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Metabolic dysregulation in acute Sars-Cov-2 infection

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The global pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), mostly presented with mild to moderate or no symptoms and patients having pre-existing metabolic disorders like diabetes, cardiovascular diseases, and obesity are at risk for severe and critical cases of infection. The metabolic landscape of COVID-19 and its association with disease severity has urged the need to understand how metabolic reprogramming occurs during the acute SARS-CoV-2 infection with the ultimate goal toward therapeutic intervention. Viral replication is dependent on extracellular carbon sources such as glucose and glutamine and induces metabolic alterations in host cell including host central carbon metabolism, nucleotide, fatty acids, and lipid synthesis that modulate viral pathogenesis and host response. SARS-CoV-2 dysregulation of PI3K/Akt/mTOR and hypoxia-inducible factor 1 (HIF-1) signaling pathways in infected cells and affect mitochondrial functions . These pathways regulate glycolysis by altering glucose transporters (GLUTs) across cell membranes. The altered extracellular glucose, mannose, and glutamate levels could be due to dysregulated carbohydrate metabolism and mitochondrial function. Host cellular response following SARS-CoV-2 infection, identified a strong acute metabolic adaptation in the lung epithelial cells (Calu-3) by modulating central carbon metabolism and indicative of mitochondrial dysfunction that is also observed in severe COVID-19 patients. Glycolysis and glutaminolysis can be essential for virus replication, and host-based metabolic strategies to inhibit viruses to weaken the viral replication by metabolic intervention could be an attractive antiviral therapy. Targeting these pathways with inhibitors such as MK2206 (Akt inhibitor) or 2-deoxy-D-glucose (2-DG; glycolysis inhibitor) can lower the viral burden in the cells in vitro.

The cytokine storm syndrome is evident in COVID-19 patients and several plasma proinflammatory cytokines including IL-6 were elevated in both mild and severe COVID-19 patients. IL-12 also plays a critical role in viral immunity by activating the natural killer cells and promoting differentiation of Th1 CD4+ T cells. In vitro studies on IL-12 administration have shown enhanced host cellular responses that generally promote virus clearance and host recovery from infection. Metabolite transporters are known to dictate immune cell activity by controlling access to nutrients, thereby maintaining cellular homeostasis. Viral infections including SARS-CoV-2 are known to enhance the glycolytic flux and increase the production of lactate from pyruvate and increased glucose, pyruvate, and lactate levels in the plasma of COVID-19 patients indicate toxic metabolic dysregulation during acute phase of infection. A significant increase in surface expression (mean fluorescence intensity) of GLUT1 in CD8+ T cells and a significant increase in surface expressioa of xCT, a cystine/glutamate antiporter that exchanges glutamate for cystine essential for maintenance of redox balance in classical and intermediate monocytes in severe COVID-19 patients. Infectivity of SARS-CoV-2 is quantified as relative E-gene levels in cell lysates and showed that both glutaminolysis and glycolysis can be essential for SARS-CoV-2 infection and progressive replication in vitro in the lung epithelial cell line.

Plasma mannose emerges as a robust biomarker of disease severity that is in line with earlier studies from China and United State and Other metabolite biomarkers, like 6-oxopiperidine-2-carboxylate, hydantoin-5-propionate, 4-hydroxy phenylacetate, eicosanedioate, and 6-bromotryptophan, were not reported earlier. Recent studies reported that plasma mannose levels were an indicator of glycogenolysis as well as glucose tolerance and associated with the future risk of developing chronic diseases, such as type 2 diabetes and increased mannose has a role to play in new-onset diabetes after SARS-CoV-2 infection. C-type lectins, such as MBL (mannose-binding lectin), recognize carbohydrates, particularly on the surface of microorganisms leading to activation of the complement cascade and phagocytosis. High mannose and/or high MBL could thus dysregulate the immune system and lead to severe damage associated with disease severity.

Most of the proteins from carbohydrate metabolism and PPP (pentose phosphate pathway) were upregulated, whereas most of the proteins of TCA cycle, oxidative phosphorylation, and fatty acid metabolism were downregulated in infected cells with the decreased mtDNA copy numbers in severe COVID-19 patients indicating a possible mitochondrial dysfunction. Interestingly, although all the mitochondrial TCA cycle enzymes were downregulated, cytosolic enzymes, such as MDH1, IDH1, ACO1, and ACLY, that convert TCA cycle intermediates outside the mitochondria were upregulated in infected Calu-3 cells. This points toward dysfunctional mitochondria caused by COVID-19 infection. Alterations in mtDNA copy number in circulating blood cells can serve as a surrogate for mitochondrial dysfunction Amino acid–related pathways were most predominantly affected during infection and amino acids such as glycine, proline, tryptophan, alanine, histidine, glutamine, and arginine, were found in lower levels in COVID-19 patients, whereas glutamate, aspartate, and phenylalanine were found in higher levels.In COVID-19 infection. kynurenine-to-tryptophan ratio is increased, suggesting the activation of the kynurenine pathway and the changes in the kynurenine pathway correlate with disease severity. Activation of the kynurenine pathway may be a result of excessive inflammatory responses in COVID-19 patients, given interferon (IFN)-γ and other inflammatory factors can upregulate IDO. The immunosuppressive effects arising from the hyperactivation of the kynurenine pathway might further delay the clearance of SARS-CoV-2 and cause cytokine storm and multiorgan failure. IDO-Kyn-AhR pathway is activated by IFN-β or IFN-γ in alveolar epithelial cells, leading to an accumulation of mucins, thus triggering hypoxia of COVID-19. Therefore, the hyperactivation of the kynurenine pathway provides a potent explanation of the COVID-19 pathological process, indicating a potential therapeutic approach by targeting the tryptophan pathway. Among the pharmacological agents targeting tryptophan pathways, IDO (indoleamine deoxygenase) inhibitors are the most clinically advanced, which prevent immune suppression caused by tryptophan depletion and kynurenine metabolites.

Biography

Ramachandran Muthiah, Consultant Physician & Cardiologist, Zion hospital, Azhagiamandapam and Morning star hospital, Marthandam, Kanyakumari District, India. Completed M.B.B.S (1983 to 1989- Tirunelveli medical college- Madurai kamaraj university), M.D. in General Medicine in 1996 (Tirunelveli medical college), D.M. in cardiology in 2003 (Madurai medical college) under Tamil Nadu Dr.MGR Medical University, Chennai, India. Worked as medical officer in Rural health services (keelachekkarakudi- thoothukudi, Aryappapuram- Tenkasi, ESI hospital- singanallur in coimbatore for 5 years and in teaching category as Assistant Professor at Madras medical college, Coimbatore medical college, Thoothukudi medical college and Professor at Dr.SMCSI Mission hospital & Medical college, Karakonam, Trivandrum and Azeezia Medical college, Kollam. Consultant at St. Thomas hospital, Pranavam hospital, Little flower mission hospital, vilakudy at Punalur, KNS hospital, kottarakara in kollam district of kerala state. Published many papers in Cardiosource, American College of Cardiology Foundation, Case Reports in Clinical Medicine (SCIRP) and Journal of Saudi Heart Association. Special research on Rheumatic fever and Endomyocardial fibrosis in tropical belts, Myxomas, Ineffective endocarditis, apical hypertrophic cardiomyopathy, Ebstein's anomaly, Rheumatic Taussig-Bing Heart, Costello syndrome and Tetralogy of Fallot.