

Coronavirus disease 2019 (COVID - 19) update: From metabolic reprogramming to immunometabolism

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REVIEW

Coronavirus disease 2019 (COVID-19) update: From metabolic reprogramming to immunometabolism

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Abstract

The field of immunometabolism investigates and describes the effects of metabolic rewiring in immune cells throughout activation and the fates of these cells. Recently, it has been appreciated that immunometabolism plays an essential role in the progression of viral infections, cancer, and autoimmune diseases. Regarding COVID-19, the aberrant immune response underlying the progression of diseases establishes two major respiratory pathologies, including acute respiratory distress syndrome (ARDS) or pneumonia-induced acute lung injury (ALI). Both innate and adaptive immunity (T cell-based) were impaired in the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Current findings have deciphered that macrophages (innate immune cells) are involved in the inflammatory response seen in COVID-19. It has been demonstrated that immune system cells can change metabolic reprogramming in some conditions, including autoimmune diseases,

cancer, and infectious disease, including COVID-19. The growing findings on metabolic reprogramming in COVID-19 allow an exploration of metabolites with immunomodulatory properties as future therapies to combat this hyperinflammatory response. The elucidation of the exact role and mechanism underlying this metabolic reprogramming in immune cells could help apply more precise approaches to initial diagnosis, prognosis, and in-hospital therapy. This report discusses the latest findings from COVID-19 on host metabolic reprogramming and immunometabolic responses.

KEYWORDS

COVID-19, immune reaction, immunometabolism, inflammation, SARS-CoV2

1 | INTRODUCTION

Recently, the field of immunometabolism has emerged as an essential process in the fates of immune response (adaptive and innate) throughout infection, cancer, and autoimmune diseases.¹⁻⁴ Several recent comprehensive investigations have emphasized the essential importance of cellular metabolism in immunity.^{3,5,6} Six important and interrelated metabolic processes mediate the immune response: glycolysis, fatty acid oxidation (FAO), the tricarboxylic acid cycle (TCA), as well recognized as the Krebs cycle, the pentose phosphate pathway (PPP), and the fatty acid synthesis, and amino acid synthesis pathway.^{7,8} Depending on cell type, development state, stimulation circumstances, and milieu, cells of the immune system predominantly adopt one or more metabolic processes.⁹⁻¹³ For example, activated T cells, M1 macrophages (pro-inflammatory phenotype), and neutrophils mainly depend on glycolysis.⁹⁻¹³

In addition, M2 macrophages (anti-inflammatory phenotype) and resting T cells are reliant on oxidative phosphorylation (OXPHOS).¹¹ Since shifting metabolic processes, also known as metabolic reprogramming, modulate the activity of immune cells activity¹⁴; hence, to escape antiviral host defense, many viruses may target cell metabolism in immune cells. It has been found several viral infections, such as the human immunodeficiency virus (HIV), respiratory syncytial virus (RSV), influenza A virus (IVA) (H1N1), Hantaan virus, dengue virus (DENV), cytomegalovirus, and others, can reprogram metabolic processes in immune cells to their benefit.¹⁵⁻¹⁸

The novel respiratory pathogen that emerged in Wuhan, China, in December 2019 is called SARS-CoV-2.¹⁹⁻²³ The SARS-CoV-2 pandemic had a destructive impact on the national healthcare system, mainly affected the world economy, and imposed much death on humanity to date.²⁴⁻²⁸ It has been recently found that after infection with SARS-CoV-2, this virus may alter the metabolism of immune cells.²⁹⁻³¹ The immune system is influential in predicting coronavirus disease 2019 (COVID-19) severity and establishing acute lung injury (ALI), or acute respiratory distress syndrome (ARDS).^{19,26,32} The recent evidence revealed that both arms of the immune system, including the innate and adaptive immune response (T cell-based), were dysregulated upon SARS-CoV-2 infection.^{19,28,32} COVID-19

patients, on the other hand, generate protective antibodies (Abs) against SARS-CoV-2.³⁰ The development of an immune response to a pathogen necessitates the generation of energy production through the immunometabolism procedure.³⁰ Immunometabolic reprogramming represents immune cells' metabolic state transition from homeostasis to a pro-inflammatory or infectious milieu.

Viruses may have developed different approaches to modify cellular metabolism for propagation and survival according to their absolute dependence on host cells for replication.^{7,33-35} Whenever a virus infects a host, it is known that particular host metabolic processes, such as glucose, fatty acid, and nucleotide metabolism, are disrupted.³⁵ Every viral species is predicted to affect the host cell to undergo a distinct metabolic reprogramming.³⁵ The transcriptome information collected by the host in reaction to COVID19 contributes to deciphering the alterations in gene expression that occur.³⁶ In reaction to COVID19, it has already been demonstrated that higher inflammatory cytokine secretion and decreased innate antiviral resistance are present in diverse hosts.³⁷⁻³⁹ Particular cell lines have also exhibited autophagic and mitochondrial malfunction, respectively.³⁸ For COVID19, a thorough perception of metabolic reprogramming in the host is still unknown. Hence, we will thus describe recent findings on the function of host metabolic reprogramming and immunometabolic responses throughout COVID-19 in the present review.

2 | OVERVIEW OF HOST METABOLIC REPROGRAMMING DURING VIRAL INFECTIONS

Many of the host's critical carbon metabolic processes have also been modified by DNA and RNA viruses, including glycolysis, pentose phosphate activities, and the generation of nucleotides, amino acids, and lipids.^{40,41} While some viruses enhance the requirement for vital nutrient compounds and glutamine and combine relevant metabolic pathways for anabolism, the precise metabolic alterations induced by specific viruses are frequently situational.^{40,41} They thus can vary slightly even within the same virus family or depend solely on the type of cell infected by the host.⁴⁰

Viruses are one of the biological entities that significantly restructure the host cell's metabolic process to survive their life cycle, naming them "metabolic engineers."⁴² Similarities and variations exist in various viruses regarding host cell invasion, proliferation, and spread.⁴³ Viruses may also attack the host's immune system, potentially directly or indirectly. The latter is particularly visible in persistent viral diseases induced by the herpes viridae family, which escape the human immune response by triggering the kynurenine pathway.⁴⁴ A natural reaction to infections, including the degradation of extracellular tryptophan to restrict virus growth, causes T cell depletion over time and the establishment of regulatory T cells (immunosuppressive).⁴⁵ Disruptions in the host metabolic process regulation, or rather the virus's reprogramming, are currently offering insight into the pathogenesis of a viral infection.⁴⁵ Beyond infections and severe disease recovery, there is an increasing agreement that the prolonged metabolic expenditures sustained by the host in recovered individuals or postrecovery are significant.⁴⁶

Some viral proteins employ host metabolic activities to induce dysregulation in various cellular pathways, increasing cancer risk.⁴³ For example, the human papillomavirus 16 E6 protein inhibited hypoxia-inducing factor- α (HIF- α) degradation and thereby enhanced glycolysis in cells infected with this virus.⁴⁷ In Vero cells, it has been found that Enterovirus EV71 can increase glutamine metabolism, whereas pharmaceutical suppression of pyrimidine metabolism enzymes reduced viral proliferation.⁴⁸ As indicated by Kesphol et al.,⁴⁹ in vitro and in vivo infection with Coxsackie B3, host protection strategies cause resistance to the viral invasion, Protein modification with ISG15 (ISGylation) of a 15 kD interferon (IFN)-stimulated gene resulted in hepatic gluconeogenesis and induction of antiviral state via releasing IFN-induced proteins. Thaker et al.⁴⁰ thoroughly examined the regulation of host cellular metabolism by various viral proteins and emphasized the critical necessity to uncover specific proteins to better comprehend virus-induced metabolic reprogramming.

