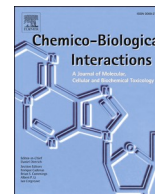




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Rapamycin as a potential repurpose drug candidate for the treatment of COVID-19

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ABSTRACT

The novel human coronavirus-2 (HCoV-2), called SARS-CoV-2, is the causative agent of Coronavirus Induced Disease (COVID-19) and has spread causing a global pandemic. Currently, there is no vaccine to prevent infection nor any approved drug for the treatment. The development of a new drug is time-consuming and cannot be relied on as a solution in combatting the immediate global challenge. In such a situation, the drug repurposing becomes an attractive solution to identify the potential of COVID-19 treatment by existing drugs, which are approved for other indications. Here, we review the potential use of rapamycin, an mTOR (Mammalian Target of Rapamycin) inhibitor that can be repurposed at low dosages for the treatment of COVID-19. Rapamycin inhibits protein synthesis, delays aging, reduces obesity in animal models, and inhibits activities or expression of pro-inflammatory cytokines such as IL-2, IL-6 and, IL-10. Overall, the use of rapamycin can help to control viral particle synthesis, cytokine storms and contributes to fight the disease by its anti-aging and anti-obesity effects. Since, rapamycin targets the host factors and not viral machinery, it represents a potent candidate for the treatment of COVID-19 than antiviral drugs as its efficacy is less likely to be dampened with high mutation rate of viral RNA. Additionally, the inhibitory effect of rapamycin on cell proliferation may aid in reducing viral replication. Therefore, by drug repurposing, low dosages of rapamycin can be tested for the potential treatment of COVID-19/SARS-CoV-2 infection.

1. Introduction

Drug repurposing, or drug repositioning, is a method that uses an existing approved drug for the treatment of a rare or difficult to treat disease. It represents an alternative drug development strategy that can be performed in a shortened timespan and is more cost-effective compared to the traditional process of developing a new drug [1]. Furthermore, since common molecular pathways often contribute to many different diseases, there are substantial opportunities in exploring the potential of drug repurposing as a treatment option [2,3]. Using repurposed drug, targeting the multiple signaling pathways may yield a significant clinical benefit for the treatment of COVID-19. For example, earlier, the anticancer drug Imatinib, a cellular Abelson (ABL) kinase inhibitor, was found to be effective against SARS coronavirus

pathogenesis [4]. Drug repurposing has many advantages over traditional *de novo* approaches to drug discovery. Since a drug candidate with potential for repurposing has already gone through the clinical trial process and has been tested for toxicity, it is generally safe to use. However, the overall strategy requires time, funding, and knowledge of clinical trials and clinical pharmacology to support the use in patients. Although drug repurposing is not a new method, it has become of mainstream interest due to its clear advantage in the reduction of drug development time and cost. Also, there are fewer numbers of parameters required for drug repurposing during clinical trials than those required for a new chemical entity to pass through the trials. Furthermore, the existing validated information about those drugs including formulations, dosing, toxicities, mechanism of actions, pharmacokinetics, and pharmacodynamics help in reducing or bypassing the steps in preclinical

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and early clinical development [5]. Therefore, through drug repurposing, a potential drug molecule incurs lesser cost and may directly enter the phase-2 of clinical trials. This compares to traditional drug discovery where phase-1 clinical trials must first be conducted to address the safety, dosing, and toxicity profiles.

That is not to say design and development of new drug molecules are less important; however, for a new drug molecule, the process to pass through clinical trials can take 10–15 years and requires an investment of around \$1 billion to reach the point of regulatory approval. Often many of the drugs never make it to that stage. In contrast, repurposing of a drug molecule can be done in a timespan of 2–6 years and only requires an investment approximating between US\$ 0.2–0.3 billion. The overall success rate of repurposed drugs is similar to that of drugs developed through the *de novo* route. Thus, it is the lack of drug efficacy that remains the primary reason for attrition during clinical trials, even for the repurposed drugs. Furthermore, if the repurposed drugs require different exposure routes than those used and approved originally, then pharmacokinetic and toxicology studies will also be required. The fact remains that reduced time and cost of repurposing drug candidates remains a prominent advantage. Additionally, since these drugs were already proven to be sufficiently safe, they are less likely to fail safety tests when used for a different indication.

