Act Farma Terap. 2020; 18(2):102-108

The mTOR pathway as a target for SARS-COV-2: Rapamycin as a possible alternative pharmacological therapeutic for COVID-19

Letícia Barbosa Teixeira[1], Wilson C. Santos[1,2¶].

1 Faculdade de Farmácia, Universidade Federal Fluminense, Niterói, RJ, Brasil.
2 Instituto Teófilo Hernando de I+D del Medicamento, Universidad Autónoma de Madrid, España.

Resumen

El número de personas fallecidas por COVID-19 ha aumentado exponencialmente en todo el mundo. La pandemia demuestra ser devastadora y, por lo tanto, existe una necesidad urgente de encontrar opciones de tratamiento que protejan a los pacientes infectados. Mientras tanto, no hay medicamentos ni vacunas disponibles para las poblaciones. Por lo tanto, la búsqueda de enfoques farmacológicos efectivos todavía se persigue y es una gran necesidad. Durante la infección por SARS-CoV-2, hay una activación agresiva del sistema inmune que conduce a la hiperinflamación sistémica, lo que causa la ola de citocinas proinflamatorias conocidas como "la tormenta de citoquinas". La diana mamífera de la rapamicina (mTOR) es una serina / treonina quinasa que funciona como un regulador central del crecimiento y el metabolismo celular. La señalización de mTOR es una vía crítica involucrada en la supervisión del metabolismo celular, el desarrollo, la supervivencia, la senescencia, la tumorigénesis y la inflamación. La rapamicina y sus derivados son inhibidores específicos de la quinasa diana de rapamicina (mTOR) de mamíferos y, como resultado, son inmunosupresores y agentes antitumorales bien establecidos. En consecuencia, en el presente artículo analizamos la posibilidad de que la vía mTOR actúe como un objetivo para el SARS-Cov-2 y la rapamicina como una posible alternativa terapéutica farmacológica para COVID-19.

Palabras clave
COVID-19, Rapamicina, SARS-COV-2.

Conflicto de intereses
Este artículo no presenta conflicto de interés.

Summary

The number of deceased individuals from COVID-19 has been exponentially increasing all over the world. The pandemic proves to be devastating and, therefore, there is an urgent need to find treatment options that protect infected patients. Meanwhile, no medicines or vaccines are available for the populations. Hence, the research for effective pharmacological approaches are still pursued and are a high necessity. During SARS-CoV-2 infection, there is an aggressive activation of the immune system leading to systemic hyperinflammation, which causes the wave of pro-inflammatory cytokines known as "the cytokine storm". The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that functions as a central regulator of cell growth and metabolism. mTOR signaling is a critical pathway involved in overseeing cellular metabolism, development, survival, senescence, tumorigenesis, and inflammation. Rapamycin and its derivatives are specific inhibitors of mammalian target of rapamycin (mTOR) kinase and, as a result, are well-established immunosuppressants and antitumorigenic agents. Consequently, in the present article we analyze the possibility of mTOR pathway to act as a target for SARS-Cov-2 and rapamycin as a possible alternative pharmacological therapeutic for COVID-19.

Key words
COVID-19, Rapamycin, SARS-COV-2.

Conflict of interests
This article does not present a conflict of interest.

Presentation

The SARS-CoV-2 coronavirus has spread rapidly since December 2019 and has now caused COVID-19 pneumonia, a contagious and infectious acute respiratory disease, in almost every country in the world. The number of deceased individuals from COVID-19 has been exponentially increasing all over the world. The pandemic proves to be devastating and, therefore, there is an urgent need to find treatment options that protect infected patients. in the present article we analyze the possibility of mTOR pathway to act as a target for SARS-Cov-2 and rapamycin as a possible alternative pharmacological therapeutic for COVID-19.