Many viruses are well-acknowledged for their capacity to modify host metabolic processes for their longevity and replication. This is supported by the results of Rayfield et al.,⁵⁰ who in the early 1970s experimented on a group of healthy men by infecting them with a virus (self-limiting) that induces mild illness and observes the results. According to observations of viral metabolic regulation, higher glucose absorption resulted in the increased viral proliferation and enhanced redirection of glucose via the hexosamine pathway, respectively.⁵¹ This pathway is well recognized for changing proteins that increase inflammation posttranslationally. For example, the IAV employs the hexosamine pathway to stimulate the expression of pro-inflammatory genes through the stimulation of IFN regulatory factor 5 (IRF5), which causes the severity of the disease.⁵²

Moreover, to alter glucose metabolism, viruses also control the production and degradation of lipids, which is essential for their proliferation and survival.⁵³ Hepatitis C virus (HCV) can cause liver injury; recently, it has been found that dodecenoyl coenzyme A-delta isomerase, which is a mitochondrial enzyme involved in FAO, is a significant target of this virus, so blocking this enzyme

pharmacologically inhibited viral replication in hepatoma cells.⁵⁴ The DENV showed that virus-induced lipid anabolic modulation was crucial for multiplication and virion production in infected cells.⁵⁵ The results of host metabolism disruption, particularly lipids perturbation, are recognized in conjunction with immunological responses, such as phagocytes and T cells responding to viral infections, which will be explored in the next section.

Changes in host lipid signaling and metabolism include three stages: viral entrance, complicated replication assembly, and the emergence of additional virions to maintain the infectious disease.^{43,56} Sterol regulatory element-binding protein (SREBP)1a, 1c, and 2 are members of the SREBP family, which transcriptionally regulates lipid biosynthesis in response to increased metabolic requirements.⁵⁷ SREBPs' downstream targets include genes involved in fatty acid biosynthesis (acetyl CoA carboxylase) and cholesterol production (3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase) through the mevalonate pathway.⁵⁷ Because of the several activities of cholesterol (including immunological control, cholesterol production, and other lipids), it may be a target for viral exploitation. For example, the cholesterol metabolite 25 hydroxycholesterols has been shown to have antiviral activity in macrophages through the signal transducer, and activator of transcription 1 (STAT1) facilitated synthesis of type 1 IFN.⁵⁸⁻⁶⁰ Substantial evidence suggests viruses influencing host lipid metabolism, including genes' activation, are implicated in lipid synthesis driven by oxidative stress, as shown with HCV-induced hepatic steatosis.⁶¹

Many efforts have been undertaken to identify important objectives in host lipid metabolism that numerous viruses exploit.⁶² Statins, for example, are a prevalent type of medication recommended to decrease blood cholesterol in high-risk individuals.⁶³ Cholesterol is widely recognized to have an essential function in the membrane trafficking of the viral protein (including hemagglutinin) and the proliferation of IAV.^{64,65} In recent years, there has been increased interest in the metabolic profiling of lipids influenced by viruses. A notable example is the nontargeted lipidomic study of plasma and lung tissue from mice infected with RSV, which showed differential management of lipids, including surfactants of the lung tissue, plasmalogens, and acylcarnitine that aggravate inflammation of the airways.⁶⁶ In vitro screening of regulators implicated in viral infection and lipid metabolism revealed that cells infected with IAV and Middle Eastern respiratory syndrome (MERS) experience significant alterations in lipid metabolism.⁶¹ Further investigation showed that the retinoic acid receptor- α agonist, 4[(5,6,7,8 tetrahydro 5,5,8,8 tetramethyl 2 naphthalenyl) carboxamido]benzoic acid (AM580), exhibited a high antiviral activity that reduced mouse death rates by blocking SREBP activation, and modifications in lipid metabolism significantly lowered DENV viral load, indicating a potential treatment strategy in viral illnesses by modulating host lipid machinery.^{61,67}

Iron is thought to be involved in the cellular metabolism of all living organisms, such as viruses and their mammalian hosts.⁴³ A differing class of mediators tightly regulates the host's concentration of iron is circulating, including both unbound and heme-bound forms,

in a way that mitigates oxidative injury (iron-mediated) and postpones the migration and development of pathogenic organisms both extracellularly (as in blood that harbor's specific parasites and bacteria) and inside cells (as fundamentally observed with viruses).⁴³ Although most intrinsic iron is recycled through the formation and destruction of erythrocytes, cells also have complicated systems for iron storage.⁴³ Inflammation is one of the metabolic processes known to modulate cellular iron content in response to tissue damage and infections. Hepatocytes in the liver alter the synthesis of the peptide hormone hepcidin in response to pathogen infection.⁴³ In contrast to those infected with hepatitis B or HCV, HIV-1 demonstrated distinct hepcidin and iron concentration profiles in the plasma of human volunteers in both the phases of illness (acute and chronic) who were taking antiretroviral therapy or other treatments.⁶⁸ This emphasizes the importance of understanding viral processes at various phases of infection, resulting in diverse consequences.

Autophagy is the controlled process of "self-eating in the cell, and its relevance in regulating cellular equilibrium, including its disruption in numerous illnesses, is well documented".⁴³ The autophagic pathway is crucial in developing antiviral defenses, although viruses can escape destruction in autophagosomes and continue to infect cells.⁶⁹ Recognition is one of the first stages after viral entrance into a vulnerable host cell, proceeded by virus pickup and processing.⁴³ Pathogen recognition receptors (PRRs), including the toll-like receptors (TLRs), notably TLR3 and TLR7, and the retinoic acid-inducible gene 1-like receptors (RLRs) for processing via autophagy, promote viral uptake.⁷⁰⁻⁷² Although autophagy is essential in cellular adaptability to chronic metabolic stress, including food deprivation, multiple studies show that autophagy can minimize viral injury and help in host healing. The attachment of the herpes simplex virus type 1 (HSV1) coding the ICP34.5 protein (a neurovirulence protein) to the Beclin1 protein suppressed autophagy, which in turn reduced signaling via the protein kinase R (PKR) axis dedicated to developing antiviral defenses.⁷³ The modulation of the PKR pathway is a remarkable example of autophagy-mediated changes in host cellular metabolism in response to pathogens, including viral infection. In cell lines subjected to the HSV1 virus, translational inhibition of the host protein machinery by phosphorylation of the eukaryotic translation initiation factor 2 identifies the involved factors.⁷⁴

3 | COVID-19 PATHOGENESIS

Previous research suggests that SARS may be divided into three stages: viral replication, immunological hyperactivity, and respiratory damage.^{75,76} The viremia episode, acute phase, and recovery period of COVID-19 have also been suggested as clinical stages.^{56,77} It is usually assumed that the disease progresses through the subsequent steps: entry and proliferation of viruses, dysregulation of immune responses, multiple organ failure, and healing.^{23,28,78,79} The virus initially enters host cells, where it multiplies, assembles, and is transported extracellularly to target cells, triggering direct harm and death of parenchymal cells such as alveolar epithelial cells.⁷⁶ Simultaneously, a significant number of the pathogen-associated molecular pattern (PAMP) and

damage-associated molecular pattern (DAMP) compounds are set to release to boost the innate immunity, elicit inflammatory processes, and secrete considerable amounts of inflammatory mediators, chemokines, free radicals, and proteases, resulting in ARDS, sepsis, and multiple organ dysfunction syndromes (MODS) pathological outcomes of COVID-19-induced pneumonia represent those shown in SARS-CoV and MERS-CoV infections.^{31,32,80,81} Following the first critical phase, the inflammatory reaction progressively resolves, the injured organ steadily recovers, and some of the injured organs progress to the fibrosis and chronic stages, including chronic critical disease, immunosuppression, catabolic syndrome, and chronic inflammation.⁷⁶ Figure 1 displays the immunopathogenesis of COVID-19.

