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Obesity and COVID-19: The mTOR pathway as a possible culprit

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1 | COVID-19 AND OBESITY

The coronavirus disease 2019 (COVID-19) pandemic, caused by a single-stranded RNA virus,[1] has demonstrated considerable variations in rate and mortality globally.[2] These variations have been explained by several factors, including age, data accuracy, and obesity.[2] The mechanisms by which obesity increases the rate/mortality of COVID-19 need to be comprehensively understood. Possible mechanisms include associated comorbidities and enhanced virus entry through the human angiotensin-converting enzyme 2 (ACE2).[2] ACE2 is the putative receptor for coronavirus entry into host cells. In adipose tissues, ACE2 expression levels exceed those expressed in the lung. Individuals with obesity present an increased volume of adipose tissues, and consequently higher ACE2 levels, which could increase their susceptibility to COVID-19.[2] Researchers are still exploring other possible explanations. Viruses largely rely on the host cell translation machinery, exploiting the translational apparatus of the infected cell to express viral proteins.[1] Certain pathways/molecules, hyperactivated in obese hosts and shared with those in coronaviruses, could further rationalize the association of obesity with COVID-19.

2 | CAP-DEPENDENT TRANSLATION IN HUMANS AND CORONAVIRUSES

2.1 | Cap-dependent translation and its regulation by the mTOR pathway in humans

Translation, the process by which a protein is synthesized from mRNA, is a crucial phase in the protein synthesis machinery and cell cycle.[1] Typically, translation is initiated by the binding of several eukaryotic initiation factors (eIFs) and ribosomes to the 5′ end of mRNA molecules termed as 5′ cap-dependent translation.[1] Especially, the proper binding of ribosomal subunits to mRNA is mediated by the eIF4F complex, which consists of three initiation factors: (1) eIF4A, an ATP-dependent RNA helicase, (2) eIF4E, the cap-binding protein, and (3) eIF4G, a scaffolding protein. In the absence of stimulation from upstream molecules, the eIF4E binding protein (4EBP), a repressor of translation, binds to eIF4E, preventing the interaction of eIF4E with eIF4G, as well as the assembly of the eIF4F complex.[1]

Assembly and activation of the eIF4F complex at the 5′ -end of mRNA are controlled by the mammalian target of rapamycin (mTOR) pathway. This pathway is composed of a series of molecules highly conserved in eukaryotes during evolution,[3] and regulates translation, protein and lipid synthesis, proliferation, and growth in response to nutrient availability.[4] An extensive list of molecules triggered downstream of the mTOR pathway has been previously reviewed. [4–6] Here, we focused on those molecules upregulated by nutrients that might favor the initial translation of coronaviruses.

mTORC1, a serine/threonine kinase, is activated by nutrients and predominantly acts through the phosphorylation of two key effectors, p70S6 kinase 1 (S6K1) and 4EBP.[4] mTORC1 directly phosphorylates S6K1, which in turn phosphorylates and activates certain substrates involved in mRNA translation initiation, including eIF4B, a positive regulator of the 5′ cap-binding eIF4F complex. mTORC1 phosphorylates 4EBP at multiple sites to induce its dissociation from eIF4E, triggering 5′cap-dependent mRNA translation by the assembled eIF4F complex.[4]

2.2 | Cap-dependent translation in coronaviruses: Hijacking the eIF4F complex

The amplification of RNA viruses is dependent on the successful hijacking of the host cell translation apparatus by viral mRNAs.[7] In cultured cells, replication of most coronaviruses is associated with the suppression of host protein synthesis.[1] Interestingly, since genomic and subgenomic coronavirus mRNAs contain a 5′cap

structure, most coronavirus mRNAs are believed to undergo cap-dependent translation using eIF4F.[1] Blocking eIF4F assembly and activity by preventing the binding of eIF4E to eIF4G reportedly suppresses human coronavirus-229E replication, indicating the importance of hijacking the host eIF4F complex for virus replication.[1,8] It needs to be determined whether the 2019 novel coronavirus is similar to other coronaviruses regarding 5′cap-dependent translation.

3 | REGULATION OF THE MTOR PATHWAY BY NUTRIENTS

The mTOR pathway integrates nutrient signals to regulate the translation initiation of mRNAs crucial for biosynthesis.[3,4,9] Upon feeding, the synthesis machinery and mTOR pathway are triggered within 30 min in the liver, remain elevated for 90 min, and return to baseline after 120 min.[10] However, following nutrient starvation, the mTOR pathway is downregulated to adjust cellular metabolism for survival.[4,5]

3.1 | Obesity/overnutrition hyperactivates the mTOR pathway

Both in-vitro and in-vivo studies have revealed the association between obesity and the mTOR pathway.[11] Notably, obesity and overnutrition trigger chronic hyperactivation of mTOR activity in multiple tissues.[11,12] In humans, increased S6K activity[13,14] and overphosphorylation of translation suppressor 4EBP have been observed in obesity.[14] Furthermore, accelerated adipogenesis and obesity have been reported in mice presenting a disrupted *4EBP* gene.[15] Indeed, targeting the mTOR pathway has been suggested as a treatment for obesity. Consistently, S6K knockout mice are found resistant to obesity owing to an impaired biosynthesis pathway downstream of mTORC1.[11]

3.2 | Hypothesis

By sensing nutrient availability, mTORC1 regulates the eIF4F complex assembly and cap-dependent mRNA translation machinery.[4] Obesity hyperactivates the machinery,[12] whose hijacking is vital to the replication of coronaviruses.[1,8] Accordingly, we hypothesize that coronaviruses might exploit the additionally available translation-related molecules in obese hosts to initiate their cap-dependent translation and replication. The accelerated replication of viral mRNAs can potentially increase susceptibility to COVID-19. Figure 1 depicts a schematic summary of our hypothesis about COVID-19 susceptibility through the mTOR pathway in obesity. Our hypothesis can be tested by investigating COVID-19 susceptibility in obese animal models deficient in the eIF4F complex.

