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Amino acid sensing pathway: A major check point in the pathogenesis of obesity and COVID-19

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Summary

Obesity and obesogenic comorbidities have been associated with COVID-19 susceptibility and mortality. However, the mechanism of such correlations requires an in-depth understanding. Overnutrition/excess serum amino acid profile during obesity has been linked with inflammation and reprogramming of translational machinery through hyperactivation of amino acid sensor mammalian target of rapamycin (mTOR), which is exploited by SARS-CoV-2 for its replication. Conversely, we have shown that the activation of general control nonderepressible 2 (GCN2)-dependent amino acid starvation sensing pathway suppresses intestinal inflammation by inhibiting the production of reactive oxygen species (ROS) and interleukin-1 beta (IL-1β). While activation of GCN2 has shown to mitigate susceptibility to dengue infection, GCN2 deficiency increases viremia and inflammation-associated pathologies. These findings reveal that the amino acid sensing pathway plays a significant role in controlling inflammation and viral infections. The current fact is that obesity/excess amino acids/mTOR activation aggravates COVID-19, and it might be possible that activation of amino acid starvation sensor GCN2 has an opposite effect. This article focuses on the amino acid sensing pathways through which host cells sense the availability of amino acids and reprogram the host translation machinery to mount an effective antiviral response. Besides, how SARS-CoV-2 hijack and exploit amino acid sensing pathway for its replication and pathogenesis is also discussed.

KEYWORDS
amino acid sensor GCN2, comorbidities, COVID-19, obesity, pro-inflammatory cytokine, SARS-CoV-2

1 | INTRODUCTION

The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), popularly abbreviated as COVID-19 pandemic, has posed a serious challenge to the human race for a collective combat globally. As of January 15, 2021, over 91,492,398 infected cases have been reported worldwide (https://covid19.who.int/), with a proportional increase in mortality rate, which has shown considerable variations based on the age, nutritional status, obesity, diabetes, cardiovascular diseases, and hypertension of the individual.[1] Of these, obesity and obesogenic associated comorbidities are recognized as the leading facilitators for the COVID-19 upsurge and increased mortality[2–5]; therefore, the mechanism of such correlations requires comprehensive understanding. One of the possible mechanisms postulated is the enhanced expression of human angiotensin-converting enzyme (ACE2) in individuals with obesity. ACE2 is the putative receptor on the host cells for SARS-CoV-2 anchorage and entry.[4] Hence, increased expression of the ACE2 receptor in COVID-19 patients could be one possible reason for the rise in infection and mortality rate. Related scientific studies collectively converge to suggest enhanced inflammation as the genesis to obesogenic comorbidities,[6–8] which further increases vulnerability to SARS-CoV-2

infection. Obesity has also been often linked with overnutrition, including excess availability of nutrients, particularly proteins and amino acids. Several convincing investigations have shown a strong correlation of upregulated plasma amino acid profiles with obesity.[9–12] Congruously, enhanced serum amino acid levels have also been reported during inflammation.[13] Our previous findings have shown that activation of the amino acid restriction (AAR) pathway abrogates intestinal inflammation and protects against viral infection.[14,15]

Because the viruses rely on host translation machinery and amino acid availability for viral protein synthesis, excess amino acids in individuals with obesity might be one of the crucial triggers involved in increased viremia and associated inflammation during SARS-CoV-2 infection. This suggests that the amino acid levels might act as a critical regulatory switch for sensing the viral footprints to program the translational machinery to restrict the viral protein synthesis[16,17] and enhance the translation of antiviral mediators on the other side. Given the importance of amino acid availability towards the maintenance of inflammatory homeostasis and in the regulation of translational machinery, the pathways involved in sensing amino acid levels might provide a possible explanation for the close association between COVID-19 and obesity. Therefore an in-depth understanding of the sensors involved in sensing AAR might provide alternate therapeutic strategies to combat obesity and COVID-19. This article focuses on the amino acid sensing pathways through which host cells sense the availability/shortage of amino acids, to reprogram the host translation machinery to mount an effective antiviral response and how viruses including SARS-CoV-2 hijack and exploit this pathway for its replication and pathogenesis.

