Amino Acid Metabolism in SARS-CoV2-Infected Patients

Subjects: Biochemistry & Molecular Biology

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The immune response to infectious diseases is directly influenced by metabolic activities. COVID-19 is a disease that affects the entire body and can significantly impact cellular metabolism. The most significant groups of metabolites include amino acids, which act as precursors for various major cellular components, such as proteins and nucleobases. Among the amino acids that make up proteins, nine cannot be synthesized from other compounds and must be obtained from food; these are also essential amino acids. The human body can use amino acids ingested from food to synthesize proteins and other biomolecules, but they can also be oxidized to urea and carbon dioxide to produce energy through oxidative pathways. Their involvement in synthesizing proteins and metabolic regulators makes them an excellent marker for diseases. Their chemical properties and compositions not only affect the structure and function of proteins, but also control the metabolic pathways associated with illness. Furthermore, amino acids ensure the immune response against diseases by being used in the activation of T and B lymphocytes, natural killer cells, and macrophages; in the cellular redox status, gene expression, and lymphocyte proliferation; and in the production of antibodies, cytokines, lymphokines, and cytotoxic substances.

SARS-CoV2 COVID-19 cell ELISA metabolomics

1. Methionine Cycle

Methionine may modulate the assembly of SARS-CoV2 by interfering with the mechanism of RNA polymerase: SARS-CoV2 RNA-dependent RNA polymerase (RdRp) is used by SARS-CoV2 to replicate and transcribe genes, and methionine has the potential to disassemble SARS-CoV2 RdRp, which could be used to develop vaccines and therapies against COVID-19 [1]. The metabolism of a cell infected by the SARS-CoV2 virus is reshaped to fulfill the need for massive viral RNA synthesis, which requires de novo purine biosynthesis involving folate and one-carbon metabolism, suggesting that SARS-CoV2 takes over folate and one-carbon pathways for its intracellular replication [2].

SARS-CoV2 triggers antibodies against the spike S1 antigen, which is measurable in PBMCs starting 2 months after infection via in vitro assays [3]. In vitro cultured and unstimulated PBMCs had a significant alteration of metabolites related to the methylation cycle, as evidenced by the results of metabolomic analysis. S-adenosylmethionine (SAM) is a molecule that is produced in the body, consisting of the essential amino acids methionine and adenosine triphosphate. The molecule S-adenosylmethionine (SAM) is the methyl group donor [4]; under normal conditions, more than 90% of the total amount of SAM in mammalian cells is utilized for methylation

reactions by AdoMet-dependent methyltransferases, during which SAM gives up its methyl group to various acceptors, including nucleic acids [5] (DNA, RNA), which play a crucial role in cell metabolism. The s-adenosyl-L-homocysteine (SAH), which is produced as a by-product of SAM-dependent methyl transfer reactions, is highly effective in inhibiting AdoMet-dependent methyltransferases and is broken down by S-adenosyl-L-homocysteine hydrolase into homocysteine and adenosine. In mammalian cells, by using 5-methyltetrahydrofolate cofactor (5-MTHF), homocysteine produced by this reaction can be remethylated to methionine and, thus, retained in the methylation cycle. Methionine is finally transformed into an SAM molecule by methionine adenosyltransferase (MAT). As a positive single-stranded RNA virus, SARS-CoV2 uses its genomic RNA both for translation and replication [6]. For proper RNA replication and translation, the cap of the viral RNA must be methylated [7]. It appears that two methylation sites are present in the viral RNA of coronaviruses; one site is required for replication and translation, and the other site may serve to allow the viral RNA to escape the host intracellular immune system, which would degrade the RNA without cap methylation [8]. The RNA cap of SARS-CoV2 is made up of a 7-methylguanosine attached to the 5′ nucleotide of the viral RNA through a triphosphate bridge. The cap is methylated at the N7 site of the guanosine, using SAM as a methyl donor, forming m7GpppN-RNA, mediated by NSP14 [9]. Then, by utilizing NSP16, the SAM-dependent 2′-O-methyltransferase attaches a methyl group to the ribose 2′-O site of the nucleotide to generate the cap (m7GpppNm-RNA) [10]. The RNA cap is involved in multiple aspects of gene expression, including boosting RNA stability, splicing, nucleocytoplasmic transport, and initiating translation, which is essential for viral RNA replication [11]. Therefore, S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) are indicators of global transmethylation and may play an important role as markers of COVID-19 severity. The risk of lung injury in patients with COVID-19 can be determined by the increased level of SAM, which is a marker of viral RNA capping's necessity for its life cycle [12].