The SARS-CoV-2 coronavirus has spread rapidly since December 2019 and has now caused COVID-19 pneumonia, a contagious and infectious acute respiratory disease, in almost every country in the world. According to data obtained from the website https://covid19.who.int on June 10, 2020, there were 7.127.753 documented cases in the world with 407.159 deaths. The pandemic proves to be devastating, therefore, there is an urgent need to find treatment options that protect infected patients, either by reducing or preventing disease progression. Prior research has shown that SARS-CoV-2 is a retrovirus with high structural homology to the coronavirus found in bats (Zhu et al., 2020), and also has significant homology with the acute and severe respiratory syndrome (SARS) virus (Lu et al., 2020). However, the new coronavirus has genomic and biochemical characteristics that can be considered the main cause of its outbreak in humans (Figure 1; Li et al., 2020). Nevertheless, the pathogenic mechanism of the virus remains unclear.

FIGURE 1

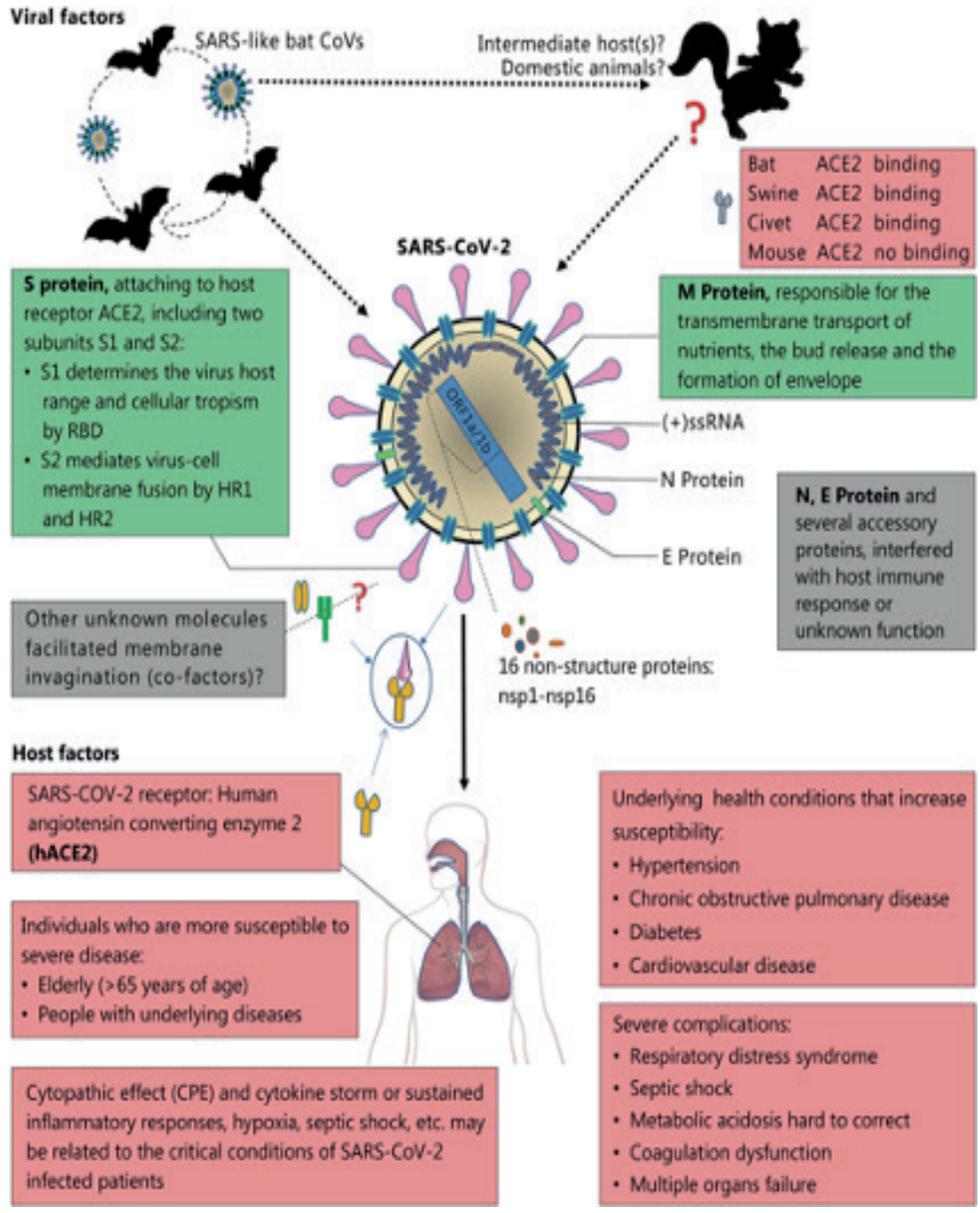

Figure 1. Viral and host factors that influence the pathogenesis of SARS-CoV-2. Bats are the reservoir of a wide variety of coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) -like viruses. SARS-CoV-2 may originate from bats or unknown intermediate hosts and cross the species barrier into humans. Virus-host interactions affect viral entry and replication. Upper panel: Viral factor. SARS-CoV-2 is an enveloped positive single-stranded RNA (ssRNA) coronavirus. Two-thirds of viral RNA, mainly located in the first open reading frame (ORF 1a/b), encodes 16 non-structure proteins (NSPs). The rest part of the virus genome encodes four essential structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein, and also several accessory proteins. S glycoprotein of SARS-CoV-2 binds to host cell receptors, angiotensin-converting enzyme 2 (ACE2), that is a critical step for virus entry. The possible molecules facilitated membrane invagination for SARS-CoV-2 endocytosis are still unclear. Other virus proteins may contribute to pathogenesis. Host factors (Lower panel) can also influence susceptibility to infection and disease progression. The elderly and people with underlying disease are susceptible to SARS-CoV-2 and tend to develop into critical conditions. RBD, receptor-binding domain; HR1, heptad repeats 1; HR2, heptad repeats 2.