2 | AMINO ACID SENSING PATHWAY

Nutrients, particularly amino acids, are essential biomolecules predominantly found in the cells which form the building block of proteins. Therefore, manipulation of amino acid levels in the cellular milieu could be an important strategy in the war between virus and the host, because viruses have been shown to hijack the host translational machinery and amino acid bioavailability for the synthesis of viral proteins.[18,19]

Eukaryotic cells recognize the footprints of viruses by sensing the availability of amino acids through the evolutionarily conserved amino acid sensing pathways that gauge the amino acid levels and play a pivotal role in determining protein synthesis by regulating global translational machinery.[20] The amino acid sensing pathway comprising mammalian target of rapamycin (mTOR) and general control nonderepressible 2 (GCN2) is primarily involved in sensing the presence or absence of an extracellular or intracellular pool of amino acids.[21] Despite these findings, the amino acid sensing regulation in response to amino acid availability still continues to stay unclear.

While mTORC1 as part of complex mTOR is involved in sensing and programming anabolic processes such as protein synthesis in the presence of amino acids, GCN2 gets activated in the absence of even a single amino acid and orchestrates catabolic events such as autophagy.[20,22]

Under normal conditions, the amino acid charged tRNA binds to the ribosome and provides the amino acids required for protein synthesis. GCN2 senses amino acid depletion through binding of accumulated uncharged tRNAs, thereby initiating its autophosphorylation, triggering the phosphorylation of eIF2α, a translation initiation factor, leading to the attenuation of global protein translation.[22]

On the other hand, mTOR senses the presence of amino acids by the amino acid receptors at the plasma membrane, which activate mTORC1 through Rag GTPases and Rheb, one of the functional complexes of mTOR.[21] The activation of mTORC1 allows its translocation to the lysosomal surface leading to the phosphorylation of 4EBP1, which releases eIF4E, thereby initiating protein synthesis.[23–25] In this regard, the amino acid transporter is called "transceptor" due to the dual role of translocation of amino acids and the activation of the signaling pathway inside the cell.[26] Additionally, mTORC1 activation involves several other functional regulatory complexes.[24] It has been shown that GCN2 activation during amino acid deprivation triggers sustained inhibition of mTORC1 kinase activity.[27,28] Therefore, GCN2 and mTOR not only dictate the destiny of protein synthesis[22] but also have the potential to promote or inhibit viral replication.[16,17]

3 | AMINO ACID STARVATION AND ITS POTENTIAL BENEFITS ON THE ADIPOSE TISSUE AND IN TURN OBESITY

Obesity is associated with a high volume of adipose tissue, which exhibits an enhanced expression of the viral entry receptor ACE2.[29,30] Therefore, individuals with obesity can host a large amount of viral load leading to the serious manifestation of the disease.[30] The adipose tissue in humans is primarily of two types, the white adipose tissue (WAT) and the brown adipose tissue (BAT).[31,32] While the WAT is associated with triglycerides and lipids, BAT is associated with upregulated uncoupling protein-1 (UCP1) stimulated thermogenesis.[31,32] In this regard, browning of WAT displays beneficial effects on metabolic disorders particularly such as obesity and its associated comorbidities.[33,34]

Therefore, it has been reported that amino acid deprivation, particularly leucine deprivation, has displayed a decrease in fat mass associated with increased lipolysis of WAT.[35] Hence, as the first responder to restriction of amino acids, activated GCN2 has also been reported to prevent the hyperactivation of mTORC1 by an ATF4 independent mechanism in diet-induced obese mice.[36] Studies also report a close association with the mTOR signaling pathway and obesity.[37] Further, it has been shown that enhanced expression of ACE2 leads to mTOR hyperactivation.[23] These observations help us speculate that amino acid sensing pathway in the adipose tissue might play a critical role in the pathogenesis of SARS-CoV-2.

