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Commentary

Induced protection of Epigenetic modifications in tuberculosis vaccination design

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Tuberculosis (TB) is transmitted from person to person through respiratory droplets containing the bacterium Mycobacterium tuberculosis. This infection primarily affects the lungs and, if left untreated, can be fatal. To protect against tuberculosis, a live attenuated vaccine known as the BCG vaccine was introduced in 1921. The vaccine is more effective against childhood tuberculosis than against adult pulmonary tuberculosis. This vaccine is one of the most widely used in the world today, and it is frequently administered as part of childhood vaccination programmes in developing countries and countries with high TB incidence. The vaccine is not included in general childhood vaccine programmes in the United States, Canada, Australia, or many Western European countries, and is only available to high-risk populations. The reasons for this policy in the United States include low TB incidence, varying vaccine effectiveness against adult pulmonary TB, and the possibility of vaccination causing a false positive TB skin test. Following the vaccine's introduction, early clinical trials were conducted to assess its efficacy. Along with TB effectiveness, these studies found a reduction in overall mortality. The World Health Organization examined epidemiological studies, including randomised clinical trials, cohort and case control studies, that investigated the effect of the BCG vaccine on all-cause mortality in 2014. Despite the fact that many of the studies had the potential for high bias, the analysis discovered a greater decrease in overall mortality than could be attributed solely to TB reductions. BCG vaccine, in particular, appeared to protect against a variety of bacterial, parasitic, and viral infections. Additional research in mouse models demonstrated the BCG vaccine's protective effects against viral infections such as influenza and herpes simplex virus 2. What role does a live attenuated bacterial vaccine play in protecting against viral infection? A long-term enhanced response of the innate immune system to infection, known as trained immunity, could be one component of this protection. The innate immune system is one of the body's first lines of defence against pathogens, producing cytokines that aid in infection elimination. Prior BCG vaccination has been linked to increased cytokine production in response to non-TB pathogen exposure.

How is the BCG vaccine involved in trained immunity? Trained immunity is mediated through epigenetics, the modification of gene expression without changing the genetic code. Histone modification seems to be the main epigenetic mechanism for BCG-induced trained immunity. DNA wraps around proteins called histones such that some genes can be accessed easily by cell proteins that "read" the gene, increasing gene expression, while others are less accessible, decreasing gene expression. Modifying these histones changes whether a gene is exposed or unexposed and therefore alters gene expression. The BCG vaccine has been shown to increase methylation of one of the histone proteins, resulting in increased cytokine production in certain immune cells. These epigenetic changes and cytokine production increases have been shown to last for at least three months after vaccination. Epigenetic changes associated with the BCG vaccine may be important in "training" immune cells and producing the observed anti-infection effects. However, more research is needed to determine how other factors, such as vaccination age, affect BCG-induced trained immunity. The mechanisms of BCG-induced trained immunity, as well as the extent of its protective effects, are still unknown. An early observation that countries where the BCG vaccine is commonly used reported fewer COVID-19 cases than other countries

sparked interest in the hypothesis that the BCG vaccine has COVID-19 protective effects. Many countries, including the United States, the Netherlands, Egypt, and Australia, are currently conducting clinical trials to test this hypothesis. The BCG vaccine is not the only one that has been shown to have nonspecific anti-infection effects. Beyond the specific diseases that the vaccines target, the measles vaccine and oral polio vaccine have been linked to lower overall childhood mortality. The nonspecific effects of these vaccines suggest that vaccines may play a role in enhancing nonspecific immunity to combat and prevent future emerging infections.

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Conflict of Interest

None