SARS-CoV-2 adheres to the outside of the epithelial barrier of the oral cavity, the mucosal surfaces of the conjunctiva, or the optic canal after viral transmission.^{41,83} The angiotensin-converting enzyme 2 (ACE2) is found in a variety of human cells, such as type II alveolar cells (AT2), oral, gastrointestinal (GI), and ileal epithelium, cardiac cells, kidney proximal tubule cells, and bladder urothelial cells, is thought to have a role in the internalization of SARS-CoV-2.^{84,85} The spike (S) protein of SARS-CoV2 is split at the S1/S2 location by a cellular enzyme called furin, and this degradation is required for viral entry into lung cells.⁸⁶ Transmembrane serine protease 2 (TMPRSS2) primes the stimulated S protein before attaching it to ACE2 ligands and entering the host cells. The genetic sequence of SARS-CoV-2 is analogous to that of SARS-CoV, as is the architecture of the S protein of both viruses highly similar.

Data demonstrated that ACE 2/angiotensin (1-7) plays a vital role in inflammation and signaling pathways that contribute to tissue damage.⁸⁷ ACE 2's physiological function is to degrade angiotensin II and produce angiotensin (1-7), which counteracts ACE II.⁸⁸ Upon viral replication in the host cell, ACE 2 decreased expression reduces angiotensin II degradation into angiotensin (1-7). A disruption in the ACE 2/angiotensin (1-7) axis reflects certain clinical aspects of COVID-19, including hypokalemia, vasoconstriction, and ARDS establishment.^{89,90} Notably, the degree of ACE 2 production in the GI, genitourinary (testis) systems, genitourinary, endocrine (pancreas), and cardiovascular is far greater than that in the virus's primary target, the respiratory system.⁸⁴ As a result, there is no relationship between viral infection rates and ACE 2 expression. Preliminary data shows that ACE 2 expression is lower in females than in males, which might explain why men have a higher incidence of COVID-19 cases.^{91,92} Furthermore, researchers at the Mount Sinai Health System in New York discovered that the production of ACE 2 is age-dependent.⁹³

The inflammatory mediators, including interleukin (IL)-2, IL-6, IL-7, IL-10, tumor necrosis factor α (TNF- α), inducible protein (IP-10), macrophage inflammatory protein-1 alpha (MIP-1A), monocyte chemoattractant protein-1 (MCP-1), and granulocyte colony-stimulating factor (G-CSF) are associated with disease severity in COVID-19.⁸³ A substantial lessening in lymphocyte count is seen in COVID-19.⁹⁴⁻⁹⁶ A flow cytometric examination of severe COVID-19 cases reveals a significant decrease in lymphocytic T cells (CD4+ and CD8+) and natural killer (NK) cells.⁹⁴⁻⁹⁶ Furthermore, in the initial stages of the illness, an elevation in the development of NK group 2A (NKG2A), PD-1, and T-cell immunoglobulin (Ig) mucin-3 (Tim-3) is

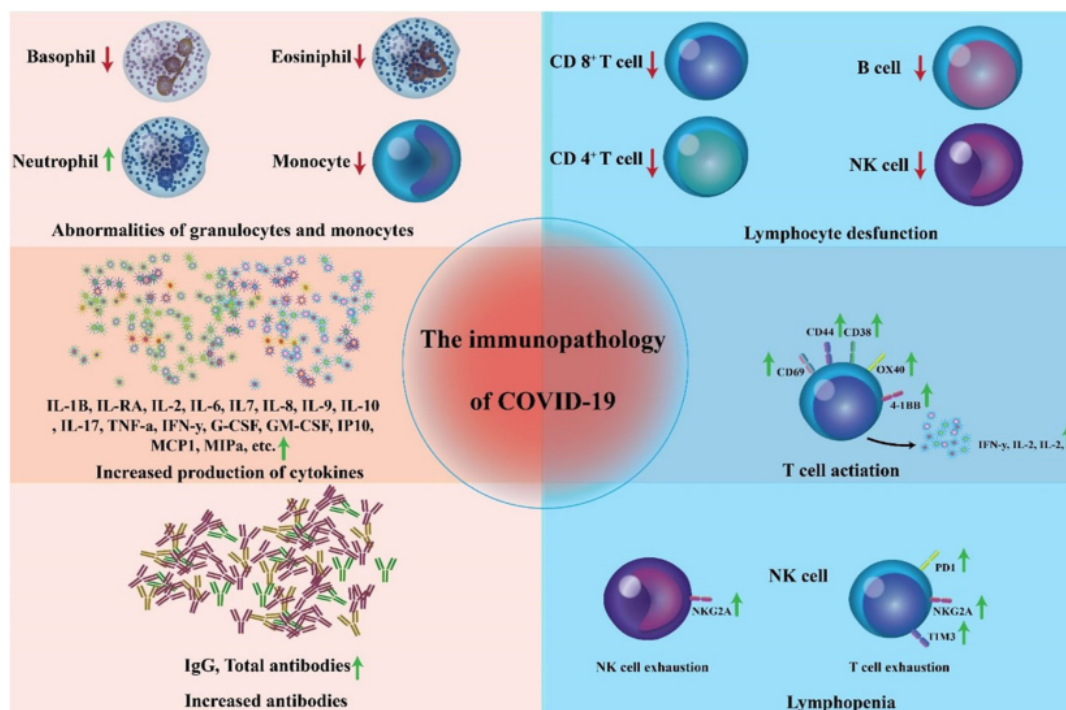


FIGURE 1 Immunopathogenesis of coronavirus disease (COVID-19). COVID-19 immunological characteristics encompass lymphopenia, lymphocyte stimulation and dysregulation, granulocyte and monocyte aberrations, enhanced cytokine secretion, and heightened antibodies. Lymphopenia is a common symptom in COVID-19 individuals, particularly in severe forms. CD69, CD38, and CD44 are significantly upregulated on CD4+ and CD8+ T cells of these patients. Virus-specific T cells from severe forms have a central memory profile with elevated amounts of interferon-gamma (IFN- γ), tumour necrosis factor α (TNF- α), and interleukin (IL)-2. On the other hand, lymphocytes show signs of fatigue due to the high production of PD-1, TIM-3, and natural killer group 2A. In serious conditions, neutrophil proportions are substantially higher, while eosinophil, basophil, and monocyte proportions were reduced. Another major feature of severe COVID-19 is heightened cytokine secretion, particularly of IL-1, IL-6, and IL-10.⁸²

related to functional exhaustion of T cells.^{94–96} NKG2A is a suppressive NKG2 family member that is present on NK cells, NK T (NKT) cells, and a fraction of CD8+ T cells. The engagement of NKG2A with histocompatibility antigen alpha chain E (HLA-E) can restrict NK and T cell activation.⁹⁷ T lymphocytes and NK cells both express PD-1. It contributes to suppressing immunological responses and promoting self-tolerance by reducing T cell activity and boosting the development of regulatory T cells.⁹⁸ Tim-3 is a coinhibitory receptor found on IFN-producing T cells and innate immune cells, including dendritic cells (DCs) and macrophages. It is crucial in suppressing T helper 1 cell (Th1) reactions and cytokine production, including TNF- α and IFN- γ .⁹⁹

4 | METABOLIC REPROGRAMMING DURING COVID-19

All viruses lack their metabolic functions and rely on the cells they infect to create the ingredients required to establish new virions.¹⁰⁰ Most viruses significantly alter the metabolism of infected cells, and

some eventually shut down all cell metabolism, causing the cell to die.¹⁰⁰ This is the typical fate of SARS-CoV-2-infected cells, and cells like respiratory epithelium must be replaced, or their function, which includes gas exchange and the synthesis of surfactants required for pulmonary function, will end.¹⁰¹ The data for documenting the metabolic implications of COVID-19 infection in vivo is being assembled. Some researchers have examined the metabolic profiles of COVID-19 patients and uninfected people; however, the relevance of these investigations is restricted since they frequently do not specify what phase of disease or severity is being evaluated.¹⁰² Longitudinal studies that repeatedly capture metabolic processes in infected individuals after they become COVID-19 positive are still needed to determine whether metabolic alterations correspond with the severity and outcome of the illness process.