4 | OBESITY/EXCESS AVAILABILITY OF AMINO ACIDS ACTIVATES MTOR PATHWAY AND SUPPORTS SARS-COV-2 REPLICATION

The evolutionarily conserved mTOR, a serine–threonine kinase, is one of the crucial sensors known to correlate obesity associated comorbidities with COVID-19. Currently, mTOR is increasingly explored for playing a huge role in alleviating the disease altogether.[38–43] mTOR is primarily composed of two subunits with distinct functions: mTORC1 and mTORC2. The upstream and downstream regulation of mTORC1 plays a pivotal role in coordinating various fundamental signaling pathways and in regulating various homeostatic functions such as autophagy, cell growth, and metabolism in response to nutrient bioavailability.[44] In addition, they also play a decisive role in programming protein synthesis machinery by dictating the translation fate of mRNA transcripts. In general, translation is a multistep event involving recruitment of ribosomes and eukaryotic initiation factors (eIFs) at the 5′ end of the mRNA transcripts (5′ cap-dependent translation).[45] In response to the availability of nutrients, mTORC1 activates the assembly of eIF4F complex and 5′ cap-dependent mRNA translation through phosphorylation of the p70S6 Kinase (S6K1) and translation repressor 4EBP.[44,46] Some of the viruses are known to hijack these processes for their own replication.[18,19] Interestingly, coronaviruses contain similar 5′ cap structures and thereby utilize the eIF4F complex for their own translation of viral proteins because blocking the assembly of eIF4F complex restricts human coronavirus viremia.[46]

The close correlation of obesity with excess nutrient availability, particularly enhanced levels of serum amino acids observed in individuals with obesity,[9,11] triggers hyperactivation of the mTOR pathway. Hence, this could be one of the possible explanations that link obesity with enhanced viral replication. However, this postulation requires comprehensive studies with regard to SARS-CoV-2. At the same time, in support of this, mTOR inhibition is also known to provide immunity to infection from influenza by modulating the antibody response.[47–49] Figure 1 illustrates the association of overnutrition/obesity/excess amino acids to upregulated levels of ACE2 receptors to which SARS-CoV-2 binds. This further activates mTOR resulting in upregulated host translation protein synthesis, which gets eventually hijacked by SARS-CoV-2 resulting in increased viral protein synthesis and increased viremia.

4.1 | Amino acid starvation triggers GCN2 activation and restriction of viral replication

Viruses are obligate parasites that hijack the host translational machinery and amino acids for the synthesis of viral proteins. As a protective measure, the host restricts global protein synthesis in order to suppress the synthesis of viral proteins during infection. GCN2 is an eIF2 kinase that is involved in sensing amino acid shortage as a footprint of viral infection by reprogramming host translational machinery. GCN2 upon activation phosphorylates eIF2-α resulting in decreased polysome formation and enforced shutdown of global protein synthesis, while triggering translation of host protective factors.[14,50,51] Notably, GCN2 has been shown to activate the innate antiviral pathway in response to many RNA viruses.[16,17,52]

Further, it has also been shown that SARS-CoV-1 significantly downregulates GCN2 to manipulate host-mediated protective responses.[53] However, the role of GCN2 and its role in viral replication during SARS-CoV-2 requires further exhaustive studies. In tune with these findings, we have also reported[15] the antiviral potential of GCN2 against dengue virus, wherein GCN2-deficient cells were significantly more prone to infection in comparison with the wild type cells. Considering these findings, we reason that GCN2-dependent amino acid starvation sensing plays a physiologically pivotal role in repressing viral progression and infection.

4.2 | Amino acid starvation sensing pathway controls inflammatory responses

Inflammation is one of the primary culprits that adversely affect the outcome of COVID-19 related pathologies.[54–57] Obesity and its associated comorbidities such as hypertension, diabetes, and atherosclerosis have been frequently linked with low-grade chronic systemic inflammation.[58–60] Correspondingly, obesity has been associated with excess availability of nutrients, particularly proteins and amino acids. However, a direct correlation between the status of amino acid availability, inflammation, and obesity during SARS-CoV-2 infection requires in-depth understanding. Emerging studies have also stressed the role of amino acid starvation sensor GCN2 in reducing inflammation[14,61,62] whereas mTOR activation in response to excess nutrients triggers enhancement in the inflammatory response.[11] This suggests an inverse proportionality of GCN2 to mTOR.[63] To this effect, it has been shown that the GCN2-deficient mice display enhanced reactive oxygen species (ROS) and interleukin-1 beta (IL-1β) production, which aggravates intestinal pathologies associated with inflammation.[14] Some reports also suggest reduced levels of inflammation in mice, which were fed with amino acid restricted diet.[14,64]