The current COVID-19 pandemic is caused by SARS coronavirus-2 (SARS-CoV-2), which is an enveloped positive-sense, single-stranded RNA virus similar to the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) viruses [6]. SARS and MERS led outbreaks are well known globally for their severe infection and lack of effective therapeutic drugs, which led to high morbidity and mortality rates. For the prevention or treatment of SARS-CoV-2 infection, there is no vaccine or drug at the present time. Antiviral agents

developed in the future for the SARS-CoV-2 will target specific viral components, but resistance to these drugs may develop due to multiple mutations in viral RNA, which leads to new viral variants. Therefore, therapeutics targeting the host-cell machinery required for essential viral functions such as entry to host cells, viral replication, assembly, and viral release must be considered for future drug development. Due to the time and monetary expenses of developing a new drug through the process of drug discovery, the drug repurposing represents a tremendously valuable and impactful avenue for cost-effective and timely treatment of COVID-19.

Rapamycin for the treatment of COVID-19: Rapamycin is a macrolide immunosuppressant that inhibits the mTOR. The mTOR is a serine/threonine protein kinase that exists in the form of two protein complexes (mTORC1 and mTORC2) with distinct protein components and substrates [7]. The mTORC1 is sensitive to rapamycin as well as environmental stimuli including amino acids, glucose, and oxygen, and also known as rapamycin-sensitive complex. The mTORC2 acts downstream of PI3K, is best characterized as an effector of insulin/IGF-1 (Insulin-like growth factor-1) signaling [8] and is known as rapamycin-insensitive complex. The mTORC1 controls protein synthesis, autophagy, and many other cellular processes through the phosphorylation of ribosomal protein S6, p70S6K and 4E-BP1, whereas mTORC2 is required for maximal activation of numerous kinases, including AKT (Protein Kinase B). Rapamycin's target, mTOR, and related pathway proteins are widely expressed in nearly all eukaryotic organisms, and also regulates proliferation, transcription, autophagy, metabolism and programmed cell death (Fig. 1). Based on the scientific rationale and due to the involvement of mTOR in the regulation of pathways related to cell metabolism, proliferation, aging, and immune regulation, here we describe potential of drug repurposing that may