According to published research on the in vivo impact on metabolism, COVID-19 infected individuals may have higher blood glucose and fatty acid concentrations and abnormalities in amino acid metabolism. Regarding the latter, genes that encode tryptophan metabolic enzymes, including kynurenine and indoleamine 2, 3-dioxygenase (IDO), were elevated.^{103,104} In infected individuals,

further intermediates implicated in arginine, aspartate, tyrosine, and lysine metabolism may be altered.^{35,103,104} These case investigations show that numerous components of normal metabolism can be disrupted during the illness process, posing a challenge for any treatment employed to reestablish metabolic balance. The last part explores the importance of targeting metabolic processes to regulate the fate of SARS-CoV-2 infection.

Ex vivo experiments on bronchial lavage cells and blood monocytes from COVID-19 patients, contrasting any metabolic alterations to control subjects using a variety of measurements such as single-cell RNA-seq, metabolomics, and transcriptomics, have also been used to record the metabolic consequences of COVID-19 disease. One such research, which used single-cell RNA-seq on bronchial alveolar cells, discovered substantial increases in glycolysis metabolites, including HIF-1 α and genes implicated in the generation of oxidative stress.^{105,106} This implies that the infected cells require increased cellular energy, which is supplied by glycolysis. Other investigations have revealed alterations in lipid metabolism and modifications in tryptophan metabolism comparable to those previously mentioned in patient examinations.¹⁰³

Investigations have been performed utilizing permissive or semipermissive cells infected in vitro, then correlating the metabolic outcomes to those in uninfected cells to establish if the COVID-19 infection directly impacts the target cell's metabolism. One investigation using peripheral blood monocytes discovered significant metabolic variations. These included enhanced HIF-1 α protein levels and enhanced transcriptional activity of molecules, including glucose transporter 1 (GLUT-1), 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), pyruvate kinase M2 (PKM2), and lactate dehydrogenase A (LDH-A).¹⁰⁶ However, with this investigation, all cells would not have been infected with the virus. Furthermore, longitudinal research that evaluates metabolic variations in different intervals after synchronized infection in a system where all cells were demonstrated to be infected may yield more potentially valuable data. As a result, it is currently unknown what direct impact COVID-19 infection has on cellular metabolism and if this knowledge might help reshape events to obtain a more positive outcome once the infection has started.

Another strategy for understanding how COVID-19 infection affects metabolism is to infect vulnerable cells in vitro and analyze the effect of changing metabolic activity on the consequence of the disease. Several investigations have been conducted to assess the effect of interference with glucose consumption with the medication 2-deoxy-D-glucose (2DG).^{106,107} This method results in a significant decrease in viral replication, and the infected cells survive. A comparable result was achieved with medications that target either cholesterol metabolism (fenofibrate) or mitochondrial OXPHOS (mitochondrial inhibitor).^{106,108} Typically, research was designed to add metabolism modulating drugs earlier or from the time of infection, but processes that can influence the infection results because once given at a later time when propagation occurrences are currently ongoing after infection may be of enhanced therapeutic intrigue. This experimental approach may better represent what might be helpful

in patients undergoing active diseases to decrease the severity of their illness.

4.1 | Metabolic reprogramming of immune cells against COVID-19

The progression of SARS-CoV-2 illness to a severe form of infection is caused by a dysfunctional immunological reaction, defined as the failure to create a prompt and robust type-I IFN host defense.¹⁰⁹ This causes a boost in viral load, which is preceded by an inflammatory reaction characterized by inflammatory mediators such as IL-6, TNF, IL-1, and IL-18, and acute phase markers.¹¹⁰ Because the development of COVID-19 to severe illness is biphasic, with the initial viral stage being preceded by the inflammatory stage, patients present later in the disease and persistently increased inflammatory markers may benefit more from anti-inflammatory medication. In the lung infected with SARS-CoV-2, the most prevalent inflammatory cells are monocytes and macrophages, which participate in the induction of cytokine storm as seen in severe COVID-19 infections.¹¹¹ SARS-CoV-2 infects a wide range of cells, most notably respiratory epithelial cells and macrophages. Macrophages infected with SARS-CoV-2 produce metabolic rewiring comparable to that caused by lipopolysaccharides (LPS), with an elevation in aerobic glycolysis, a decrease in the TCA cycle, and a rise in reverse electron transport (RET).¹⁰⁶ This reprogramming in metabolic pathways is facilitated by the manufacturing of mitochondrial reactive oxygen species (ROS) (mtROS), which stabilizes HIF-1 and glycolytic genes (mediated with HIF-1) implicated in glucose transfer and glycolysis, such as PFKFB3, PKM2, GLUT-1, and LDH-A.¹⁰⁹ LDH, a key enzyme in glycolysis in inflammatory macrophages (M1 phenotype), has also been demonstrated to be a predictive biomarker of disease severity in SARS-CoV-2 diseases, highlighting the importance of glycolysis in viral infections such as COVID-19.¹¹² Ex vivo investigations with monocytes infected with SARS-CoV-2 from cases with COVID-19 revealed that HIF-1 α protein levels were considerably higher than in uninfected individuals. Also, research on infected monocytes with SARS-CoV-2 demonstrates that elevated glucose levels and glycolysis accelerate SARS-CoV-2 proliferation, but inhibiting glycolysis reduces viral propagation. Table 1 and Figure 2 show the metabolic reprogramming of immune cells throughout COVID-19.

Moreover, enhanced glycolysis elevates IL-1 β synthesis, promoting COVID-19's inflammatory reaction. HIF-1 α is involved directly in viral proliferation and pro-inflammatory mediators secretion in these in-vitro investigations, as SARS-CoV-2 proliferation has been demonstrated to be inhibited by HIF-1 α inhibition, and also HIF-1 α stimulation enhanced viral proliferation. Also, HIF-1 α suppression inhibited the release of inflammatory cytokines linked to serious COVID-19, such as IFN- α , IFN- β , IL1 β , TNF, IL-6, and ACE2. This provides concrete proof for addressing mtROS-HIF α -metabolic pathways reprogramming as a possible therapy for the severe form of COVID-19 disease by suppressing viral proliferation and inflammatory mediators.¹⁰⁶

TABLE 1 Metabolic reprogramming among immune cells during COVID-19.

