Fighting TB might be a matter of 'flipping a switch' in immune response

June 22 2009, by Emily Caldwell

Scientists are focusing on a new concept in fighting airborne pathogens by manipulating what is called the "switching time," the point at which a highly regulated immune response gives way to powerful cells that specialize in fighting a specific invading bug.

In the case of tuberculosis, Ohio State University researchers are using mathematical modeling to determine whether a change to the natural switching time would result in a more effective immune response. They also are analyzing which parts of the immune response are most important to striking a balance between properly timing the switch and completing the task at hand - killing the microbe.

The complex modeling takes into account the huge assortment of cells and molecules at work in the human immune response to *Mycobacterium tuberculosis*, the microbe that causes TB. The response to all airborne pathogens is particularly complicated because it takes place in the highly protective environment of the lung. Human lungs are programmed to minimize immune responses as a way to avoid inflammation, which could interfere with breathing.

The modeling suggests that the average switching time occurs about 50 days after tuberculosis invades the lung, which roughly coincides with clinical expectations that a skin test will turn up positive for TB between four and eight weeks after infection.

By that time, bacteria have settled in and are harder to kill, even with the

more robust immune response. Because TB is highly evolved and adapted to the human host, the launch of the stronger immune response goes unnoticed in about 90 percent of infections.

With less adapted but virulent pathogens, on the other hand, an individual becomes acutely ill, and sometimes dies, when the switching time occurs. As the immune response kicks into high gear, toxic infection-fighting warrior cells cause what could be considered collateral damage by harming lung tissue at the same time that they kill the invading bugs.

The researchers say mathematical models that predict relationships and interactions in the immune response could guide planning for therapies that would be designed to either accelerate or slow the switching time, depending on the pathogen.

"A great problem in developing drugs and vaccines against airborne pathogens is this apparent bottleneck in the immune response and the inability to quickly and effectively eradicate microbes in the lung environment," said Larry Schlesinger, professor of internal medicine and director of the division of infectious diseases at Ohio State and a senior author of the study. "Understanding that bottleneck is an important part of this paper, and brings new insight into how to override the problem with tuberculosis and other pathogens."

The research is scheduled to appear in the online early edition of the *Proceedings of the National Academy of Sciences*.

About 2 billion people worldwide are thought to be infected with TB. 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. Both active and latent infections are treated with a combination of antibiotics that patients take

for at least six months.

In the event of infection, two immune responses occur: The innate immune response begins a fight against any pathogen. The acquired immune response follows, with components designed to attack the specific pathogen causing the infection. When that change occurs is referred to as the switching time.

At the point of infection in the lung, TB bacteria are absorbed by what are called alternatively activated macrophages. These macrophages activate specific molecules that make pieces of the bacteria visible to infection-fighting T cells, a process that triggers an eventual T-cell response and the recruitment of classically activated macrophages, those that are more effective at killing bacteria.

The mathematical modeling in this study simulates the entire cascade of events in the immune response to TB, setting the stage for testing what the outcome would be if changes were made along the way - for example, if a drug were developed to artificially inhibit or activate part of the process.

In this research, the scientists sought to determine what it would take to shorten the switching time and reduce the number of bacteria in the lung.

Two cytokines, interferon gamma and tumor necrosis factor alpha, are known participants in the conversion from one type of immune response to the other. Cytokines are proteins mobilized when the body is injured or has an infection, and often cause inflammation in their repair efforts.

Many previous studies testing interferon gamma's potential as a TB therapy have suggested that the protein is effective in the fight, but isn't effective enough on its own to treat the infection. The mathematical

modeling simulating such a treatment reinforced these findings.

The model showed that early introduction of interferon gamma during the immune response would shorten the switching time and reduce the bacterial load, but would not completely clear bacteria from the lung after 100 days - a population referred to as the residual bacterial load. The researchers speculate that manually introducing one cytokine is not enough to optimize the signals needed to activate certain macrophages.

The findings suggest that interferon gamma might be one component of a cocktail approach to new TB therapies, the researchers said.

There would be a benefit to reducing that residual load of bacteria, Schlesinger noted. TB treatments take so long and currently require a cocktail of antibiotics specifically to address the long-term persistent bacteria in the lung and other parts of the body.

"If we could shorten the treatment for TB, that would be very powerful in breaking the transmission cycle," said Schlesinger, also director of Ohio State's Center for Microbial Interface Biology.

The precision of the modeling allows the researchers to simulate outcomes resulting from multiple tweaks to the values assigned to the various immune response activities.

"It's like turning the knobs up and down on an equalizer, only in this case to figure out when the immune response and different mediators of that response are at the right levels to do their jobs - without blowing the speakers, so to speak," said Judy Day, a postdoctoral researcher in Ohio State's Mathematical Biosciences Institute and lead author of the study.

The researchers conducted a number of sensitivity tests to check the validity of the models. The models use what are considered ordinary

differential equations, but finding the values to plug into those equations required an exhaustive search of previous research on tuberculosis.

"To pin down quantitatively what the effect of A is on B and C, we had to search the literature to find evidence of these parameters. When we didn't find them, we had to make educated guesses and then subject them to sensitivity analysis," said Avner Friedman, a senior author of the paper and Distinguished University Professor of mathematical and physical sciences at Ohio State.

Friedman, who was the founding director of the Mathematical Biosciences Institute, predicts this line of mathematical modeling of the immune response has paved the way for new research into combination therapies against a variety of pathogens.

"Switching time is a new concept. We will be talking about switching time in a few years about this disease, or that disease," he said.

Source: The Ohio State University (news : web)