Furthermore, we have shown that pharmacological mimetics that mimic amino acid starvation like conditions suppress ROS and IL-1β production through riboclustering and autophagy.[50] Congruously, we have also shown that enhanced dengue virus infection in GCN2-deficient cells is correlated with increased production of pro-inflammatory cyclooxygenase-2/prostaglandin E2 (COX-2/PGE2) through profound activation of nuclear factor kappa B (NF-κβ) pathway.[15] All these findings collectively suggest an important role for amino acid sensing in the regulation of inflammation-associated with viral pathogenesis.

5 | THE HYPOTHESIS

Amino acid sensing pathway through the amino acid sensor GCN2 senses amino acid starvation and triggers homeostatic processes to

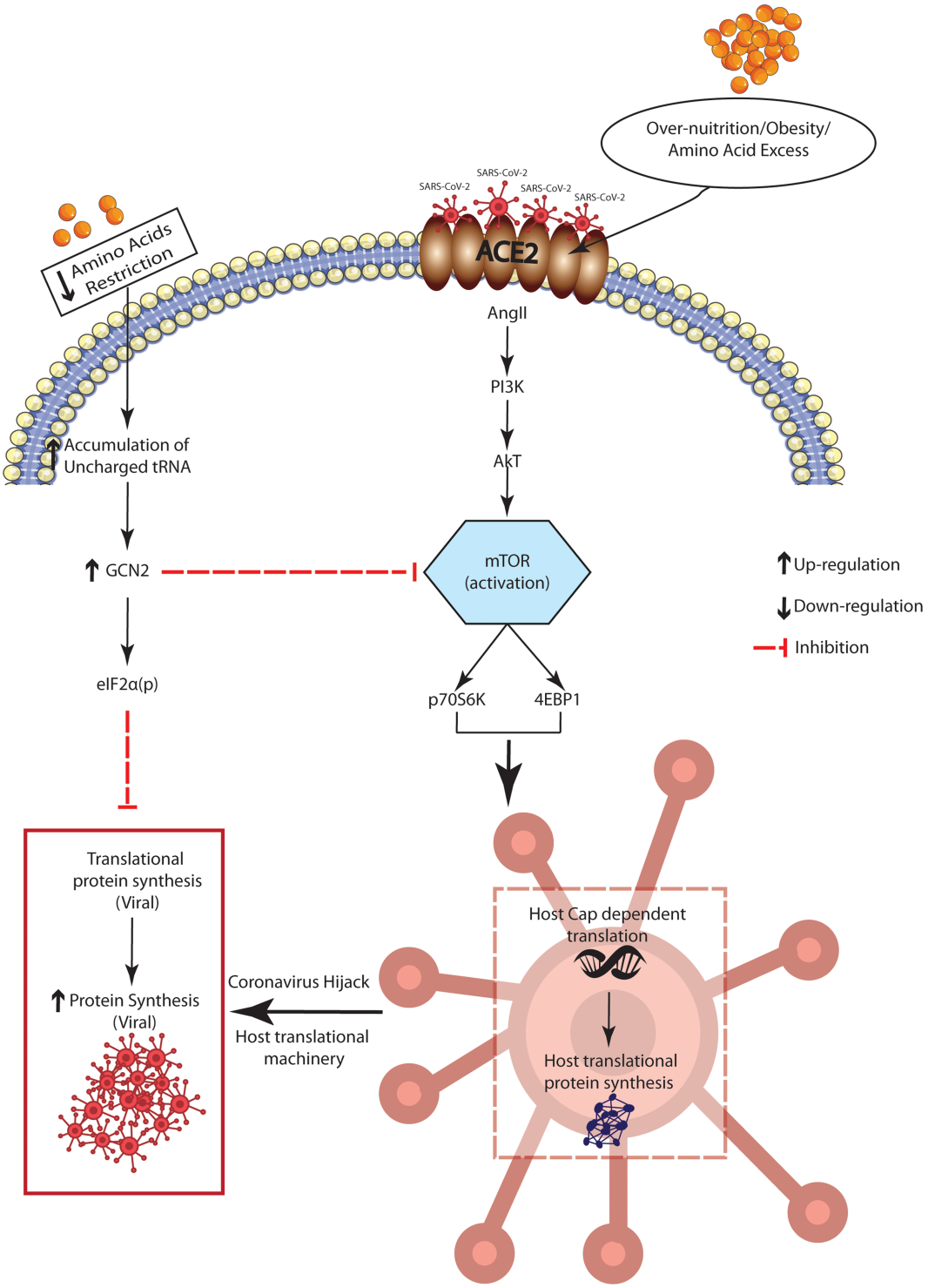

FIGURE 1 A schematic illustration depicting the association of overnutrition/obesity/excess amino acids to angiotensin-converting enzyme (ACE2) receptors leading to the hyperactivation of mammalian target of rapamycin (mTOR). The upregulated host translation is hijacked by the coronavirus resulting in increased viremia. On the contrary, activation of the amino acid sensor general control nonderepressible 2 (GCN2) inhibits viral protein synthesis and replication

restrict inflammation and viral replication.[15,50] On the other hand, mTOR programs the host translation machinery in response to the amino acid abundance which has also been reported to be exploited by Coronaviruses for their own multiplication.[65] Obesity is associated with excess amino acids and mTOR hyperactivation, which make individuals with obesity highly susceptible to viral infections. Moreover, there is a crosstalk between GCN2 and mTOR.[63] Thereby, we hypothesize that fine-tuning of the activity of amino acid starvation sensor GCN2, using pharmacological mimetics or development of nutraceuticals, might reduce the severity of infection and