Immune cells	Metabolic reaction	Outcome	Description	References
Macrophage	Glycolysis	Pro-inflammatory cytokine, chemokine generation, virus	The current study found that high glucose levels boost severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus replication and release of inflammatory mediators in macrophages taken from the lungs of severe coronavirus disease 2019 (COVID-19) patients, culminating in a cytokine storm.	[30,106,113,114]
		Replication, activation of hypoxia-inducible factor 1 alpha (HIF-1 α)	The extreme inflammatory process and cytokine storm in the respiratory system of COVID-19-induced acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) patients creates a sepsis-like microenvironment, leading to more significant HIF-1 α transcription in infiltrated macrophages, which generate pro-inflammatory cytokines mediators and chemokines, causing catastrophic COVID-19-induced ALI/ARDS.	[5]
			Increased glycolysis in M1 macrophages (pro-inflammatory phenotype) results in the buildup of Krebs or tricarboxylic acid (TCA) cycle byproducts such as succinate and citrate and TCA cycle-derived itaconate, which affects inflammatory gene expression.	[5]
			Periphery CD14+ monocytes in COVID-19 patients do not create pro-inflammatory mediators to cause a systemic cytokine storm; therefore, immunometabolic remodeling from oxidative phosphorylation (OXPHOS) to glycolysis and HIF-1 α overexpression does not occur.	[5]
Dendritic cell (DC)	Glycolysis, OXPHOS	Reduced mammalian targets of rapamycin (mTOR) signaling, reduced interferon (IFN)- α production	According to a recent study, COVID-19 inhibited mTOR signaling and IFN- α production via toll-like receptor (TLR) 3 and TLR7/8 signaling, indicating poor immuno-metabolic reconfiguration in plasmacytoid DCs (pDCs). Because type 1 IFN synthesis is restricted, pDCs infected with SARS-CoV-2 do not exhibit the autocrine IFN-IFNAR signaling generated by type 1 IFN synthesis and adherence to the IFN- α receptor (IFNAR), which suppresses an increase in OXPHOS and FAO. Through interferon regulatory transcription factor 3 (IRF3) phosphorylation, SARS-CoV-2 infection reduces TANK-binding kinase-1 (TBK1) and IKK ϵ -mediated type 1 IFN generation as well as nuclear factor- κ B (NF- κ B)-mediated pro-inflammatory cytokine production in DCs. Due to a deficiency of HK-II, the metabolism changes to OXPHOS, rendering DCs infected with SARS-CoV-2 unable to meet the increased energy requirements required to build protection against viral illness. As a result, SARS-CoV-2 illness may lower the number of DCs in the circulation, lymph nodes, and several organs, including the lungs, by disrupting the immunometabolic remodeling process (OXPHOS to glycolysis).	[30,115,116]

(Continues)

TABLE 1 (Continued)

Immune cells	Metabolic reaction	Outcome	Description	References
Natural killer (NK) cell	Glycolysis, OXPHOS	mTORC1 signaling	NK cells depend on both OXPHOS and (at a reduced level) glycolysis for energy during immunological maintenance. A high dose of interleukin-15 (IL-15) stimulates mTORC1 signaling, which accelerates glucose absorption through glucose transporter 1 (GLUT-1) or solute carrier family 2 member 1 (SLC2A1) and, as a result, glycolysis.	[30]
T lymphocyte	Glycolysis, glutaminolysis	mTORC1 signaling, induction of HIF-1 α	As seen in the lungs of severe COVID-19 patients, increased mTORC1 activation in T helper 1 (Th1) cells causes their switch to T helper 17 (Th17) cells. In response to hypoxia, Th17 cells increase glycolysis and glutaminolysis in the lungs of severe COVID-19 individuals, leading to the activation of HIF-1 and mTORC1 signaling to promote pro-inflammatory activity.	[30]
B lymphocyte	Glycolysis	mTORC1 signaling generates antibodies (Abs)	As a result, in COVID-19 instances, B cells create Abs by a glycolysis-dependent mechanism. In this process, plasma cells develop from B cells to synthesize immunoglobulin (Ig) IgG, IgM, and IgA, and glycolysis in B cells is not suppressed.	[30,117]

Immunometabolism, or metabolic rewiring within and between immune cells, is important in the pathogenesis of inflammatory response and other inflammatory conditions, such as sepsis, in which cytokine storm development performs a critical function in the initiation of ALI/ARDS or multiorgan collapse.^{30,39} As a result, it is crucial to monitor immunometabolic reprogramming amongst immune effector cells throughout SARS-CoV2 pathophysiology.

According to previous research, high glucose levels promote SARS-CoV2 propagation and the production of inflammatory mediators in macrophages derived from the lungs of serious COVID-19 victims, resulting in cytokine storms.¹⁰⁶ This is caused by the increased expression of many genes implicated in glycolysis in these macrophages after COVID-19. The infiltration of macrophages derived from monocyte into the lung of COVID-19 patients following enhanced expression of HIF-1 α demonstrates glycolytic pathway initiation, which supplies common energy as contrasted to OXPHOS, throughout homeostasis where it represents a source of energy for macrophages to transcriptions and translates pro-inflammatory genes including chemokines and cytokines.¹⁰⁶ In pulmonary macrophages, the metabolic switch from OXPHOS to glycolysis enhances the mammalian target of rapamycin complex 1 (mTORC1), elevating GLUT-1 in macrophages via Akt to promote glycolysis.¹¹⁸ Therefore, HIF-1 α supports SARS-CoV-2 proliferation in infected macrophages by promoting glycolysis. During COVID-19, HIF-1 α suppression also reduces cytokine production from SARS-CoV2-infected macrophages.¹⁰⁶ Enhanced glycolysis in M1 macrophages (pro-inflammatory) causes the accumulation of Krebs or succinate and citrate (TCA cycle metabolites) and TCA cycle-derived itaconate, which regulates the expression of genes (pro-inflammatory gene).^{56,113,114} The succinate delivered to the cytosol immediately suppresses the action of prolyl hydroxylase (PHD) to reinforce HIF-1 α , so enhancing glycolysis.^{106,113,119} Complex II or succinate dehydrogenase (SDH) stimulates RTE in the mitochondria, enhancing mtROS formation from complex 1, suppressing PHD.^{106,113,119} As a result, succinate oxidation is essential for SARS-CoV2 proliferation in macrophages infected with SARS-CoV-2.

DCs perform an axial function in the Antigen (Ag) presentation and viral infections.³⁰ The features of DCs as being one of the numerous innate immunity throughout the acute phase of infection, such as sepsis, have already been detailed elsewhere by the author.¹¹⁹ The specifics of DC immunometabolism under various situations have been addressed previously.^{120,121} A previous SARS-CoV study discovered limited viral proliferation in monocyte-derived DCs (moDCs) following infection, with no increase in virus loads.¹²² Even these DCs generate low antiviral type 1 IFNs and cytokines (IL-12p40) produced in minimal amounts, as are pro-inflammatory mediators, including IL-6 and TNF- α .¹²² These DCs, on the other hand, have considerably higher volumes of the chemokines essential to promote neutrophil, monocyte/macrophage, and T cell recruitment. The moDCs infected with SARS-CoV2 indicate no productive virus proliferation, no antiviral IFN I, II, or III production, and limited inflammatory cytokines secretion.¹²³

