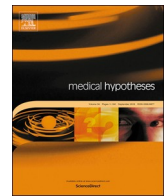




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Lithium chloride combination with rapamycin for the treatment of COVID-19 pneumonia



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To the Editor,

Dear Sir,

The current rapid spread of the coronavirus disease (COVID-19) originating from Wuhan, China, has been recently declared a pandemic by the world health organization [1]. Meanwhile the number of deceased individuals from COVID-19 has been exponentially increasing. Any live-attenuated vaccines may take time and give a low level of cross-strain immunity which renders the research for effective antiviral agents a high necessity.

Lithium chloride is a known efficacious treatment for bipolar disorder mainly because of its direct inhibition on glycogen synthase kinase 3 β , a phosphorylating and inactivating agent of glycogen synthase involved in energy metabolism, neuronal cell development, and body pattern formation [2]. Since lithium chloride has been demonstrated efficient in the treatment of human herpes simplex virus via its role in inhibiting viral DNA synthesis, it has been essayed as an antiviral agent especially for coronaviruses infections in many studies. As a matter of fact, lithium chloride seems to be a protective agent against the infective effect of the avian coronavirus infectious bronchitis virus mostly through an inhibition of viral protein production at the level of genomic RNA and subgenomic mRNA synthesis without affecting host cell protein production [3,4]. In addition, lithium chloride has been shown to inhibit the entry and replication of the porcine epidemic diarrhea virus into cells [5].

Rapamycin and its analogs are clinically important macrolide compounds produced by *Streptomyces hygroscopicus*. Streptomyces are bacteria that live in symbiosis with plants and it is expected that rapamycin is one of the products that helps the plants fight against pathogens such as other bacteria, fungi and viruses [6]. The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that functions as a central regulator of cell growth and metabolism. Rapamycin and its analogs are specific inhibitors of mTOR kinase and, as a result, are well-established immunosuppressants and antitumorogenic agents that play a role in cell proliferation and survival as well as macroautophagy suppression [7]. When rapamycin forms a complex with its receptor and interacts with mTOR, this blocks the cell-cycle progression of T cells thereby suppressing their induced proliferation by cross-linking of the T-cell receptors, antigenic peptides or cytokines such as interleukin-2

(IL-2) [8]. On another level, mTOR complex and glycogen synthase kinase 3 β have a direct mutual influence in order to regulate the immune response since mTOR complex inhibition regulates pro- and anti-inflammatory cytokine production via its capacity to inactivate glycogen synthase kinase 3 β [9]. In the transmissible gastroenteritis virus, autophagy seems to play an important role in this coronavirus infection. Treatment with rapamycin seems to induce autophagy and to protect cells against viral replication [10].

Patients with the most important lung injury related to COVID-19 are those who have a dysregulated response for the viral infection predominating in T cells function [11]. It might be hypothesized that COVID-19 may delay the interferon response until the virus has sufficiently replicated which causes a sensitization of T cells towards apoptosis and macrophage stimulation. Patients with the highest threshold for interferon-response such as the elderly seem to be most affected by COVID-19 pneumonia. The rationale of combining lithium chloride and rapamycin consists on reducing the possibility of viral replication at its lowest by reducing viral entry to cells and viral RNA synthesis (the effect of lithium due to protein synthesis inhibition via glycogen synthase kinase 3 β deactivation) from one part, and regulating the immune response and stimulating autophagy without apoptosis from another part (the effect of rapamycin via mTOR inhibition and T cell regulation). Clinical studies are further needed in this domain.

Conflict of interests

I certify that I don't have any conflict of interest to declare behind the manuscript entitled: "Lithium chloride combination with rapamycin for the treatment of COVID-19 pneumonia".

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.109798>.

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