Extract from: Guo et al. Military Medical Research (2020) 7:11.

Results have shown that SARS-CoV-2 can attack the beta-1 chain of hemoglobin, causing it to dissociate from Fe+2 and release porphyrin, thus inhibiting metabolism of the heme group and producing biochemical abnormalities in the blood of infected patients (Liu and Li, 2020) . Additionally, as Fe+2 dissociates from hemoglobin in the blood, oxygen transport becomes highly compromised. It is believed that a combination of viral proteins plus porphyrins (the heme group of hemoglobin) causes a variety of inflammatory reactions in the patient, thus producing the severity of the disease. Several compounds are being investigated in clinical tests as potential pharmacological agents against SARS-CoV-2, including through the process of drug repurposing (Rosa and Santos 2020). Drug repurposing (reprofiling, drug repositioning, or re-tasking) is the process that redevelops a drug for use in a disease other than that of its original use. As such, drug repurposing is an essential and universal strategy in drug development, via identifying approved drugs that are authorized for the treatment of other diseases and applying them for new uses. The basic principle underlying drug repurposing is that a common molecular pathway can be responsible for many diseases, and previously approved drugs already have precise information available regarding formulations, dose, toxicity, pharmacology, and clinical trial data. We have recently described some advantages of this strategy: a) lower costs and reduced time to reach the market because some clinical trial steps may not be required, especially phases I and II; b) existing pharmaceutical supply chains are available for formulation and distribution; c) the possibility of combination treatment with other drugs that could be more effective than monotherapy; and d) it may facilitate the discovery of new mechanisms of action for existing drugs, as well as new classes of medicines (Rosa and Santos, 2020).

Rapamycin, or sirolimus (Figure 2), is an antiproliferative and immunosuppressive drug that is recommended in organ transplants and in the treatment of some cancer types. Rapamycin was discovered around 1970 by researchers who were analyzing the soil of Easter Island (Rapa Nui), from which rapamycin derives its name. Rapamycin was identified as a metabolic product of Streptomyces hygroscopicus, an actinobacterium resident in the soil of the island (Seto, 2012).