The ratio of SAM to SAH determines whether methyltransferase reactions can occur. The higher the ratio, the greater the methylation potential [13]; in contrast, if the ratio of SAM to SAH is low, methyltransferase reactions do not occur and coronavirus RNA is not methylated [14]. As a result, the virus cannot replicate and the viral genomes present in the cell are susceptible to degradation [6].

In this context, inhibition of the enzyme AdoHcy hydrolase may be used as a therapy against viral infections, as it indirectly limits the bioavailability of SAM and the methylation of the 5′-cap of the viral messenger RNA, as has already been found in the Ebola virus and the African swine fever virus [15][16]. At the same time, the strong increase in AdoHcy in IgGm+ PBMC suggests an inhibition of s-adenosyl-L-homocysteine hydrolase and, consequently, an imbalance in the SAM/AdoHcy ratio. Blocking viral mRNA caps could be a preliminary step in the development of antiviral therapies [3].

2. Arginine Metabolism

Arginine (Arg) is involved in many different biological processes and recent reports indicate that it could also play a crucial role in COVID-19 [17]. The amount of arginine available in the body has a significant impact on the normal immune system. Arginase-1 (Arg1), which has a pivotal role in immune cells, can be expressed in most of the myeloid cells, e.g., neutrophils and macrophages, and it is well known that it is an essential component of certain

granulocyte subsets and can be released either locally or systematically during an immune response. The suppression of antiviral immune responses is associated with Arg1 [18]. Additionally, given the beneficial effects of arginine to significantly improve endothelial function, the control of long-term COVID-19 could be improved with arginine supplementation, as chronic inflammation and endothelial dysfunction are fundamental in COVID-19 progression [19][20]. Arg is a non-essential amino acid that is used by healthy humans to synthesize proteins and the urea cycle, and it is a precursor for various molecules, such as citrulline and nitric oxide (NO), which is a bioactive molecule with immunological and antimicrobial cytotoxic activity [21]. Arg can be provided in the diet or formed in certain cells through the complete or partial urea cycle. The synthesis of arginine as part of the urea cycle begins in the mitochondria, where carbamoyl phosphate condenses with ornithine through the action of ornithine transcarbamoylase to form citrulline, which leaves the mitochondria. In the cytosol, argininosuccinate synthase adds aspartate to citrulline, producing argininosuccinate, AMP, and pyrophosphate. The cleavage of argininosuccinate by argininosuccinate lyase yields arginine and fumarate. Arginine is then hydrolyzed by arginase to the final product, urea, and, simultaneously, ornithine is regenerated to re-enter the mitochondrion in exchange for citrulline via the ORNT1 transporter [22]. In addition, arginine can be transported from the extracellular space via the cationic amino acid transporter (CAT) and regenerated from citrulline, a product of nitric oxide synthase (eNOS), resulting in the citrulline–NO cycle in which nitric oxide is generated (NO) [23]. When arginase 1 (Arg1) degrades arginine in the urea cycle, it produces both urea and ornithine. When eNOS degrades it, there is a significant amount of NO and citrulline in the products [24]. NO is a substance produced by macrophages that are activated by either cytokines, microbial compounds, or both and is used to inhibit tumor growth both in vitro and in vivo [25]. In patients with IgG memory, arginine depletion via the urea cycle has become a substrate for the production of NO by iNOS, which plays a role in the first innate inflammatory immune response to viral infections. The production of NO is a characteristic of true cells of the immune system (dendritic cells, NK cells, mast cells, and phagocytic cells including monocytes, macrophages, microglia, Kupffer cells, eosinophils, and neutrophils) [26] and manages a variety of processes. The differentiation and proliferation of immune cells, proliferation and cell death, the production of cytokines and other soluble mediators, the expression of costimulatory and adhesion molecules, and the synthesis and deposition of extracellular matrix components are among these processes [27][28]. The progression of COVID-19 infection reduces the formation of NO, as infections lead to an increase in inflammatory cytokines in the peripheral circulation and trigger a strong cytokine storm [29]. In addition, inappropriately intense inflammation contributes to an imbalance of reactive oxygen species (ROS), leading to oxidative stress [30]. In the serum of patients with severe COVID-19, inflammatory cytokines and chemokines are found to promote excessive ROS production in mitochondria, ultimately leading to oxidative damage and cell death [31]. ROS also alter vascular tone by increasing intracellular calcium concentration and decreasing NO bioavailability [32]. Thus, NO has non-specific antiviral effects in various viral diseases and has been implicated in SARS-CoV2 virus replication [33]. In particular, Akaberi et al. confirmed that NO, which is derived from the NO-donor S-nitroso-N-acetylpenicillamine (SNAP), can delay or completely prevent the development of the viral cytopathic effect of SARS-CoV2 in treated cells and that the observed protective effect correlates with the degree of inhibition of viral replication [34]. In addition, inhaled NO can be used for COVID-19 prophylaxis and treatment in many phases, including the prevention of viral entry, symptom relief in critically ill patients, and supportive care in mechanically ventilated patients [35]. In the IgGm+ sample, activation of the urea cycle release of NO confirms that

