TB Treatment For The Elderly Likely Requires A Boost To Immune Response

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Manipulating the immune system in elderly people appears to be the most likely way to help older patients wage an effective battle against tuberculosis, a new study suggests.

Mathematical modeling of how mice respond to TB infection suggests that potential therapy options for elderly TB patients could either increase their white blood cell count or enhance infected cells' interaction with their immune system.

Simulations of TB infection in an old mouse showed that increasing the number of infection-fighting white blood cells, called CD4 T cells, could be particularly effective at bolstering the mouse's immune response, which naturally slows with aging. Older humans have similar delays in their immune response, meaning that they have a much more difficult time controlling TB than do younger people with an active infection.

The math modeling also suggested that making changes to macrophages, cells that essentially eat infecting bacteria, could enhance those cells' interactions with other warriors in the immune system, reducing the concentration of bacteria in the lungs associated with TB infection.

Both findings suggest potential strategies for development of vaccines or treatments specifically for elderly TB patients, said Joanne Turner, lead author of the study and an assistant professor of internal medicine at Ohio State University.

“This modeling is giving us clues as to what would help an older person control infection,” Turner said. “In thinking about therapies, if we find a way to make older people have a better T-cell response, such as with vaccination, or by giving them a post-exposure therapy in the lung that would activate the macrophage better, either way they should be able to control infection more effectively.”

The research appears in a recent issue of the journal Experimental Gerontology.

About 2 billion people worldwide are thought to be infected with TB bacteria, Mycobacterium tuberculosis. People who are infected can harbor the bacterium without symptoms for decades, but an estimated one in 10 will develop active disease characterized by a chronic cough and chest pain. In the United States, the Centers for Disease Control and Prevention reported 14,093 active cases of TB in 2005. Another 10 to 15 million people in the United States are believed to have latent TB. An active infection is treated with a combination of antibiotics that patients take for at least six months.

The elderly are considered highly susceptible to both reactivation of latent TB infection and newly acquired infections, especially in long-term care facilities, where people are generally sicker and transmission can occur more rapidly. Many older patients cannot tolerate the antibiotic regimen required to treat active TB.

For this line of research, Turner has turned to mathematical modeling to test various scenarios in an old mouse’s immune response to infection with the TB pathogen. The modeling allows researchers to simulate outcomes resulting from multiple tweaks to assumptions about immune response activities. Outcomes in a young mouse model are used for comparison. The findings can be verified later in highly targeted animal studies.

The immune response to TB infection is complex, and aging affects that process. In fighting infections, two immune responses occur: The innate immune response begins a fight against any pathogen. The acquired immune response follows, with components designed to fight the specific pathogen causing the infection.

Older people, and mice, have a strong innate immune response that enables them to initially control bacteria from TB and other infectious diseases.

“But you absolutely have to have an acquired immune response to control TB infection, and that’s where the old mice do poorly. They generate that very slowly, giving the bacteria time to grow to higher levels in the lung,” said Turner, also an investigator in Ohio State’s Center for Microbial Interface Biology.

At the point of infection, TB bacteria are absorbed by a macrophage, also called an antigen-presenting cell. The macrophage activates specific molecules that make pieces of the bacteria visible to the infection-fighting T cells, which triggers an eventual T-cell response to come to the macrophage’s aid.

“These bacteria are very smart, and they find ways to hide from the immune system. So you have a delay before the T cells can see the infection, allowing the bacteria to grow fairly unrestricted in the lung to quite a high number,” Turner said.

Eventually, during the acquired immune response, T cells that are specific for TB infection are generated and travel to the lung to help the macrophages. These CD4 T cells secrete a substance called interferon gamma, which activates the macrophage to help it kill the bacteria.

If the immune response fails to prompt macrophages to kill the TB

bacteria, the infected macrophages eventually burst and release TB bacteria into the lungs.

For this work, Turner and Barbara Szomolay, a postdoctoral researcher in Ohio State's Mathematical Biosciences Institute and a study co-author, set up a model that would allow them to alter assumptions with hopes of trying to improve an old mouse's acquired immune response. Szomolay assembled multiple equations to allow for variations in quantities of T cells, specialized molecules, macrophages and bacteria counts, as well as related substances that trigger certain immune functions.

The two most effective methods found to improve infection control in the old mouse model were increasing the number of CD4 T cells present early on in the infection, and increasing the number of specialized molecules on the surface of macrophages, enhancing the visibility of the TB bacteria.

"We showed that we could change the control of infection, but we could never get that old mouse to look like a young mouse, which means that there's more to the immune system defect than just the initial interaction between the T cell and macrophage," Turner said.

Conventional wisdom suggests the strong innate response is good for old mice and people, but the question remains: Could the acquired response be stronger if the innate response didn't kick in first? Turner and Szomolay are currently developing a new math model that will eliminate the innate response in an old mouse to observe the infection outcome under those circumstances.

Source: Ohio State University