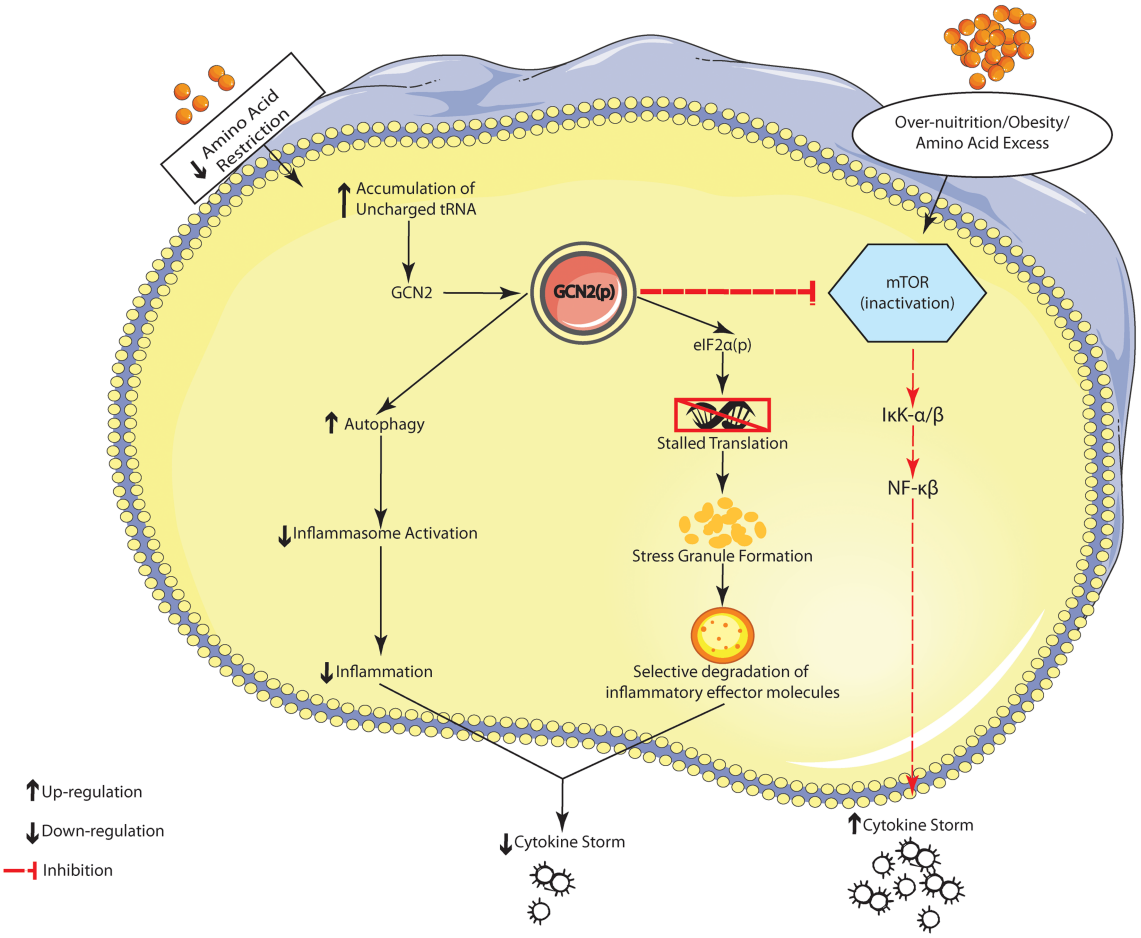

FIGURE 2 Graphic illustration of the proposed hypothesis showing the link between overnutrition/obesity/excess amino acids with inflammation reduction. The model represents the activation of the amino acid sensor general control nonderepressible 2 (GCN2), which senses amino acid restriction, stalls polysome formation, increases stress granule formation, and selectively degrades inflammatory molecules through the activation of autophagy. This upregulation culminates in the decrease of cytokine storm. On the other hand, excess nutrients, particularly amino acids, activate the mammalian target of rapamycin (mTOR) pathway and result in enhanced cytokine storm

inflammation in patients affected by SARS-CoV-2 (Figures 1 and 2). This calls for concerted efforts for an in-depth understanding.

Our previous studies[15,50] have shown that activation of GCN2 pathway leads to viral restriction, upregulation in autophagy, and downregulation in inflammation culminating in decreased cytokine storm. The hypothesis can be investigated by performing in vitro and in vivo studies on wild type and GCN2-deficient cells and animals, respectively.

6 | CONCLUSION

Obesity and obesogenic comorbidities are often associated with excess nutrients, particularly amino acids that trigger hyperactivation of mTOR-mediated amino acid signaling pathways. Hyperactivated mTOR signaling observed in individuals with obesity prepares an ideal platform for SARS-CoV-2 infection by hijacking the host translational machinery for viral replication and inflammation. Conversely, activation of AAR sensor GCN2 has shown to play a pivotal role in maintaining host immune homeostasis. Previous studies in our laboratory have demonstrated that GCN2 activation restricts dengue virus infection[15] and triggers suppression of intestinal inflammation by inhibiting pro-inflammatory IL-1β cytokine production.[50] However, the role of GCN2–AAR axis in the pathogenesis of SARS-CoV-2 needs further investigation.