FIGURE 2

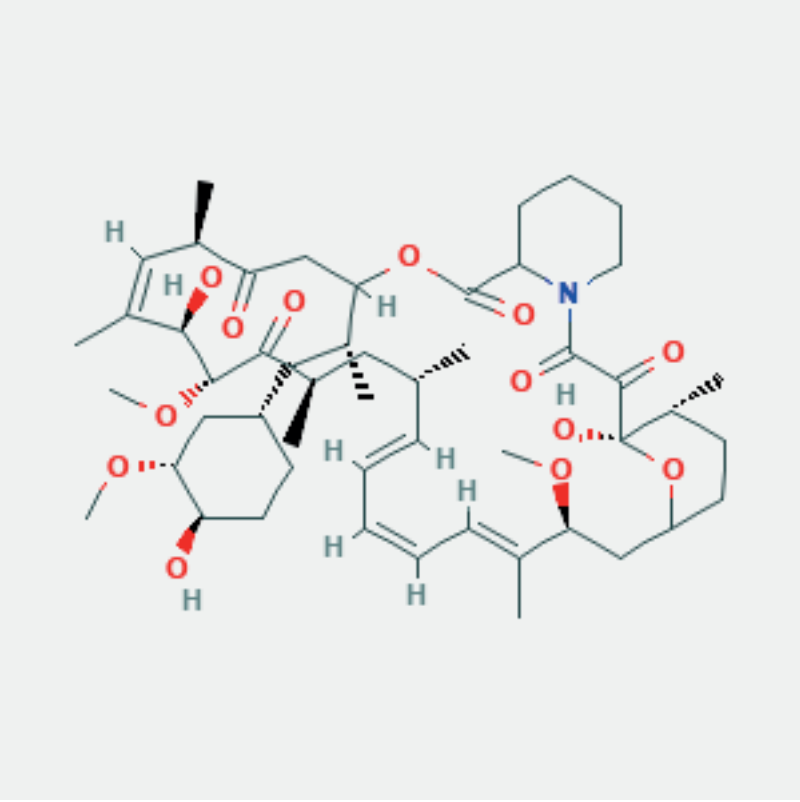

Figure 2. Rapamycin (Sirolimus); C51H79NO13 (from https://pubchem.ncbi.nlm.nih.gov/compound/Rapamycin-_TN, acessed in June 10th 2020).