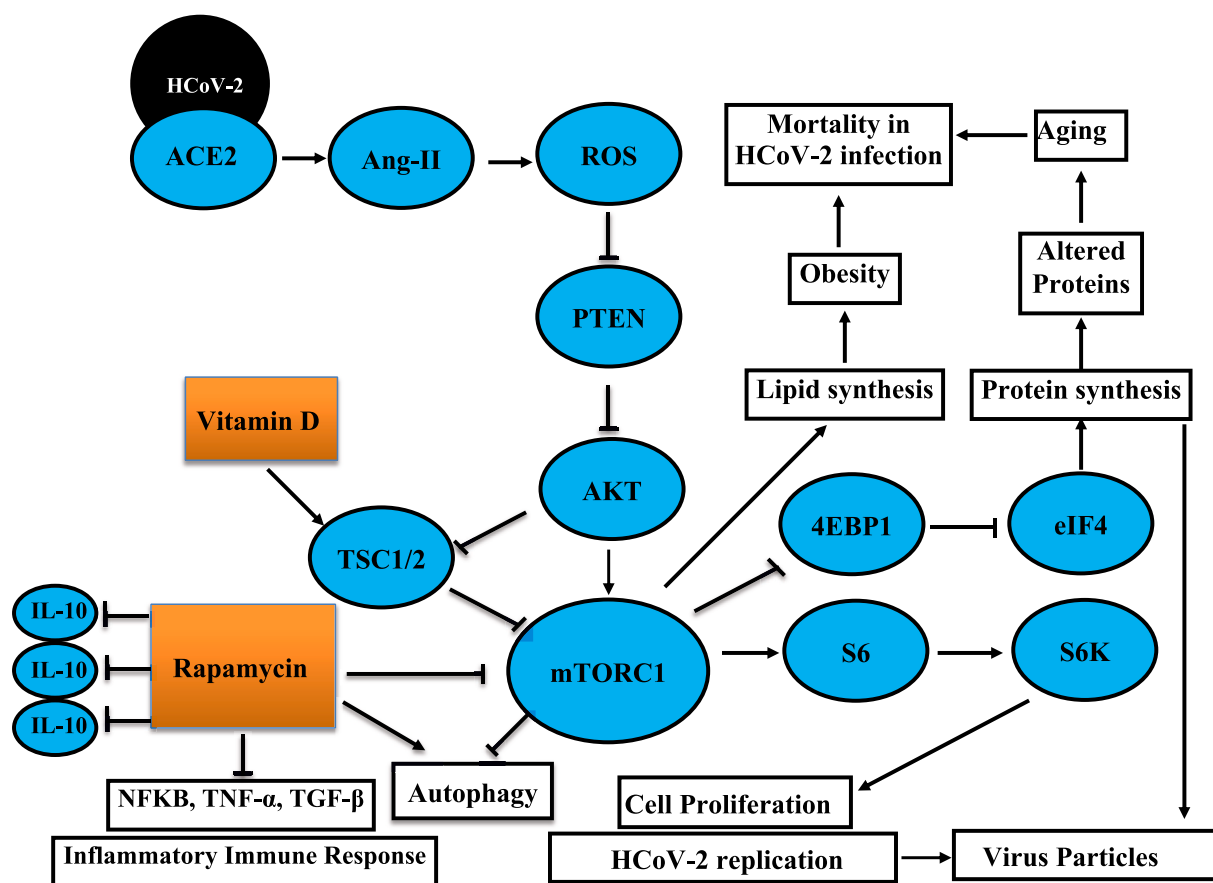


Fig. 1. Schematic of mTOR signaling and effect of rapamycin in mammalian cells: Rapamycin inhibits protein synthesis, cell proliferation, aging, obesity and increases the autophagy. As a drug repurposing candidate, rapamycin may have a potential therapeutic impact for the treatment of COVID-19 patients.

offer an opportunity to consider rapamycin as a drug candidate for the treatment of COVID-19.

Rapamycin inhibits protein synthesis and cell proliferation: Although rapamycin was originally described as an anti-fungal agent, it was soon discovered that it inhibits T-cell proliferation as an immunosuppressive agent [9,10], and reduces protein synthesis by inhibiting the initiation of translation. Being an FDA-approved drug for the selected indications, rapamycin has been used for a diverse set of applications including for treatment of renal cancer [11,12]. Mutations of upstream regulators of the mTOR pathway, including phosphoinositide 3 kinase (PI3K), can lead to hyperactivation of the mTOR, which causes unconstrained cell growth. Whenever the growth factors are not abundant, the PI3K signaling is inhibited by PTEN (Protein encoded by the phosphatase and Tensin homolog gene) [13], which reduces the mTOR activity. Similarly, serine/threonine kinase 11 (STK11) and the tuberous sclerosis complex (TSC1/TSC2) negatively regulates mTOR activity in energy deprived (low ATP) conditions [14,15]. On the opposite end, cells lacking functional PTEN, STK11, or TSC2 due to genetic mutations or deletions exhibit constitutively active mTOR signaling and results in multiple types of tumors. Such tumor cells also show an increase in phosphorylation of the mTOR downstream targets such as Eif-4EBP1 (eukaryotic translation initiation factor 4E binding protein 1) and S6 kinase due to uncontrolled mTOR signaling. In endometrial tumors, which exhibit PTEN inactivation, the rapamycin has been predicted to be efficacious, and have responded well to the treatment with temsirimolimus, a rapamycin derivative, using the precision medicine approach [16]. In multiple studies, it has been shown that rapamycin also suppresses the viability and proliferation of endothelial cells as determined by MTT assays using cultured endothelial cells treated with rapamycin. The mTOR, as a threonine kinase, phosphorylates S6K1 and 4E-BP1 to promote translation of the key genes associated with the cell cycle transition from G₁ phase to S phase. As an mTOR inhibitor, the rapamycin blocks the G₁ to S transition of the cell cycle. Interaction of SARS-CoV-2 with human proteins such as LARP1 and FKBP7, which are regulated by the mTORC1 pathway, suggest that mTOR is a key pathway in SARS-CoV-2 infection. The AKT mediated mTORC1 activation has been also observed in case of influenza virus infection. Also, the virus M2 protein mediated downregulation of mTORC1 inhibitor REDD1, and promoting mTORC1 activity, suggests that mTOR is the key pathway in other related virus infections as well (Fig. 1). Therefore, inhibition of mTOR by rapamycin would be pivotal to control the viral protein synthesis and replication in the case of human coronavirus infections.