In addition to controlling viral infections and inflammation, GCN2-mediated AAR sensing has been shown to play an important role in vaccine-induced immunity.[66] Earlier, it has been shown that the yellow fever vaccine, which is one of the most successful vaccines, works through activation of GCN2–AAR axis through enhanced autophagy and antigen presentation.[67] We have recently shown that activation of GCN2-mediated AAR sensing by pharmacological mimetic augments vaccine efficacy.[66] As we have progressed into the vaccination phase of COVID-19 with some of the vaccines already approved by Food and Drug Administration (FDA), we still believe that the involvement of AAR mimetic in the vaccine formulations as a nutraceutical adjuvant might be an effective strategy for design and development of a safe vaccine against COVID-19.

The above findings suggest that the amino acid sensing pathway plays a crucial role in the maintenance of cellular homeostasis. Availability of excess amino acids during obesity has been associated with chronic hyperactivation of mTOR, which favors viral replication and inflammation while AAR via GCN2 has an opposite effect. The clinical benefits of amino acid sensing could be extrapolated through activation of GCN2–AAR pathway or suppression of mTOR signaling, which might provide an effective therapeutic approach to control COVID-19 and its associated inflammatory pathologies. However, this merits further investigation in deciphering the role of GCN2/mTOR axis in COVID-19 susceptibility.

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CONFLICT OF INTEREST

No conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

NK conceptualized the idea. NK and AMP wrote the manuscript. AMP prepared the figures. All the authors have read and approved the manuscript for submission.

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