TB vaccine gets its groove back

May 19 2009

A team of Vanderbilt University Medical Center investigators has cracked one of clinical medicine's enduring mysteries - what happened to the tuberculosis vaccine. The once-effective vaccine no longer prevents the bacterial lung infection that kills more than 1.7 million people worldwide each year.

Their solution, reported in the journal *PLoS ONE,* could lead to an improved TB vaccine and also may offer a novel platform for vaccines against other pathogens.

"Our findings represent nearly a 180-degree reversal from the dogma of the last 60 years - that the TB vaccine stopped working because it became over-attenuated and was too 'wimpy' to be effective," said Douglas Kernodle, M.D., associate professor of Medicine.

Instead, Kernodle and colleagues found that the TB vaccine has acquired some traits that make it less effective in evoking a sustained immune response. When they take away these traits, the TB vaccine induces stronger immune responses in mice.

The current TB vaccine, known as BCG (bacille Calmette-Guérin), has been around since the 1920s. It was made by weakening (attenuating) a strain of bacteria that causes tuberculosis in cows and that genetically is 98 percent identical to the human TB germ.

During the early years of its use, BCG was 80 percent effective against pulmonary TB. But because there were no long-term storage options for

bacterial strains until the 1960s, BCG was grown continuously in culture, with "sub-cultures" of the original BCG maintained in laboratories around the world. Over time, BCG changed - the original vaccine ceased to exist and the daughter sub-cultures lost effectiveness against pulmonary TB.

Today, although BCG no longer protects against lung disease, it is still 80 percent effective against "disseminated TB" (TB infection in many parts of the body) in early childhood. Because of this protection, BCG is given annually to 100 million newborns worldwide - not in the United States and a few other countries - and is estimated to prevent about 40,000 cases each year of TB meningitis and other disseminated TB, Kernodle said.

But the question of why BCG lost its effectiveness against pulmonary TB has not been fully investigated. Researchers accepted the notion that as BCG was grown in culture, it changed genetically and became too weak to evoke the kind of immune response needed for protection.

Kernodle and colleagues came to the problem of BCG's poor activity against pulmonary TB from a different angle. They had reported in 2001 that one way TB itself evades the immune system is by producing antioxidants. Since BCG also produces antioxidants, they suggested that removing BCG's antioxidant-producing capacity might improve the vaccine.

"Our idea to take something away from BCG - and therefore theoretically attenuate it even further - was met with a lot of skepticism," Kernodle said. "But we believed our data that we could make BCG more immunogenic and safer."

Two years ago, after the Kernodle group had modified BCG and was beginning to test it for immune responses, researchers at the Institut

Pasteur in Paris published a paper describing the genomic evolution of BCG. They found that in addition to containing gene deletions consistent with attenuation of the vaccine, the BCG genome also had regions of gene duplication and increased gene expression. Some of the duplicated and over-expressed genes were for antioxidants already being targeted by the Kernodle group.

It was suddenly obvious what had happened to BCG, Kernodle said.

"It had not become too weak - instead, by making more antioxidants it had become better at suppressing immune responses."

In the current studies, first author Lakshmi Sadagopal, Ph.D., research instructor of Medicine, vaccinated mice with a modified BCG (genetically changed in three ways to reduce or eliminate the production of several antioxidants) and examined the immune response in the days following vaccination and later with a "challenge" dose of BCG.

She found that, compared to BCG, the modified BCG induced greater cytokine (immune regulatory factor) production during the early phase of the immune response, more CD8 cell-killing T cells at the peak of the primary response, and more CD4 helper T cells during the memory phase. Modified BCG also produced greater recall immune responses and was eliminated better by the vaccinated host animal than the parent BCG vaccine, which might correlate with improved safety in humans.

"At each time point of the immune response, the modified BCG vaccine worked better than the parent BCG vaccine," Kernodle said. "By targeting antioxidants that had increased in expression during decades of cultivation, we ended up making BCG more like it was back in the 1920s when it was 80 percent effective against pulmonary TB. We fixed it."

Using modern molecular techniques to reduce the activity of

antioxidants below levels in naturally occurring strains, "it should be possible to make it even better than the original BCG," he added.

The Aeras Global TB Vaccine Foundation, supported by the Bill & Melinda Gates Foundation, has already licensed the modification technology developed by Kernodle and colleagues. Aeras is working to make the best possible modified BCG vaccine, and it has built the infrastructure to conduct clinical trials in South Africa, Kenya and India - countries with a high incidence of TB.

Kernodle and colleagues say the results are also encouraging for other vaccine development. Because the modified BCG produces a better immune response profile than existing vaccine technologies, it could be a useful vector for vaccines directed against other pathogens, including HIV and the parasites that cause malaria.

Source: Vanderbilt University Medical Center (news : web)