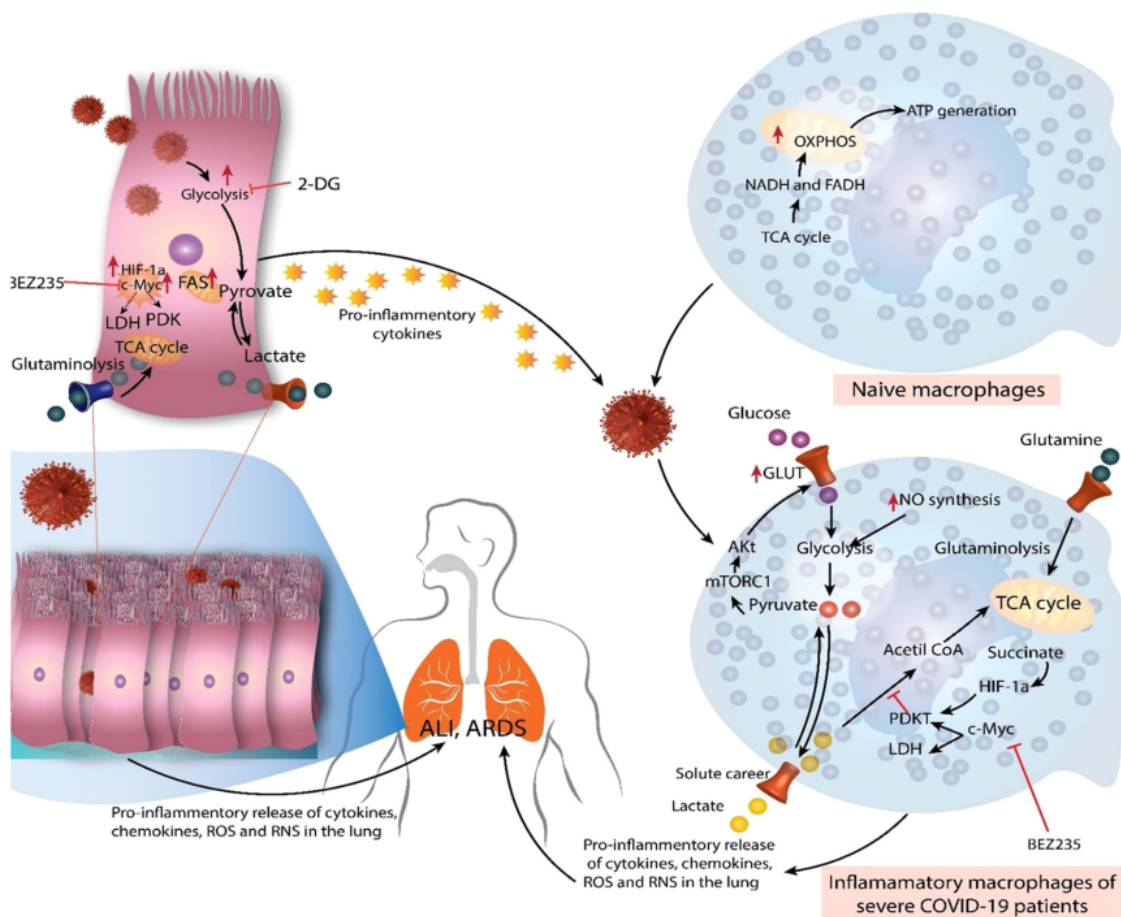


FIGURE 2 Immunometabolic reactions during coronavirus disease (COVID-19). During homeostasis, naive macrophages (M0) do not demand substantial energy and rely primarily on oxidative phosphorylation (OXPHOS) and tricarboxylic acid (TCA) or the Krebs cycle for ATP production. Nevertheless, under the effect of the virus and pro-inflammatory mediators generated by respiratory or pulmonary epithelial cells throughout severe acute respiratory syndrome coronavirus 2 disease, they exhibit a metabolic change. Therefore, these macrophages switch to glycolysis for fuel, which delivers faster energy than OXPHOS. The enhanced glucose absorption by these inflammatory macrophages is caused by excessive glucose transporter 1 (GLUT-1) production, which is activated by mTORC1 signaling and causes Akt to boost GLUT1 expression. Hypoxia-inducible factor 1-alpha (HIF-1α) and C-Myc levels also increase, enhancing glycolysis by promoting lactate dehydrogenase (which converts pyruvate to lactate) and PDK1. The deposition of succinate, a TCA cycle byproduct, raises HIF-1α concentrations. The elevated glutaminolysis contributes to the higher energy consumption of inflammatory macrophages. As a result, augmented cytokine, chemokine, reactive oxygen species (ROS), and reactive nitrogen species (RNS) production by inflammatory macrophages in the lungs leads to the "cytokine storm" that causes acute lung injury (ALI)/acute respiratory distress syndrome (ARDS). Similar to pro-inflammatory macrophages, respiratory or alveolar epithelial cells infected with SARS-CoV2 exhibit enhanced glycolysis, glutaminolysis, HIF-1α, and c-Myc overexpression. This increases the secretion of pro-inflammatory mediators, which contributes to the "cytokine storm" and neutrophil and monocyte recruitment in the lungs of severe COVID-19 individuals. These cells of innate immunity and immunometabolic remodeling processes cause ALI/ARDS in patients with severe COVID-19.³⁰

Nevertheless, moDCs infected with SARS-CoV-2 do not generate the same chemokines as SARS-CoV. The virus hijacked a robust antiviral protective immunity by declining to produce numerous antiviral type 1 IFNs and stimulating minimal amounts of pro-inflammatory mediators. The innate immune cells infected with SARS-CoV2, for instance, suppress cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS)-stimulator of IFN genes (STING)

signaling-dependent antiviral type 1 IFN production, RLR, and nuclear factor κ B (NF- κ B)-dependent pro-inflammatory mediators. Furthermore, moDCs infected with SARS-CoV2 suppress IFN signaling in moDCs and phosphorylation in STAT1.¹²⁴ It is important to note that DCs infected with SARS-CoV does not cause maturation or apoptosis.¹²³ Severe COVID-19 cases, on the other hand, have a lower amount of conventional DCs (cDCs) and plasmacytoid DCs (pDCs).

Dormant or naive T cells during normal settings for energy sources rely on OXPHOS.¹²⁵ Pyruvate is generated by glycolysis, which is required for OXPHOS, FAO, and glutaminolysis due to stimulating TCR signaling and IL-7-IL-7 R coupling to support growth, diversity, longevity, stimulation, and performance.¹²⁵ Naive T cells viability is often supported by the interplay of sphingosine 1-phosphate (S1P) and S1P receptor (S1PR), which keeps OXPHOS and FAO under control.¹²⁶ Tonic TCR signaling decreases respiration and glycolysis in periphery CD4+ T cells engaged with peripheral self-MHC, indicating an inverted link between tonic TCR signaling and basal metabolism.¹²⁷ As a result, higher CD4+ T cell engagements with periphery self-MHC led to decreased basal metabolic rate and vice versa. This reduces the likelihood of autoimmunity and maintains the immune function in balance.

A glycolytic enzyme which is called phosphoglycerate mutase 1 (Pgam1) catalyzes the conversion of 3-phosphoglycerate (3-PG) to 2-phosphoglycerate (2-PG), which is also crucial in glycolysis. Pgam1 deletion in T cells affects glycolysis, impairing immunological responses from T cells (CD4+ and CD8+ cells).¹²⁸ As a result, T cells required the glycolysis pathway for performing immunological reactions, including growth and maturation. Recently, features about T cell metabolism were explored.^{125,126} Low plasma S1P levels in COVID-19 subjects alter S1P-S1PR signaling and mitochondrial mass or frequency in naive T cells, resulting in induction of apoptosis.¹²⁹ The lack of DCs following SARS-CoV2 infection also affects effector CD8+ T cell performance and memory CD8+ T cell production, which are both dependent on them.³⁰ Due to the lack of DCs following severe form of COVID-19, decreased IL-7 signaling and Ag presentation. The proportion of B cells stays unchanged or rises in severe COVID-19 patients.³⁰ Plasmablasts cells produce IgG, on the other hand, predominate in severe COVID-19 cases with the highest levels of NAbs. Exhausted memory B cells, also known as CD21-CD27-B cells, have been promoted in both mild and severe COVID-19 subjects. TLR3 and TLR9 are exclusively expressed by human B cells, although TLR3, TLR7, TLR8, and TLR9 are expressed by human plasma cells.¹³⁰

Consequently, activating these TLRs in differentiating plasma cells promotes Ig synthesis.¹³⁰ In naive or noninfected B cells, the STING protein is not detectable.¹³¹ In response to viral infection, they express STING; however, their cGAS-STING signaling pathway remained defective, blocking them from producing type 1 IFNs.¹³¹ Another research indicates that in the presence of T cell-dependent antigens, B cells have STING play a critical function in building Abs.¹³²

Nevertheless, in the existence of alum, cGAS-STING signaling is inert (adjuvant).¹³² Effective Ab response requires RLR-dependent signaling.¹³³ As a result, exclusively cytosolic TLRs, RLRs, and cyclic GMP-AMP synthase (cGAS)-STING signal transduction pathways are needed for SARS-CoV-2 RNA and DNA identification and Ab production. Since they have increased the number of T cells, including such follicular helper T cells (TFHs), Ab manufacturing may be both T cell-dependent and independent in mild to moderate COVID-19 instances, but this should be a T cell-independent process

in severe COVID-19 cases since all types of T cells decrease, and only CD4-CTLs, Th17 cells, and CD8 T cells boost in the lungs, in which it is a T cell-dependent procedure.³⁰ This one should be investigated. For instance, B lymphocytes do not produce ACE2, but only effector, not naive; B cells exhibit CD147.¹³⁴ As a result, this virus neither infects nor manipulates B cells' cytosolic PRR-based type 1 IFN and cytokine secretion, which is required for increased Ig and Ab synthesis. These data imply that SARS-CoV-2 may alter the metabolism of immune cells to advance its pathogenesis; acknowledging the virus's processes for this purpose may, as a result, contribute to the development of novel medicine in treating viral disorders.

