-cancer agent [135]. 4-MU is a well-tolerated oral drug. and in one clinical trial, prolonged (3 months) oral doses as high as 2400 mg/day were safely administered [135]. Recently, a clinical trial using high doses (up to 3600 mg/day) of 4-MU to block HA production has begun [136]. Positive results of this trial will justify the use of 4-MU in COVID-19.

NAD^+ boosting drugs (Niacin, NR, NMN)

Increasing NAD^+ levels with NAD^+ boosting agents in high-risk people could be associated with a range of beneficial effects, and the application of NAD^+ boosting drugs in COVID-19 has been proposed by several groups [137, 138]. Using a mouse-adapted SARS-CoV-2 model, Jiang et al. reported that a global gene expression analysis of the infected mouse lungs revealed the dysregulation of genes associated with NAD^+ metabolism, correlating with the results from COVID-19 patients [139]. They found that the pneumonia phenotypes, including excessive inflammatory cell infiltration and embolization in SARS-CoV-2-infected murine lungs, were significantly rescued with an intraperitoneal injection of NAD^+ [139]. In addition, recently developed first-in-class drug for diabetes, imeglimin, has been reported to enhance glucose-stimulated ATP generation and induce the synthesis of NAD^+ [140]. One concern is that during the infection, NAD^+ boosters cannot completely restore SIRT1's anti-HAS2 activity, as the expression of SIRT1 is critically impaired in severe COVID-19 [39, 103]. Therefore, NAD^+ boosters would be effective for the prevention of COVID-19 or immediately after the infection with SARS-CoV-2.

Vitamin D

1,25 Dihydroxyvitamin D (vitamin D) reportedly inhibits HAS2 expression [141]. However, it also suppresses glutamine metabolism [142], indicating a possible reduction of α-KG that may result in high $FoxP3^+$ Treg differentiation.

II. DRUGS TARGETING STAT3

STAT1 activators

The SARS-CoV-2 virus has mechanisms to inhibit the activity of STAT1, which initiates a cascade of deleterious events, including the activation of STAT3 [2]. Therefore, STAT1 activators will have the effect of inhibiting STAT3. Like interferons, retinoids increase STAT1 expression, up-regulate its phosphorylation, and enhance its translocation to the nucleus [143]. Retinoids inhibit infections by measles, norovirus, and HCV through IFN-I signaling in several ways [144]. A recent report showed that the retinoid inducible gene-I (RIG-I) had dramatic antiviral activity in an in vitro model of SARS-CoV-2 infection [145]. It is important to carefully modulate IFN inducing signaling in COVID-19 because it may worsen the disease in the late stages of infection [2].

STAT3 inhibitors

Besides the use of the STAT3 targeting drugs, Danvatirsen and Napabucasin [2], the regulation of the upstream signaling molecules is also important. Wang et al. reported that, in A549 cells, decreased NAD^+ inactivated SIRT1, resulting in increased STAT3 acetylation and phosphorylation, and STAT3 activation. Repletion of nicotinamide or nicotinic acid inactivated STAT3 [146]. However, as mentioned above, we cannot expect the full restoration of SIRT1 activity by NAD^+ boosters, as SIRT1 expression is inhibited by SARS-CoV-2 infection. We should also keep in mind that glutamine has been reported as a STAT3 activator in some cancer cell lines [84, 147], whereas others found that glutamine has STAT3 inhibiting activity [83, 148].

EGFR inhibitors

EGFR signaling is upregulated in SARS-CoV-2-infected cells in vitro [149, 150], and we believe that this signaling is responsible for maintaining the STAT3 activity in severe COVID-19 [2]. Repurposing drugs targeting EGFR, such as Erlotinib, Gefitinib, Cetuximab, and others, are already used in some cancer therapies. The major concern is that these treatments often cause severe interstitial pneumonia that resembles pneumonia in COVID-19, and will thus make a differential diagnosis more difficult [151].

Immune checkpoint inhibitors (ICIs)

A hallmark of COVID-19 is lymphocytopenia, and efforts have been made to restore T-cell competency by ICIs. In fact, immune checkpoint proteins may be connected to other types of immunosuppression seen in COVID-19. Glutamine deficiency increases the expression of PD-L1 [152], which is known to be activated by STAT3 [153], and biopsy results indicated increased PD-L1 expression in the infected lung tissue of COVID-19 patients [3]. Several groups are exploring anti-PD-L1 and anti-CTLA-4

antibodies, alone or in combination with anti-IL-6R, and clinical trials are underway [154].

In this review, we have focused on the major risk factors of COVID-19 that are: aging, hypertension, cardiovascular disease, diabetes, and obesity [1]. These major risk factors generally fit the profile as described in Table 1. However, there are many other risk factors such as chronic lung disease including COPD (chronic obstructive pulmonary disease), interstitial pneumonia, asthma, and CF (cystic fibrosis), chronic kidney disease, cerebrovascular disease (e.g., stroke), chronic liver disease, and more [1, 155]. The glutamine levels in these risk-groups of COVID-19 need to be properly delineated, as most of those studies have conflicting or meager information regarding their plasma levels of glutamine. HA levels, on the other hand, are consistently elevated in plasma/serum of risk groups such as chronic lung disease (COPD [156], interstitial pneumonia [157], asthma [158]), chronic kidney disease [159], stroke [160, 161], and chronic liver disease [162]. CF exhibited a normal level of serum HA [163], however, CF sputum had 20-fold excess of HA than healthy controls [21]. Similarly, asthma [164], and COPD [165] had elevated levels of sputum HA. Therefore, irrespective of glutamine levels, any disease leading to increased HA production may have a predisposition to severe COVID-19. Thorough and uniform analyses of glutamine and HA regulation in all putative risk groups of COVID-19 are necessary to ascertain the limitations of this metabolic profile.

The vast majority of SARS-CoV-2 infections result in mild to oppressive common cold-like symptoms that resolve in weeks without long-term effects. Unfortunately, the virus is rapidly mutating into more contagious variants and even a small percentage of the infected leads to an unacceptably large number of fatalities. We may have identified a common mechanism in high-risk groups that confers more susceptibility to severe COVID-19. We suggest a simple nutritional supplementation that could neutralize this susceptibility and restrict the disease to common cold-like symptoms. Glutamine deficiency and HA overproduction appear to be the primary metabolic commonalities that not only are shared amongst the COVID-19 comorbidities, but also contribute to the immunological dysfunction that is exacerbated by SARS-CoV-2 infection. While it is presently unclear whether glutamine supplementation post-infection leads to an overall positive outcome, addressing glutamine deficiency prophylactically for those in high-risk groups is a safe and simple strategy for their protection in the era of COVID-19.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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