Rapamycin delays aging: Over the last decade, it has become clear that reducing the expression or pharmacological inhibition of mTORC1 by rapamycin delays aging. By fine-tuning dosage and delivery systems, the drug has increased longevity in male and female mice [17]. Parallel studies also explored the potential of rapamycin as an important regulator of aging in yeast and *Caenorhabditis elegans* [18]. Rapamycin has shown to be effective against mouse models of age-related diseases, including cancer and Alzheimer's disease, and has even shown to rejuvenate the hearts of aged mice [19]. In a short-lived mutant strain of mice, rapamycin extends the life span up to nearly three-fold [20]. The drug extends the life span in normal mice as well as in yeast, worms, and flies, and prevents age-related conditions in humans [21]. In 2006, it was suggested that rapamycin could be used to slow down aging and age-related diseases in humans, becoming an "anti-aging drug" [22]. Rapamycin-mediated prolonged life span in mice has been observed at doses that have no noticeable side effects [23]. Additionally, rapamycin has been reported to actually rejuvenate tissues including aging hearts as well as hematopoietic stem cells [24]. There is also pharmacological and genetic data available showing that inhibition of mTORC1 increases the lifespan of multiple model organisms, therefore, making rapamycin a potential drug to increase longevity in humans. In addition, rapamycin prevents age-related diseases including atherosclerosis [25,26], neurodegeneration, retinopathy [27,28], and cardiomyopathy in rodents [29]. Considering the impact of rapamycin on aging, there is a need to

understand the underlying mechanism of rapamycin mediated longevity and how this can help in the treatment of COVID-19. Due to continuous protein synthesis, there is an accumulation of damaged and misfolded proteins, which is a hallmark of aging and age-related diseases. Inhibiting mTORC1 activity reduces protein synthesis and induces autophagy, a cellular recycling process that helps in eliminating the damaged proteins, and malfunctioning organelles such as damaged mitochondria [30]. As the mitochondria get older, there is an increase in the production of reactive oxygen species and a decline in their ability to generate ATP, which is considered a sign of aging. Although the interplay between rapamycin treatment, autophagy induction and protein degradation is not completely understood, the impact of rapamycin in delaying the aging is evident. Since the recent data has demonstrated a higher mortality rate in elderly people infected with SARS-CoV-2, rapamycin as an anti-aging drug may provide resistance to COVID-19 progression.

Although comparing worldwide data on COVID-19 mortality seems challenging, some countries showed higher COVID-19 mortality compared to others. Multiple factors may play a role, including the proportion of elderly people, accessibility of quality healthcare, and economic condition. One of the factors that recently investigated mortality rates in SARS-CoV-2 infected patients, is blood vitamin D concentration. There are studies that established the association of low vitamin D levels with increased chances of infectious disease including infections in the upper respiratory tract. Recently published clinical data provides that COVID-19 is linked with the vitamin D status of infected patients [31]. Elderly infected patients with normal levels of vitamin D were shown to have a better recovery rate than the patients deficient in vitamin D. According to the study, the effect comes from vitamin D supported defense in the respiratory epithelium, thus becoming infected with the virus and development of COVID-19 symptoms is less likely. Secondly, vitamin D might help to reduce the inflammatory response to SARS-CoV-2 infection, which is deregulated in COVID-19 especially the renin-angiotensin system [32]. Vitamin D is known to interact with angiotensin converting enzyme 2 (ACE2), which is used by SARS-CoV-2 as an entry receptor. In supplement, vitamin D is known to inhibit mTOR signaling and cell proliferation in multiple cell types [33,34], which is a synergistic effect to rapamycin. The hormonal form of vitamin D, 1, 25-dihydroxy vitamin D (1,25(OH)₂D) performs multiple functions beyond its classical role in calcium homeostasis. Inhibiting mTOR and anti-proliferative effects of 1,25(OH)₂D have underlined the potential of vitamin D to be used for the treatment of common cancers too. Regulation of mTOR by vitamin D has shown that 1,25(OH)₂D regulates mTOR by stimulating expression of DNA damage-inducible transcript 4 (DDIT4), also known as regulated in development and DNA damage response 1 (REDD1), a suppressor of mTOR activity. The DDIT4-mediated inhibition of the mTOR pathway will also play a pivotal role in the delay of aging and mediating cellular responses to 1,25(OH)₂D. Vitamin D also inhibits osteoblast cell proliferation through the induction of DDIT4, and the expression of tumor suppressors, TSC1 and TSC2, in HuLM (human uterine leiomyoma) cells [35], which also reduce mTORC1 activity. Overall, the Vitamin D mediated survival of the patient might stem from multiple pathways converging around the mTORC1. The mTORC1 as a kinase controls autophagy, protein synthesis, cell proliferation, cell growth, metabolism, aging, and obesity. Therefore, rapamycin can impact all these processes by inhibiting mTORC1 pathway. In response to nutrients, mTOR signaling also acts as a key regulator of cell metabolism to coordinate the balance between anabolic and catabolic processes. During fasting, there are glucose deprived conditions that cause muscles and the liver to produce glucose via breakdown of glycogen (glycogenolysis), and the adipose tissues undergo cleavage of triglycerides into fatty acids through the lipolysis. However, during glucose-rich conditions, glycogen synthesis (glycogenesis) is favored in muscles and the liver, and lipid uptake is favored in adipose tissue. Inhibition of the mTOR pathway by rapamycin has been shown to have beneficial effects and protect against high fat