Similarly, the biochemical profile of COVID-19 patients has a significant impact on their survival.⁴⁶ To investigate this issue, current findings obtained proteomic, transcriptome, and metabolomic measures from COVID-19 patients and discovered several connections between specific molecular alterations and disease prognosis.^{135,136} Nevertheless, there is a paucity of an integrated view of metabolic alterations that may be important in controlling immune function in COVID-19 as well as other severe acute infections. Lee et al.¹³⁷ investigated the metabolic alterations linked with the peripheral immune reaction in 198 people with COVID-19 using an extensive examination of plasma metabolite and protein concentration and single-cell multiomics assessment from sequential blood sampling obtained within the first week upon diagnosis. They discovered that rising illness severity coincides with the formation of uncommon but metabolically dominating T cell subgroups and the polarization of monocytes onto two biologically different subsets. We found metabolic rewiring that is extremely precise to distinct immune cell categories, and this switching is linked to alterations in the plasma metabolome and clinical aggravation. They also discovered systemic metabolite classifications of pathogenicity and clinical outcome predictions. This integrative strategy offers the opportunity for researchers to better comprehend the metabolic processes underpinning the immunological response to COVID-19.

SARS-CoV-2 is essentially a pulmonary virus; it has also become apparent that it affects a wide range of organs throughout the body, not only the lungs and airways.¹³⁷ As a result, severe COVID-19 episodes are commonly described as multisystem dysfunction. COVID-19 induces immediate breathing difficulties in the lungs due to infiltration of inflammatory cells mainly by lymphocytes, extensive pulmonary destruction, and respiratory failure.¹³⁸ Furthermore, COVID-19 individuals have neurological symptoms and renal and hepatic impairment.¹³⁹⁻¹⁴¹ Vascular impairment and thromboembolisms add to the disease's reported multisystem destruction and increased mortality.¹⁴² Schmelter et al.¹⁴¹ used an experiment to evaluate the metabolic and lipoprotein profiling of hospitalized COVID-19 cases to many healthy controls and a group of cardiogenic shock cases receiving in the same intensive care unit (ICU) who tested negative for COVID-19. When COVID-19 cases were compared to healthy controls, their blood metabolomics signature revealed significant dyslipidemia. Very-low-density lipoprotein and intermediate-density lipoprotein molecules and related

apolipoprotein B and intermediate-density lipoprotein cholesterol were dramatically increased, whereas cholesterol and apolipoprotein A2 were considerably lowered.¹⁴¹ Furthermore, when 1-week course was examined, a similar disrupted profile was observed as compared to other patients with cardiogenic shock in the ICU, showing intimate linkages among COVID-19 and lipid metabolism.¹⁴¹ This indicates that lipoprotein patterns may be a paradoxical risk factor for COVID-19, stratifying patients.

Viral sepsis has also been offered as an appropriate terminology to cover all multiorgan impairment and clinical findings in critically ill patients with COVID-19.¹⁴⁴ Acceptance of this terminology may contribute to the adoption of more precise initial detection, diagnosis, and in-hospital therapeutic options. Oostdam et al.¹⁴⁴ discovered a comprehensive host-dependent imbalance of inflammatory markers, neutrophil-activating chemokines, mitochondrial metabolism, polyamine synthesis glycolysis, lipid metabolism, glycolysis, and amino acid metabolism. In moderate and severely ill cases, dysfunctional metabolites and cytokines/chemokines revealed varied association patterns, showing an interaction among metabolic profile and hyperinflammation.¹⁴⁴

5 | METABOLIC DISORDERS AND COVID-19

Metabolic disorders (including obesity and diabetes) are related to a heightened incidence of viral, parasitic, mycotic, and bacterial infections.¹⁴⁵ Drucker et al. demonstrated that severe respiratory disease is associated with the fast evolution of transitory insulin resistance in other more healthful euglycemic healthy body weight and overweight individuals, showing that pathogens significantly enhance diabetic lethality.¹⁴⁶ A retrospective investigation revealed that the death rate in elderly diabetes individuals was higher.¹⁴⁷ Diabetic condition is implicated considerably in microbial infections and poorer consequences resulting from a combination of impairment of innate immunity and inflammatory pathways.^{148,149} Also, secondary bacterial infections may aggravate COVID-19 diseases related to diabetics' reduced epithelial barrier integrity in the lungs and GI system.¹⁴⁶

Chronic inflammation and associated cytokine secretion throughout viral infection cause neutrophilia, coagulation activity, and kidney damage, ultimately contributing to the mortality of SARS-CoV-2 victims.^{150,151} Various investigations have found that in diabetic individuals infected with SARS-CoV-2, the overall number of lymphocytes in blood samples is much reduced, whereas the total number of neutrophils is significantly greater.¹⁵² Furthermore, diabetic SARS-CoV-2 individuals had elevated blood levels of numerous inflammatory-related markers than nondiabetic SARS-CoV-2 cases.¹⁵³ These individuals are distinguished by high blood levels of C reactive protein (CRP) I, TNF- α , serum ferritin, and IL-6. In patients with COVID-19, most investigations indicated that the IL-6 is a biomarker of disease severity and outcome, and its production period is higher than that of other pro-inflammatory cytokines, including IL-1 and TNF- α .¹⁵⁴ Also, Guo et al. observed evidence of increased ferritin in diabetes patients, demonstrating the stimulation

of the monocyte-macrophage axis, which seems to be a critical component of the cytokine storm.^{150,154} The scientists determined that diabetic individuals are more likely to experience a cytokine storm, which causes a fast worsening in SARS-CoV-2 individuals.¹⁵⁴

Ultimately, hyperglycemia is a significant risk factor for adverse coagulative equilibrium and platelet activation, contributing to the increased thromboembolic abnormalities found in dead COVID-19 subjects.¹⁵⁵ Multiple pathways have been investigated in diabetic patients that correlate with inflammatory response and coagulative equilibrium.¹⁵¹ At first, the inflammatory process activates plasmin, which elevates D-dimer levels. Second, inflammatory conditions and hypoxia stimulate thrombin. The activation of monocyte-macrophages results in the overexpression of several tissue elements and modulation of the exogenous coagulation pathway, resulting in significant hypercoagulable conditions or even dispersed intravascular coagulation.^{150,151} Furthermore, higher D-dimer concentrations have been repeatedly documented, and their steady rise during the disease course is mainly related to the progression of the disease.¹⁵⁶ In sum, longitudinal monitoring of lymphocyte number changes and inflammatory markers such as CRP, ferritin, and IL-6 during the illness processes may aid in the detection of persons with poor prognoses and early therapy to improve outcomes.