successful treatment and prevention options can be developed by manipulating this pathway. In addition to NO, arginine also plays a critical role in COVID-19 [17]. In COVID-19 patients, there is a high ratio of L-arginine to ornithine, which suggests a higher level of arginase activity [36]. In another study, it was found that the severity of COVID-19 was inversely correlated with plasmatic L-arginine levels [37]. In fact, a decrease in L-arginine bioavailability has been shown to lead to decreased T-cell response and function, and thus increased susceptibility to infection [38]. It is probable that the restoration of arginase (Arg1) is behind the accumulation of this amino acid in IgGm+. Arg1 has been found to be present in the cytoplasm and has a high expression level in the liver. In addition to its metabolic role in the hepatic urea cycle, it could also affect immune responses. Indeed, in humans, arginase is detected in peripheral blood mononuclear cells (PBMCs), and several studies show that Arg1 inhibits immunity to intracellular pathogens and suppresses T-cell-mediated inflammatory damage. In COVID-19 patients, an increase in Arg1 expression may be linked to an increase in viral load. Since Arg1 can limit the bioavailability of l-arginine, the inhibition of Arg1 can drive the recycling of l-citrulline to generate l-arginine for the production of NO, which contributes to the development of antiviral immunity in IgGm+.

3. Tryptophan Metabolism

According to Hikari Takeshita and Koichi Yamamoto, clinical studies have suggested that the kynurenine pathway of tryptophan metabolism is selectively enhanced in patients with severe COVID-19 [39]. Additionally, a study conducted by Gardinassi et al. revealed that inflammatory networks were heavily involved and genes implicated in tryptophan metabolism were upregulated in COVID-19 patients [40]. Tryptophan and its metabolites, including melatonin, can enhance the immune system and decrease inflammation in a variety of conditions [41]. The only way for humans to consume tryptophan (Trp) is through the diet, as it is an essential amino acid. Even though a small percentage of free Trp is employed for protein synthesis and the production of neurotransmitters like serotonin, over 95% of free Trp is used as a substrate for the kynurenine pathway of Trp degradation, which results in the generation of numerous bioactive metabolites in the immune response. The rate-limiting stage of the Kyn pathway involves the enzymatic transformation of Trp into N-formylkynurenine (NFK) by indoleamine 2,3-dioxygenase 1 (IDO1), IDO2, and tryptophan 2,3-dioxygenase (TDO) [42]. NFK is rapidly metabolized by kynurenine formamidase to L-kinurenine (L-Kyn). L-Kyn is an important metabolite that has potent immunoregulatory functions through its binding to the aryl hydrocarbon receptor (AhR) [43]. AhR binds to its response element XRE (or DRE) in the promoter of IL -6, thereby maintaining endogenous production of IL -6 and enhancing the inflammatory state [44]. In an inflammatory context sparked by cytokines such as interferon-γ, tumor necrosis factor α, and pathogenic infections such as influenza A virus or SARS-CoV2 infection [45], the activation of IDO-1 leads to the production of Kyn. The activation of Ahr by Kyn [46] regulates the immune response by suppressing the activity of natural killer cells, dendritic cells, monocytes, and macrophages, blocking the proliferation of T cells and promoting the proliferation of regulatory T cells [47]. In a recent study of COVID-19, some authors [40] reported increased activity of the tryptophan metabolic pathway, as evidenced by decreased TRP, increased KYN levels, and an increased KYN/TRP ratio [48][49], reflecting the activity of IDO [50]: acute inflammation rapidly triggers an “inflammatory storm” maintained mainly by the secretion of inflammatory cytokines, of which IL -6 is the most potent [51], enhancing the initial proinflammatory cytokine phase and suppressing the endogenous antiviral response. Several studies

increasingly demonstrate that tryptophan and its metabolites, including melatonin, can reduce inflammatory responses and enhance the immune system [52][53]. Therefore, Kyn and other metabolites of the Kyn pathway have been proposed as potential biomarkers for COVID-19 [54]. In addition, IDO inhibitors may enhance the antiviral activity of COVID-19 [49]. In the post-infection stages (>60 days), when immune memory is responsible for protection against SARS-CoV2 reinfection, the BMC showed increased tryptophan levels, almost unchanged serotonin levels, and greatly decreased indole pyruvate levels, supporting the hypothesis of the restoration of kynurenine metabolism by attenuating the activity of IDO.

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