Controlling inflammation in the elderly with BCG vaccination

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The tuberculosis vaccine BCG may protect against inflammation in the elderly as well as offer an option for protection from SARS-CoV-2 in developing countries.

Inflammaging refers to the chronic, low-grade systemic inflammation that develops with age, leaving the elderly more susceptible to many non-congenital diseases, including cancer, diabetes mellitus, and cardiovascular disease (*1*). Aging also leads to immune senescence, which involves the inadequate functioning of innate but especially adaptive immune cells, leaving the elderly with an impaired immune response against newly encountered pathogens (*2*).

Kumar *et al.* (*3*) recently found that a century-old tuberculosis vaccine, Bacillus Calmette-Guérin (BCG), lowers systemic inflammation in elderly people. Previously, BCG vaccination was shown to increase the production of innate and adaptive cytokines upon microbial stimulation (*4*) in elderly people (*5*). This could suggest that BCG reverses both inflammaging and immune senescence (Fig. 1), a finding that could have tremendous implications to prevent immune-related diseases associated with inflammaging, e.g., cardiovascular diseases, as well as infectious diseases associated with immune senescence.

NON-SPECIFIC EFFECTS OF BCG

The research findings resulted from a study undertaken during the COVID-19 pandemic to learn more about the effects of BCG vaccination on circulating inflammatory proteins in the elderly. Although the vaccine's ability to protect against tuberculosis is suboptimal, it has received considerable attention recently for its ability to protect against other, unrelated infectious diseases. This has been confirmed by a number of randomized controlled trials (*4*), in which BCG was also shown to protect against respiratory tract infections in the elderly (*5*).

Researchers attribute this non-specific protection induced by BCG to the generation of innate immune memory, known as trained immunity (*4*). In this process, innate immune cells are reprogrammed after exposure to a certain infection or vaccine, after which they exhibit enhanced responsiveness to other microbial stimuli. For this reason, BCG is currently being tested in numerous trials for its ability to protect against COVID-19 (*6*), and recently, BCG was shown to reduce COVID-19 incidence in the elderly (*7*). Since the number of cases in this study is low, we are still awaiting the results from other randomized controlled trials for confirmation.

EFFECT OF BCG ON INFLAMMATORY PROTEINS

Because BCG vaccination leads to enhanced responsiveness of innate immune cells, Kumar *et al.* wanted to investigate if the vaccine could also be harmful for COVID-19 patients, since disease severity is clearly linked to excessive inflammation and high levels of circulating cytokines (*8*). In their study, Kumar *et al.* vaccinated 82 people between 60 and 80 years old with BCG. Blood was drawn before vaccination and 1 month after. Remarkably, BCG vaccination led to a decrease in the concentration of proinflammatory cytokines (including TNF-α, IL-6, and IL-1β), chemokines (including CCL2 and CXCL10), acute phase proteins (including CRP), and matrix metalloproteinases. Therefore, the authors concluded that BCG vaccination could potentially provide protection against severe COVID-19 in the elderly through modulation of systemic inflammation.

While it remains to be seen if BCG actually decreases the risk of developing COVID-19 through the induction of trained immunity, Kumar *et al.* provide a second hypothesis through which BCG could provide protection. In addition to the BCG-induced enhanced responsiveness of innate immune cells, which could improve the eradication of SARS-CoV-2 upon exposure, BCG might also be able to restrain excessive inflammation in severe COVID-19. Considering that currently, there are already a number of effective COVID-19 vaccines in use (*9*), the upcoming results of the clinical trials testing BCG's protectivity against COVID-19 might seem trivial. However, it is important to realize that in developing countries, COVID-19 vaccines might not be widely available on short notice, which is where BCG vaccination could be used as a temporary solution. In addition, lessons learned about BCG's ability to protect against respiratory infections could provide us with useful knowledge to battle future infectious disease challenges.

QUESTIONS STILL TO ANSWER

Although the potential of BCG seems vast, there are a number of very important questions that remain to be answered. First, what is the duration of the effects observed by Kumar *et al.*? In this study, the decrease in inflammatory proteins was observed 1 month after vaccination, while an earlier study by our group in a younger population (mean age, 26 years) observed a decrease in inflammatory proteins 2 weeks and 3 months after BCG vaccination (*10*). It is currently unknown how long these effects will last. However, the findings appear robust since similar observations were made in very

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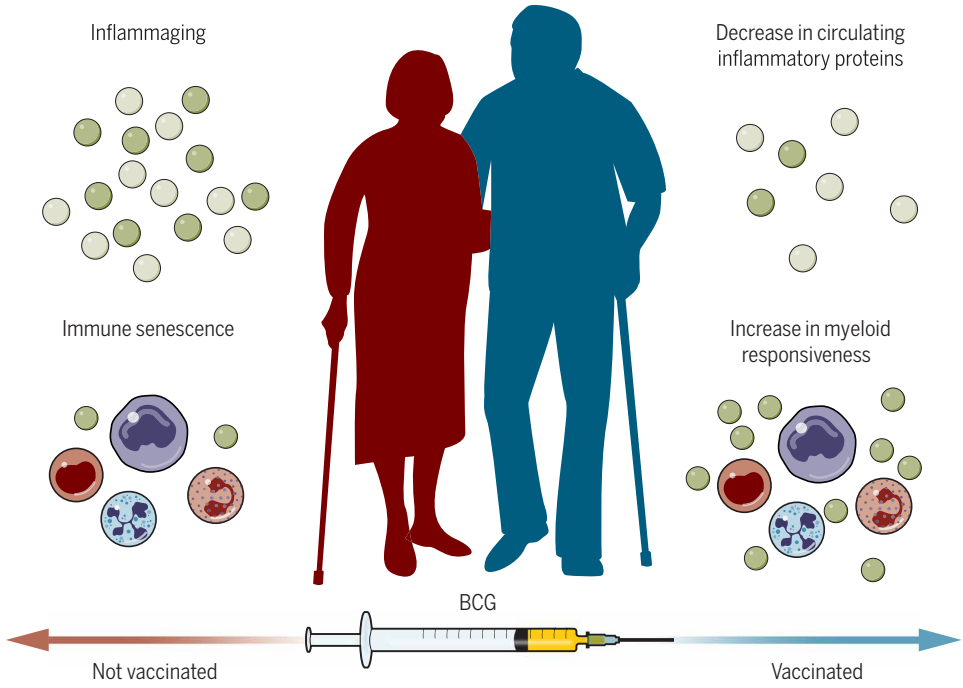

Fig. 1. In the elderly, BCG vaccination leads to a decrease in circulating inflammatory proteins and an increase in innate immune responses upon stimulation. These results provide an opportunity for utilizing BCG as a tool to counteract inflammaging, a chronic low-grade inflammation, as well as immune senescence, the gradual deterioration of the immune system, which develop with advanced age. Credit: Ashley Mastin/*Science Advances*.

different settings. Another important element to discover is whether the decrease in inflammatory proteins is of any clinical significance. This will require a randomized placebo-controlled trial and following vaccinated individuals over time while monitoring the onset of immune-related diseases. In addition, the mechanism of action remains elusive. We need to understand how this decrease in circulating inflammatory proteins is induced, which tissues are involved, and how this relates to the simultaneous enhancement of myeloid function, known as trained immunity.

Finally, it will be interesting to study if these effects are also induced by other live-attenuated vaccines. For other vaccines, including the measles and oral polio vaccines, research shows that these also protect against unrelated infectious diseases (*4*). It will be interesting to see if they have a comparable effect on systemic inflammation. When questions such as these get answered, we might be able to employ BCG for much more than just protection against tuberculosis.

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