Vaccines for COVID-19 may require a pharmacologic booster in elderly populations

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Resumen

Los adultos mayores y los inmunodeprimidos o que viven en centros de atención a largo plazo se han visto muy afectados por la pandemia de COVID-19. El plan para una vacuna COVID-19 debe considerar las alteraciones del sistema inmunológico en estas poblaciones para lograr los resultados esperados. Debe considerarse la adición de un agente farmacológico como método para mejorar la respuesta inmune de la vacuna..

Palabras clave

COVID-19, mTOR, rapamicina, vacunas.

Conflicto de intereses

Este artículo no presenta conflicto de interés.

Summary

Older adults and those who are immunosuppressed or living in long-term care facilities have been greatly affected by the COVID-19 pandemic. The plan for a COVID-19 vaccine must consider the immune system alterations in these populations in order to achieve the expected results. The addition of a pharmacological agent as an approach to improve the immune response of the vaccine should be considered.

Key words

COVID-19, mTOR, rapamycin, vaccines.

Conflict of interests

This article does not present a conflict of interest.

The COVID-19 pandemic is still devastating the world. According to data obtained from the World Health Organization website (https://covid19.who.int) on November 26, 2020, there were 59.816.510 confirmed cases worldwide and 1.410.378 deaths. No vaccines or medicines are currently available to mitigate or eradicate the SARS-CoV-2 infection. The world is still waiting for a route to end this devastating pandemic and try to return to normal life, as it once was. In the meantime, research on vaccines for COVID-19 have recently been proved to come close to a conclusion.

A recent report by Cassandra Willyard, published in Nature, raised some important questions about the effectiveness of a COVID-19 vaccine in the elderly population, as these individuals account for the majority of serious COVID-19 cases and associated deaths. The loss of activity of the immune system with age is a phenomenon known as immunosenescence, which can leave the body susceptible to infections and may also impair the response to vaccines. Thus, it is necessary to find tools to address this issue and provide the elderly with the best treatment options for COVID-19.

The search for a COVID-19 vaccine is being pursued by many pharmaceutical companies, and there is a consensus that the COVID-19 vaccine would have to protect at least half of vaccinated individuals to be considered effective. However, it remains unclear whether it will be possible to achieve this goal in the special elderly population considering the immunosenescence observed in these individuals. Thus, the testing of SARS-CoV-2 vaccine candidates in older populations is of critical importance. Every component of the immune system can be naturally affected by age, and some cell types can even be depleted in older individuals. Therefore, it is of great importance to potentiate the immune system response to a SARS-CoV-2 vaccine in this population.