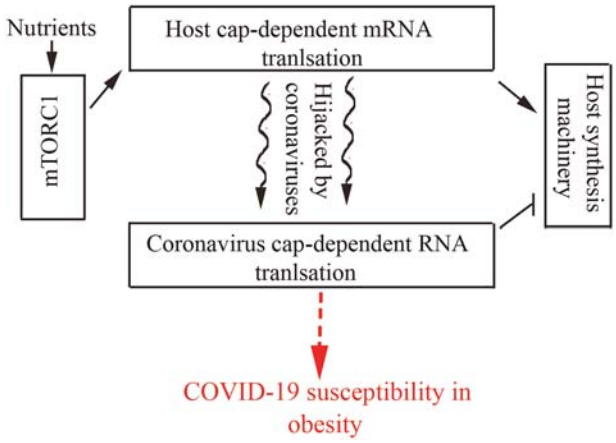

FIGURE 1 A schematic illustration of COVID-19 susceptibility through a hyperactivated mTOR pathway in obesity. mTOR pathway regulates cap-dependent mRNA translation and synthesis machinery in humans. Coronaviruses are RNA viruses, hijacking the host cap-dependent translation machinery to replicate. Obesity hyperactivates the mTOR pathway and likely enhances the virus replication and COVID-19 susceptibility

4 | CONCLUSION

In conclusion, mTOR pathway hyperactivation and enhanced translational apparatus in obesity/overnutrition might provide an ideal platform for coronavirus replication, demonstrating translation dependent on the host cells. Further research is crucial to elucidate the role of the mTOR pathway in COVID-19 susceptibility.

CONFLICT OF INTEREST

The authors declared no conflicts of interest.

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REFERENCES

1. Nakagawa K, Lokugamage KG, Makino S. Viral and cellular mRNA translation in coronavirus-infected cells. *Adv Virus Res*. 2016;96:165-192.
2. Kassir R. Risk of COVID-19 for patients with obesity. *Obes Rev*. 2020;21(6):e13034.
3. Bolourian A, Mojtahedi Z. Streptomyces, shared microbiome member of soil and gut, as 'old friends' against colon cancer. *FEMS Microbiol Ecol*. 2018;94(8):fiy120. https://doi.org/10.1093/femsec/fiy120
4. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. *Cell*. 2017;168(6):960-976.
5. Jung CH, Ro SH, Cao J, Otto NM, Kim DH. mTOR regulation of autophagy. *FEBS Lett*. 2010;584(7):1287-1295.
6. Martelli AM, Buontempo F, McCubrey JA. Drug discovery targeting the mTOR pathway. *Clin Sci (Lond)*. 2018;132(5):543-568.
7. Bushell M, Sarnow P. Hijacking the translation apparatus by RNA viruses. *J Cell Biol*. 2002;158(3):395-399.
8. Cencic R, Desforges M, Hall DR, et al. Blocking eIF4E-eIF4G interaction as a strategy to impair coronavirus replication. *J Virol*. 2011;85(13):6381-6389.

9. Bolourian A, Mojtahedi Z. Monitoring of CD8(+) T-cell activity in mTOR inhibitor-treated cancer patients for successful immunotherapy. *Arch Med Res*. 2016;47(5):401-402.
10. Gazzaneo MC, Orellana RA, Suryawan A, et al. Differential regulation of protein synthesis and mTOR signaling in skeletal muscle and visceral tissues of neonatal pigs after a meal. *Pediatr Res*. 2011;70(3):253-260.
11. Tavares MR, Pavan IC, Amaral CL, Meneguello L, Luchessi AD, Simabuco FM. The S6K protein family in health and disease. *Life Sci*. 2015;131:1-10.
12. Mao Z, Zhang W. Role of mTOR in glucose and lipid metabolism. *Int J Mol Sci*. 2018;19(7):2043.
13. Catalan V, Gomez-Ambrosi J, Rodriguez A, et al. Expression of S6K1 in human visceral adipose tissue is upregulated in obesity and related to insulin resistance and inflammation. *Acta Diabetol*. 2015;52(2):257-266.
14. Lastres-Becker I, Nonis D, Eich F, et al. Mammalian ataxin-2 modulates translation control at the pre-initiation complex via PI3K/mTOR and is induced by starvation. *Biochim Biophys Acta*. 2016;1862(9):1558-1569.
15. Le Bacquer O, Petroulakis E, Paglialunga S, et al. Elevated sensitivity to diet-induced obesity and insulin resistance in mice lacking 4E-BP1 and 4E-BP2. *J Clin Invest*. 2007;117(2):387-396.

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