High obesity increases the risk of severe COVID-19 and lethality through various processes, such as increased inflammatory presses, hypercoagulation, and mechanical impairment.¹⁵⁷ One potential risk factor for serious consequences in those with severe COVID-19 and obesity is physiological stress on respiration caused by diaphragm excursion restriction. Diabetes and overweight are also implicated in developing chronic obstructive pulmonary disease (pulmonary fibrosis) and a decreased pulmonary rate.⁴⁶ The risk of stroke and cardiovascular issues was significantly increased in obesity, obesity, diabetes, and hypertension, and these risk factors are implicated in the induction of severe COVID-19 presentation.¹⁵⁸ These COVID-19 cases have an aggravated coagulation reaction to thrombogenic factor upregulation, including coagulation factors (II, VII, VIII, IX, XI, and XII), PAI-1, and von Willebrand factor, which, particularly combined with pre-existing disorders, might lead to higher rates of stroke or collapsed lung.^{159,160}

Type 2 diabetes (T2DM) is a chronic condition characterized by insulin resistance, inflammatory processes, and endothelial and -cell abnormalities.¹⁶¹ In situations with severe COVID-19, the inflammatory response to SARS-CoV-2 infection can increase insulin resistance and vascular dysfunction. The interaction between COVID-19 and T2DM and obesity may intensify the inflammatory reaction and inhibit the activity IFN defenses, resulting in emerging diseases severity in diabetic and obese patients.¹⁶² In addition to stress signaling, Renin-angiotensin-aldosterone system (RAAS) dysfunction and decreased expression of ACE2 can promote insulin resistance.¹⁶³ Hence, insulin resistance increases the potential of pulmonary failure and cardiac collapse in diabetic cases by promoting airway hyperreactivity COVID-19.¹⁶³

In addition to their involvement in the immunological reactions to viral diseases, cytokines stimulate the hypothalamic-pituitary-adrenal axis, causing the production of adrenal glucocorticoids.¹⁶⁴ Glucocorticoids, in

turn, have a negative feedback effect on immune cells, suppressing more cytokine production and secretion. As a result, the host gets a partly protecting signal against the harmful effects of an excessive immune reaction, including tissue injury, septic shock, and autoimmunity.¹⁶⁵ Such adverse effects have also been clinically recorded following dexamethasone therapy, which is the more successful treatment for those with severe COVID-19 with respiratory complications at the time of writing.¹⁶⁶ Moreover, inhalation of glucocorticoids (e.g., budesonide) has been observed to shorten the time to partial recovery following initial COVID-19 infection.¹⁶⁷ These data have resulted in a broad prescription of glucocorticoids to treat individuals with moderate-to-severe COVID-19 and, commonly, mild forms.

Upon SARS-CoV-2 infection, TLRs 2, 3, and 4 are stimulated, resulting in the production of inflammatory mediators, including IL-1 and IL-6.¹⁶⁸ Metaflammation in individuals with metabolic diseases enables a hyperimmune activation that may progress to pathological levels. This inflammatory mediator's secretion promotes fever, inflammation, and sepsis.¹⁶⁸ According to their pathophysiology, infectious disorders, such as viral infections and impaired endocrine and metabolic organs, lead to new-onset hyperglycemia or insulin resistance in COVID-19 survivors. SARS-CoV-2 can infect and spread in cells of the exocrine and endocrine pancreas, according to studies involving islets taken from human donors infected with SARS-CoV-2 and data from postmortem samples from patients who died from COVID-19.¹⁶⁹ Moreover, in COVID-19 individuals, inflammatory cells recruitment and necroptosis in the endocrine and exocrine pancreas have been seen.¹⁷⁰ These findings point to COVID-19 illness of β -cells may either indirectly or directly impair-cell performance, resulting in different degrees of metabolic imbalance.

Diabetes, ketoacidosis, hyperglycemia, and severe metabolic comorbidities related to prediabetes are frequently seen in COVID-19 subjects.¹⁷⁰ Diabetes ketoacidosis and severe ketoacidosis at diabetes diagnosis rose dramatically during the SARS-CoV-2 pandemic, especially in children under the age of six, according to data from the German Diabetes Prospective Follow-up Registry diabetes-patienten-verlaufsdokumentation. This countrywide registration covers more than 90% of pediatric patients with T1D.¹⁷¹ Furthermore, alterations in parental behavior and availability of health care may have had a role in the rise of new-onset T1D among children in recent decades.¹⁷² Despite this, evidence is mounting that COVID-19 may be a contributing factor or catalyst to developing new-onset diabetes.¹⁷³ There have also been reports of pancreatitis after the administration of COVID-19.¹⁷⁴ However, whether COVID-19 can induce new-onset diabetes or increase the course of pre-existing undetected diabetes or prediabetes is still up for debate.¹⁷⁵

6 | TARGETING OF HOST METABOLISM FOR THE TREATMENT OF COVID-19

According to new research, extracellular vesicles, particularly exosomes, contain microRNA (miRNA) targeting immunological and biochemical pathways, such as those affecting the peroxisome

proliferator-activated receptors (PPARs).^{4,176-178} Exosomal miRNAs, like miR-155, are increased in obese mice (adipose tissue macrophage) and promote insulin resistance. TNF- α treatment of human adipocytes resulted in increased miR-155 synthesis and inflammation, highlighting the relevance of miR-155.¹⁷⁷ MiR-155 inhibits PPAR gamma (PPAR γ), activating the pro-inflammatory NF- κ B pathway.^{177,179} TLR4-induced NF- κ B signaling pathways were modulated by other miRNAs, including miR-223, miR-200b/c, miR-146a/b, and miR-203.¹⁸⁰⁻¹⁸² TNF- α production is also boosted by some miRNAs, including miR-125b, miR-221, miR-579, and miR-16, resulting in a pro-inflammatory state.^{183,184} Since these microRNAs impact the inflammatory reaction on their own, Let-7 boosts IL-6 concentrations while also promoting glucose intolerance and decreasing pancreatic insulin production.^{185,186} Some miRNAs, which have a dual function in immunometabolic processes, might be used as potential therapeutics in individuals with metabolic disorders and COVID-19.

COVID-19 is being treated with antibody cocktails that are either obtained directly from infected people or synthesized.²⁹ Regeneron is sponsoring antibody research targeting COVID-19, and Eli Lilly is two examples of pharmaceutical companies, both of which have been granted urgent Food and Drug Administration (FDA) approval for the management of COVID-19.²⁹ Nanobodies (small antibody-like molecules) relying on organically released antibodies by camelids are being developed and may be selected due to their cheaper cost and simpler manufacturing procedure.¹⁸⁸ The possible synergistic benefits of combination therapies that reduce inflammation while also controlling metabolism might ameliorate hyperimmune activation in SARS-CoV-2 cases with underlying metabolic disorders caused by T2DM or obesity.²⁹

7 | CONCLUSION

Substantial ongoing research into immune cell metabolism provides an overwhelming volume of data. Also, it has been found that immunometabolism has an axial role in the fate of viral infection, including SARS-CoV-2. Studies on how SARS-CoV-2 changes intracellular metabolism in immune cells such as innate immune cells reveal exciting biochemical aspects such as increased glycolysis and altered OXPHOS. Targeting biochemical (metabolite) alterations in immune cells like macrophages might pave the way for new immunomodulatory strategies such as anti-inflammatory and antiviral drugs. However, the potential to restrict metabolic rewiring in immunity associated with the viral infection and other infected cells to lessen the raised inflammatory reaction shown throughout the advanced stages of COVID-19 disease is an intriguing option for treating people who develop from mild to severe COVID-19 disease. Future investigations should focus on how viruses alter the metabolism of immune cells to advance their pathogenesis since identifying these mechanisms may provide a new therapeutic avenue for better management of viral infections. Innovative treatment methods, such as antagomirs and antibody cocktails, either alone or

in conjunction with established anti-inflammatory medications, including steroids, offer an exciting opportunity to escape the negative consequences of COVID-19 disease in cases with metabolic abnormalities.

AUTHOR CONTRIBUTIONS

Mohammad Rudiansyah, Saade Abdalkareem Jasim, Rumi Iqbal doewes, Abduladheem Turki Jalil, and Zeinab Gol Mohammad pour have the idea for and planned the study and contributed to the writing of the paper. Sara Sohrabi Athar, D. O. Bokov, Yasser Fakri Mustafa, Ali Salimi Jeda, and Mina Noroozbeygi contributed to the writing of the manuscript. Sajad Karampoor and Rasoul Mirzaei contributed to the critical revision of the report. All authors read and approved the final version.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

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