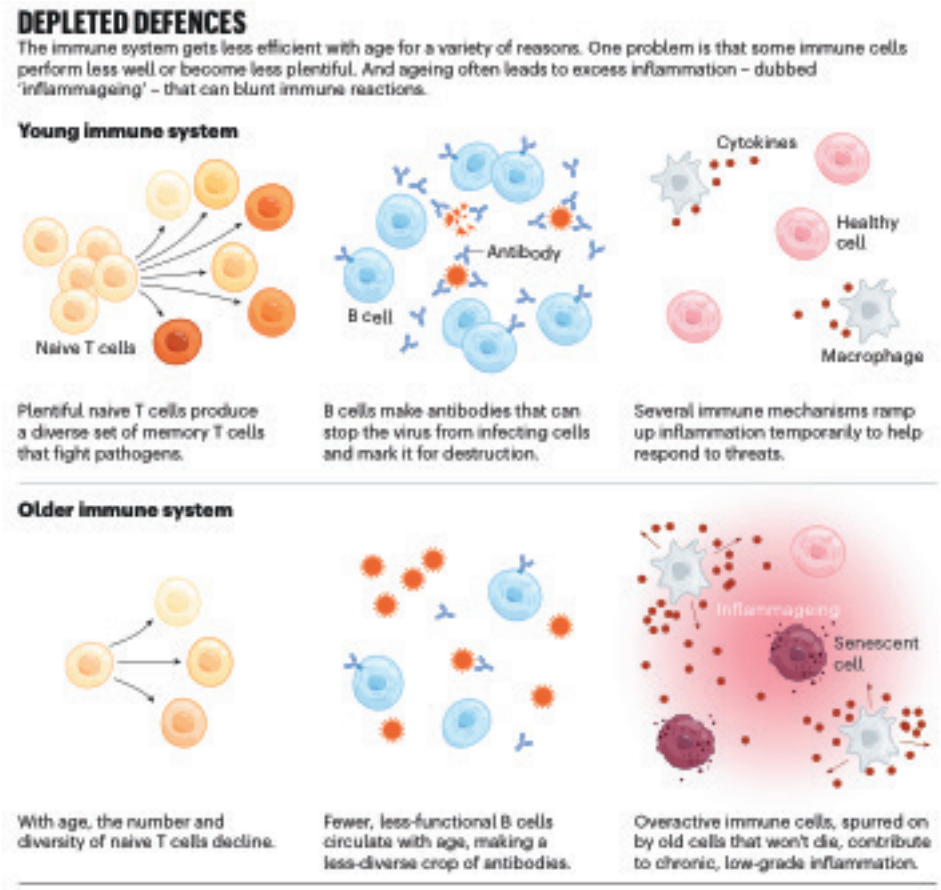

Figure 1. Comparison of the immune systems of younger and older people. Figure reproduced from Cassandra Willyard, Nature, volume 586, 15 October 2020, page 352.

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In a press release from November 16, 2020, the biotech company Moderna, based in Cambridge, Massachusetts, reported that its vaccine candidate mRNA1273 is more than 94% effective at preventing COVID-19 based on an analysis of 95 cases in its ongoing phase III efficacy trial. However, whether the vaccine works as well in higher-risk groups such as older adults is still an open question. The company reported that, of the 95 cases included in the analysis, 15 were aged over 65 years; however, they did not indicate which arm of the trial these participants were in.

A recently published paper by the consortium led by researchers at Oxford University, UK, reported the safety and immunogenicity of the chimpanzee adenovirus-vectored vaccine ChAdOx1 nCoV-19 in a wide range of participants, including adults aged 70 years and older. The authors reported that the vaccine appeared to be better tolerated by older adults than by younger adults, but that it has similar immunogenicity across all age groups. However, they pointed out that the results should be interpreted with caution as comorbidities in the older group were not assessed in the results presented.

According to Willyard, scientists all over the world are devoting efforts to overcome the obstacle presented by immunosenescence for the development of vaccine candidates for SARS-CoV-2. The current strategy is focused on the development or testing of drugs that could ameliorate the reduced response of older adults to vaccines in order to obtain a better immune response. The mechanistic target of rapamycin (mTOR) protein has been proposed as a putative target to act in synergy with SARS-CoV-2 vaccines to enhance their therapeutic effect. mTOR is a 289-kDa serine/threonine protein kinase encoded by the *FRAP1* gene. The mTOR signalling pathway is a critical pathway involved in the regulation of cellular metabolism, development,

survival, senescence, tumorigenesis and inflammation. mTOR is recognised as a classic anti-ageing target, among others. It is well known that the protein plays a role in the changes that occur with ageing that lead to inflammation (Teixeira and Santos, 2020). Therefore, researchers believe that inhibiting the mTOR pathway is the most promising putative therapy for anti-ageing effects and to overcome immunosenescence (Mannick et al., 2018). Specifically, the drug rapamycin (sirolimus), which is an effective inhibitor of the mTOR pathway, has been proposed as an important therapeutic approach for treating COVID-19 or even as a booster to enhance the effects of a SARS-CoV-2 vaccine.

Considering that vaccine development is costly and time-intensive, the strategy of developing a pharmacologic booster for COVID-19 vaccines appears to be a promising alternative. Time is running out, and more and more people all over the world are being affected by SARS-CoV-2. Furthermore, the healthcare systems and the economy of countries may not support an extended recovery from the pandemic. The need for a quick response to such an unknown virus really matters, and it potentiates the damage the world is facing. Based on such arguments, the need to support the older immune system should be a priority, and an immune-boosting medication for use with the COVID-19 vaccine represents a promising approach. Can rapamycin be such a medicine? Some authors have pointed out that in SARS-CoV-2 infection, the cytokine interleukin (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 the hyperinflammatory state seen in viral infections such as SARS-CoV-2. Thus, it is reasonable to consider the use of rapamycin as an alternative therapeutic agent for COVID-19 (Pandey et al. 2020). The use of rapamycin by older adults, one of the risk populations for COVID-19, together with a future vaccine may confer health benefits by targeting multiple aspects of biological ageing and immunosenescence. Indeed, at least one researcher has pointed out that if rapamycin works in the same way in humans as it does in mice, it could reduce COVID-19 mortality by 90% (Willyard, 2020). Thus, considering the vaccine race and our knowledge of the mTOR pathway, there are reasons to believe that an end to the detrimental effects of the pandemic may be achievable in the near future.

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