Rapamycin's intracellular effects are mediated through the mechanistic target of rapamycin (mTOR) protein and its associated pathways through the mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2). mTOR is a 289-kDa serine/threonine protein kinase and is encoded by the FRAP1 gene. mTOR signaling is a critical pathway involved in overseeing cellular metabolism, development, survival, senescence, tumorigenesis, and inflammation (Zou et al., 2016). Considering the regulatory functions mediated by mTORC1 and that its activation is increased in cancer cells, rapamycin is considered an important tool against cancer. Rapamycin allosterically inhibits the activity of mTORC1 by binding to immunophilin FK-506-binding protein 12 (FKBP12), forming a complex which then attaches to the FKBP12-rapamycin-binding domain (FRB) at the carboxy (C) -terminal of mTOR and interferes with its function. The mTORC1 complex is associated with several important metabolic functions, including very intricate regulatory mechanisms that integrate cell growth and proliferation, protein, lipid, and nucleotide synthesis, energy metabolism, and autophagy. When investigating the effects of rapamycin on mTORC1 and mTORC2 individually, it was found that rapamycin induces an extremely sensitive short-term inhibition of mTORC1, followed by inhibition of mTORC2 with long-term exposure (Zou et al., 2016). The potential use of rapamycin and its rapalogs (synthetic analogs) in the treatment of SARS-CoV-2 is based on the thought that these therapeutics may decrease the overproduction of macrophages seen in the lungs of infected patients similar to the way by which they prevent rejection of newly transplanted organs. During SARS-CoV-2 infection, there is an aggressive activation of the immune system leading to systemic hyperinflammation, which causes the wave of pro-inflammatory cytokines known as "the cytokine storm" (Guo et al., 2020). In SARS-CoV-2 infection, the cytokine interleukin 37 (IL-37) produces an immunosuppressive response through mTOR and is capable of increasing the activity of AMPK (Maiese, 2020). IL-37 inhibits class II histocompatibility complex (MHC) molecules and inflammation by blocking IL-1beta, IL-6, TNF, and chemokine (C-C motif) ligand (CCL). As a result, IL-37 with its ability to modulate mTOR and AMPK, could be considered a new target for controlling hyperinflammation seen during viral infections such as SARS-CoV-2. Thus, it is reasonable to consider the employment of rapamycin as an alternative therapeutic agent in COVID-19 (Pandey et al. 2020). Additionally, studies have shown that mTOR is capable of regulating viral infection activity. For example, the growth and expression of West Nile virus is dependent on mTORC1-mediated regulation of various cytokines. However, activation of mTOR has also been shown necessary for anti-hepatitis C activity. There are indications that rapamycin is able to inhibit the intracellular activities of the virus and its subsequent release, effectively blocking the expression of viral proteins and the release of virions (Moccia et al, 2020). Previous studies have revealed potential clinical applications of rapamycin, such as by reducing Middle East respiratory syndrome coronavirus (MERS-CoV) infection by up to 60%, as well as by significantly improving the prognosis of patients with severe pneumonia due to H1N1 (Dyall et al, 2017). Rapamycin binds to immunophilin in the cell to form an immunosuppressive complex that inhibits the mammalian target of rapamycin (mTOR) kinase, in turn halting formation of the mTORC1 protein complex that is thought to play an important role in viral replication. Studies have shown that rapamycin inhibits mTOR signaling pathways and thereby is capable of inhibiting MERS-CoV. Zhou et al. (2020) considered potential synergism between rapamycin and dactinomycin (an inhibitor of RNA synthesis used in the treatment of various cancers) to inhibit the mTOR signaling pathway and RNA synthesis, thus inhibiting DNA topoisomerases 2-alpha and 2-beta in HCoV infected cells.

Furthermore, studies have indicated that rapamycin can be neuroprotective in Alzheimer's disease (AD; Cai and Yan, 2013). Increasing evidence suggests that the accumulation of aggregated proteins in AD may be caused by mTORC1-mediated protein synthesis and defective autophagic degradation. It is believed that the mechanism by which rapamycin is able to reduce signs of age in tested animals is through the activation of autophagy, since mTORC1 is also an important modulator in maintaining longevity. It has been shown that genetic or pharmacological inhibition of mTOR signaling prolongs the useful life of invertebrates, including yeasts, nematodes, and fruit flies. To test the hypothesis that rapamycin may delay aging in mice, Wilkinson et al. (2012) used a genetically heterogeneous mouse model and analyzed various age-related pathologies, as well as the age-dependent spontaneous activity of 9-month-old mice after treatment with rapamycin. Their results suggested that age-dependent changes occurred more slowly in mice treated with rapamycin, including changes in the heart, liver, endometrium, and adrenal glands. Rapamycin has also been shown to decrease the age-related decline in spontaneous activity in mice. Schinaman et al. (2019) showed that treatment with rapamycin improved proteostasis in elderly muscles in an autophagy dependent manner in Drosophila melanogaster.

Rapamycin as a prophylactic proposal for the most severe cases of COVID-19 common to the elderly

The elderly are considered a high-risk group for serious symptoms or the worsening of pre-existing comorbidities due to infection by SARS-CoV-2. Concerning the elderly, it is broadly known that many physiopathological consequences arise as a result of natural aging, for instance cardiovascular, metabolic, and neurological diseases, as well as those arising from an inefficient immune system.