diet-induced obesity in C57BL/6J mice [36]. Further, statistical analysis of patients admitted to hospitals and died due to COVID-19 suggests that a higher number of young people died of COVID-19 in the USA than in Italy. A contributing factor to this higher mortality is greater occurrences of obesity in young people in the United States as compared to Italy. Therefore, rapamycin mediated anti-aging and anti-obesity effect may benefit COVID-19 patients when treated with this drug.

Rapamycin inhibits the secretion of Interleukin-10 (IL-10) and other cytokines: The COVID-19 patients show heterogeneous clinical symptoms from mild effects in the upper respiratory tract to severe pneumonia-like conditions or even acute respiratory distress syndrome (ARDS) in severe cases. The over-activation of the immune system due to infection leads to a cytokine storm in severely sick COVID-19 patients, which may lead to multiple organ failure and even death [37]. The cytokines released in such conditions include IL-2, IL-7, IL-10, MCP-1 (monocyte chemoattractant protein), MIP1A (Macrophage Inflammatory Proteins) and TNF- α (Tumor Necrosis Factor- α) [37]. Although cytokine response is meant to prevent the infection, because it is an unbalanced response, it can be very damaging to patients. Rapamycin is an immunosuppressant, and due to its ability to decrease secretion of cytokines such as IL-6, IL-2, and IL-10, can potentially control the cytokine storm in COVID-19 patients. Several published studies showed the inhibitory effect of rapamycin on IL-10 mRNA and protein levels, its regulator STAT-3 (signal transducer and activator of transcription-3), and on pro-inflammatory signaling in general [38]. Clinically, rapamycin has been in use as an immunosuppressive agent in allogeneic transplantation and may have mild side effects including anemia, fever, and glomerulonephritis. Another study presented that rapamycin inhibits the growth of tumors established from the EBV (Epstein Bar Virus) infected B cells in xenogeneic mouse models of post-transplant lymphoproliferative disease (PTLD). This effect of rapamycin on tumor growth was found via cell cycle arrest, induction of apoptosis, and inhibition of IL-10 secretion [39] (Fig. 1). The rapamycin mediated reduced IL-10 production was shown to be accompanied by a decrease in the constitutive activation of the STAT1 and STAT3, the growth-promoting transcription factors [39]. Moreover, the *in vitro* and *in vivo* data clearly showed the inhibition of IL-10 secretion by rapamycin in multiple studies [38,39]. In addition, the tumor cells treated with rapamycin showed a significantly suppressed secretion of IL-6, a cytokine that regulates the immune response and hematopoiesis with other functions. Several studies identified IL-6 as an important trigger for angiogenesis and lymphangiogenesis in tumors [40]. Since high levels of IL-6 are associated with COVID-19 as well as with lung lesions in these patients, a monoclonal antibody Tocilizumab targeting the IL-6 receptor is also being explored against COVID-19 in the clinical trials. Although monoclonal antibodies along with other small molecules are being explored, rapamycin brings distinct advantages due to its pleiotropic inhibitory nature on multiple cytokines, and other key pathways related to protein synthesis, aging, and obesity, all regulated through mTORC1.