Rapamycin is often called a “youth drug” based on results of anti-aging laboratory tests. According to Zhavoronkov (2020), COVID-19 can be designated as “gerolavic infection” due to the rates of infection, severity, and higher lethality in the population over 60 years old. The greatest weakness of this group is the comorbidities common to people of this age. Thus, the use of rapamycin and rapalogs as protective agents with respect to the appearance of age-related comorbidities and immunosenescence might be relevant to all diseases that require a high level of immunocompetence to fight off the pathogen. With the possibility of the future availability of a COVID-19 vaccine, this idea suggests that the concomitant use of this vaccine as a “geroprotector” may enhance the immune response.

Additionally, various effects from the binding of rapamycin to its receptor have been described with properties beyond immunosuppression. Paradoxically, the drug and its rapalog derivatives have demonstrated an immunostimulatory effect (Mannick et al, 2014), such as an increase in the response of T cells when encountering a pathogen, either due to infection or vaccination. It is possible that an immunosuppressive agent could, in a special dose regimen, assume an immunostimulatory function. In fact, studies have demonstrated the immunostimulatory effects of rapamycin on the response of memory T cells (CD 8+) after infection by pathogens. More recent studies have been able to demonstrate that treatment of monkeys with rapamycin increases memory immune responses (Tunner, 2011).

Therefore, the use of rapamycin, or its derivatives, as a prophylactic measure and method to improve immune function prior to exposure to pathogens, such as SARS-CoV-2, may be a powerful pharmacological tool, especially if combined with specific prophylactic therapies, such as vaccination, to enhance its beneficial effects.

Indeed, careful tests must be elaborated to validate this proposal for therapeutic use; studies that aim to determine the role of biological age might be important in helping to develop proposals for clinical trials regarding COVID-19. Consequently, to evaluate the pharmacokinetics, pharmacodynamics, virological efficacy, tolerability, and safety of rapamycin as an adjuvant therapy in treating patients with COVID-19 seems to be of importance.

Given the challenges presented by COVID-19, and that the current care is primarily symptomatic, enormous resources are being utilized in attempts to develop new therapeutic strategies and possible vaccines. A number of investigations seek to repurpose existing antiviral treatments for COVID-19, however, other drugs not traditionally considered to have antiviral properties may also prove exceedingly useful. In this respect, mTOR and its associated pathways with mTORC1, mTORC2, and AMPK offer exciting potential as new antiviral therapies.

References

1. Cai, Z., Yanb, L.J. Rapamycin, Autophagy, and Alzheimer's Disease. J. Biochem. Pharmacol. Res. 2013, 1(2), 84–90.
2. Dyall, J., Gross, R., Kindrachuk, J., Johnson R., Olinger Jr., G., Hensley, L. Frieman,M, Jahrling, P. Middle East respiratory syndrome and severe acute respiratory syndrome: Current therapeutic options and potential targets for novel therapies. Drugs, 2017, 77, 1935–1966.
3. Guo, Y.R., Cao, Q.D., Hong, Z.S., Tan, Y.Y., Chen, S.D., Jin, H.J., Tan, K.S., Wang, D.Y., Yan, Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Military Medical Research (2020) 7 (11), 2-10.
4. Li, S., Yuan, L., Guo Dai, G., Chen, R.A., Liu, D.X., Fung, T.S. Regulation of the ER Stress Response by the Ion Channel Activity of the Infectious Bronchitis Coronavirus Envelope Protein Modulates Virion Release, Apoptosis, Viral Fitness, and Pathogenesis. Front. Microbiol. 2020, 10: article 3022.
5. Liu, W., Li, H. COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. ChemRxiv 2020. Preprint. https://doi.org/10.26434/chemrxiv.11938173.v4
6. Lu, R., Juan Li, X.Z., Niu, P., Yang, B., Wu, H., Wang, W., Baoying Huang, H.S., Yuhai Bi, N.Z., Ma, X., Zhan, F., Tao Hu, L.W., Zhenhong Hu, H.Z., Zhou, W., Zhao, L., Yao Meng, J.C., Wang, J., Jianying Yuan, Y.L., Jinmin Ma, Z.X., Liu, W.J., Wenbo Xu, D.W., Holmes, E.C., Gao, G.F., Wu, G., Chen, W., Shi, W., Tan, W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020, 395: 565–74.
7. Maiese, K. The Mechanistic Target of Rapamycin (mTOR): Novel Considerations as an Antiviral Treatment. Current Neurovascular Research, 2020, 17, 1-6.
8. Mannick JB, Del Giudice G, Lattanzi M, Valiante NM, Praestgaard J, Huang B, Lonetto MA, Maecker HT, Kovarik J, Carson S, Glass DJ, Klickstein LB. mTOR inhibition improves immune function in the elderly. Sci Transl Med. 2014; 6:268ra179.
9. Moccia F., Gerbino A., Lionetti, V., Miragoli, M., Munaron, L.M., Pagliaro, P., Pasqua, T., Penna, C., Rocca, C., Samaja, M., Angelone, T. COVID-19-associated cardiovascular morbidity in older adults: a position paper from the Italian Society of Cardiovascular Researches. GeroScience Published on line May 20, 2020. https://doi.org/10.1007/s11357-020-00198-w.
10. Pandey, A., Nikam, A.N., Shreya, A.B., Mutalik, S.P., Gopalan, D., Kulkarni, S., Padya, B.S., Fernandes, G., Mutalik, S., Prassl, R. Potential therapeutic targets for combating SARS-CoV-2: Drug repurposing, clinical trials and recent advancements, Life Sciences, 2020, 256 (117883). https://doi.org/10.1016/j.lfs.2020.117883.
11. Rosa SGV and Santos WC. Clinical trials on drug repositioning for COVID-19 treatment. Rev. Panam. Salud Publica, 2020, 44 (20), 1-7.
12. Schinaman, J.M., Rana, A., Ja, W.W., Clark, R.I., Walker, D.W. Rapamycin modulates tissue aging and lifespan independently of the gut microbiota in Drosophila. Scientific Reports, 2019, 9, 7824, 1-10.
13. Seto, B. Rapamycin and mTOR: a serendipitous discovery and implications for breast cancer. Clinical and Translational Medicine 2012, 1 (29), 1-7.
14. Turner A.P., Shaffer V.O., Araki K., Martens C., Turner P.L., Gangappa S., Ford M.L., Ahmed R., Kirk A.D., Larsen C.P. Sirolimus enhances the magnitude and quality of viral specific CD8+ T-cell responses to vaccinia virus vaccination in rhesus macaques. Am. J. Transplant. 2011, 11,613–618.
15. Wilkinson, J.E., Burmeister L., Brooks S.V., Chan, C.C, Friedline, S., Harrison, D.E., Hejtmancik, J.F., Nadon, N., Strong, R., Wood, L.K.,Woodward, M.A., Miller, R.A. Rapamycin slows aging in mice. Aging Cell, 2012, 11, 675–682.
16. Zhavoronkov, A. Geroprotective and senoremediative strategies to reduce the comorbidity, infection rates, severity, and lethality in gerophilic and gerolavic infections. Aging 2020, 12 (8), 6492-6510.
17. Zhou Y., Hou Y., Shen J., Huang Y., Martin W., Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discov. 2020, 6, 14. Published 2020 Mar 16. doi:10.1038/s41421-020-0153-3.
18. Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G.F., Tan, W. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 2020, 382 (8): 727- 733.
19. Zou, Z., Chen, J., Yang, J., Bai, X. Targeted Inhibition of Rictor/mTORC2 in Cancer Treatment: A New Era after Rapamycin. Current Cancer Drug Targets, 2016, 16, 288-304.