2. Conclusion

Although a complete coverage of mTOR signaling towards hormone signaling, proliferation, viability, autophagy, and nutrient availability is beyond the focus of this review, it is important to mention that these factors play a key role in the replication of the SARS-CoV-2, its assembly, and release from the infected cells. The mTOR pathway is also a master regulator of these processes and has been shown to get modulated by viruses, including Influenza A, for the virus release from the cell. In one human study, H1N1 influenza patients were treated with rapamycin and the outcome was improved when the drug was used with steroids. However, in other studies due to immune suppression by rapamycin, the treatment caused higher morbidity and enhancement in viral replication. Many viruses including Cytomegalovirus (CMV) and human herpesvirus (HHV) require the pro-survival protein kinase pathway,

AKT, for the propagation of virus-laden cells. Inhibition of mTOR blocks downstream effects of AKT activation, inhibiting the over-growth of virus cell lines [41]. Additionally, rapamycin has also been shown to inhibit viral protein synthesis of pUL44 and pp65, key proteins necessary for CMV replication in macrophages [42]. One of the recently published studies has compared the immune responses in 76 COVID-19 patients and 69 healthy individuals and showed a reduced expression of HLA-DR and pro-inflammatory cytokines in myeloid cells, and impaired mTOR-signaling and IFN- α production by plasmacytoid DCs in infected patients [43]. In another study, a cohort of 115 patients has received sirolimus for prophylaxis of renal and/or pancreas transplant rejection. Out of these 115 patients, 80 patients switched late to sirolimus while 35 patients were with *de novo* use of sirolimus. Among those 80 patients, 11 patients were identified with interstitial pneumonitis, however, all of the 35 patients with *de novo* use of the drug did not show any symptoms of pneumonitis [44]. When Sirolimus was discontinued or the dose was reduced, the pneumonitis was resolved within 14–28 days in all the patients tested. Other studies also suggest that although the mTOR signaling is considered to be a key pathway in multiple diseases, and that has promoted the development of mTOR signaling inhibitors, including rapalogs (sirolimus, temsirolimus, everolimus, and deforolimus), but clinical development of these mTOR inhibitors has revealed that these drugs don't come without side effects. Some of these side effects could be unpredictable despite pharmacological efforts to develop drugs with an improved safety profile [45]. Therefore, with an mTOR inhibitor like rapamycin, strategies needed to be in place for the careful and proactive monitoring to reduce the risk of serious or irreversible adverse side effects. In general, most of the adverse effects associated with mTOR inhibitors are mild to moderate and dose-related or reversible upon cessation of treatment. However, the patients should be well educated on the potential side effects of mTOR inhibitors, with a decision support system based on individual patient characteristics [46]. Other published studies have shown that rapamycin significantly enhanced lysosomal accumulation of mTOR [47]. Two distinct Ras-related small GTPases, Rag and Rheb, associated with lysosomal membranes, activates the mTORC1. Rag recruits mTORC1 to the lysosomal surface where Rheb directly binds to mTORC1 and activates it [48]. There are fragments of evidence that implicate role for lysosomal dysfunction in inflammatory and autoimmune disorders, neurodegenerative diseases, and metabolic disorders such as lupus, rheumatoid arthritis, multiple sclerosis, Alzheimer disease, Parkinson disease, and even in cancers, which can bring the opportunities to therapeutically target the lysosomal proteins and processes [49]. A number of preclinical studies involving lysosomal regulators have been conducted over the years to explore the therapeutic opportunities, but only a handful of those therapeutics have so far moved into clinical development. One of the biggest advances in developing such strategies would be the adoption of a personalized approach by identifying the genetic signature that would allow those patients most likely to respond to a selected therapy. However, at this stage considering the limited knowledge of specific lysosome-directed drugs, predicting the potential responders based on genetic signature is still challenging. Therefore, further investigations are required to consider rapamycin as a potential drug to treat the COVID-19 patients, which obviously will also depend on the severity and heterogeneity of this disease from person to person.

Since rapamycin has been used for the treatment of various tumors, it is evident that the patients with a hyperactive mTORC1 signaling that drives tumor growth may respond better to rapamycin treatment. Therefore, mutations in mTOR and related upstream and downstream molecules have been used as a biomarker to predict the efficacy of rapamycin and its analogs [50].

It is already established that mTOR is activated by PI3Ks via AKT, and the PIK3CA is frequently mutated in a wide variety of common human tumors [50]. Recently, Weigelt et al. have demonstrated that breast cancer cells with PIK3CA mutations respond better to everolimus [51]. There are published studies that identified oncogenic variants of

PIK3CA and KRAS as determinants of response to everolimus [52]. It has been shown that human cancer cells that originated from different tissue types and harbor alterations in the PI3K pathway are responsive to everolimus. However, resistance to everolimus has been observed in a cohort of metastatic cancer patients when treated [52]. Similarly, PTEN (Phosphatase and tensin homolog), which is a negative regulator of PI3K, when deleted, may activate PI3K and downstream mTOR signaling and can be considered as a predictive marker for the everolimus response. Since the response to rapamycin and analog drugs vary person to person, the same may hold true when rapamycin to be considered for the COVID-19 treatment. Further, information about genetic aberrations may help in predicting the response but the disease microenvironment can add to the complexity to match the prediction with the real outcome.

The mTORC1, which is a major signaling intermediary to stimulate anabolic processes, promotes skeletal muscle growth by increasing the adipogenesis and lipogenesis [53], and therefore inhibiting mTOR contributes to tumor cachexia. Cachexia is a result of complex metabolic alterations and causes morbidity and mortality in patients with advanced cancers such as undifferentiated (anaplastic) thyroid carcinoma [54]. It has been recently shown that the severe COVID-19 patients show cachexia like conditions but such studies would need more data to make conclusions. Treatment with mTOR inhibitor may further add to already existing cachexia conditions in the COVID-19 patients. Since rapamycin has been shown to be both beneficial and detrimental, we postulate that using a lower dosage of this drug would be an effective strategy for treating COVID-19 without causing many side effects. Also, mild immunosuppression may reduce the cytokine storm and would have a positive impact on infected patients. It is very likely that regular rapamycin intake for the treatment of other conditions may have additive advantages in those individuals for developing some resistance against COVID-19. This needs to be confirmed and currently lacks clinical data to support this hypothesis. It is also very evident that for some reason, the COVID-19 patients with advanced chronological age showed a considerably higher mortality rate, which brings the question to whether there is a functional association between COVID-19 infection and the aging. The host receptors CD26 and ACE-2 (angiotensin-converting enzyme 2), which are the key receptors in COVID-19, show association with senescence [55]. The ACE-2 is a known inhibitor of cell proliferation and the CD26 is also known to be a cell surface marker of senescent cells. Even the drugs Azithromycin and Quercetin, which are proposed for the treatment of COVID-19 infection, show significant senolytic activity [55]. In addition, vitamin D, which has clearly shown to have anti-aging effects, was found to be deficient in severely sick COVID-19 patients than the patients recovered. There are *in vitro* and *in vivo* studies along with clinical data that support mTOR as a central pathway for regulating aging, metabolism, protein synthesis and cell proliferation, and strongly suggests the potential of rapamycin for the treatment of COVID-19. Importantly, recently, it has announced that a new trial will be performed soon by the Chinese University of Hong Kong to investigate the effect of rapamycin (sirolimus) and oseltamivir on the normalization of respiratory status and more depth in measuring in cytokines, pro-inflammatory mediators in influenza patients [56]. Also, there are *in silico* studies that identify mTOR as one of the central molecules in COVID-19 progression based on data from other human coronavirus infections using the network-based drug repurposing model [57]. Therefore, using a low dosage of rapamycin as a therapy to treat COVID-19, may be considered, however, first, it has to be tested on viral infected cells, in pre-clinical studies and followed by the clinical trials on COVID-19 patients, which may result in better recovery of patients infected with SARS-CoV-2.

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Authorship contribution statement

Amjad Husain and Siddappa N. Byrareddy equally contributed to the ideas and conceptualization, writing and editing of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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