Experimental TB drug explodes bacteria from the inside out

November 27 2008

An international team of biochemists has discovered how an experimental drug unleashes its destructive force inside the bacteria that cause tuberculosis (TB). The finding could help scientists develop ways to treat dormant TB infections, and suggests a strategy for drug development against other bacteria as well.

A report describing the research, led by Clifton E. Barry, III, Ph.D., of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, is published in the Nov. 28 issue of *Science*. Dr. Barry's collaborators included scientists from NIAID and from the Novartis Institute for Tropical Diseases in Singapore.

One-third of the world's population is infected with Mycobacterium tuberculosis (M. tb), the bacteria that cause TB. "Currently, there are no drugs available that specifically target latent tuberculosis infections in which bacteria are present but are not actively dividing," notes NIAID Director Anthony S. Fauci, M.D. "Dr. Barry and his colleagues have now given us a detailed picture of how the candidate TB drug PA-824 is metabolized inside Mycobacterium tuberculosis. Their discovery is a promising step towards developing effective drugs against latent TB as well as other bacteria."

Previously, Dr. Barry and his collaborators found that M. tb mutants lacking a specific bacterial enzyme were resistant to PA-824, but at that time, they did not know the function of the enzyme.

"It took several years, but at last we were able to recreate in the test tube what happens inside mycobacterial cells when the bacterial enzyme, which we named Ddn, and a second bacterial component called a cofactor, interact with PA-824," says Dr. Barry. The key event in PA-824 metabolism, they found, is the production of nitric oxide (NO) gas. "This highly reactive molecule," he adds, "is akin to a bomb blast that kills the bacteria from within."

NO gas is produced naturally by certain immune system cells after they engulf M. tb or other bacteria. This is one way that people with healthy immune systems can contain M. tb infection. However, this natural immune response is not always enough to completely rid the body of TB bacteria. In essence, PA-824 performs similarly to the NO-producing immune cells--but the drug's effect is more specific and triggered only after it enters the bacteria.

The non-dividing M. tb bacteria characteristic of latent TB infections are walled off by immune cells that aggregate around the bacteria to form a body called a granuloma. Oxygen levels are low inside granulomas. In their latest research, the scientists observed that NO-generation during PA-824 metabolism is greatest when oxygen levels are low. This observation suggests how PA-824 may work against non-dividing M. tb.

PA-824 was originally designed to work best under aerobic, or oxygenated, conditions. With this new understanding of how the bacterial enzyme and cofactor act on PA-824 under low-oxygen conditions, Dr. Barry says, scientists can design drugs with a chemical structure similar to PA-824 but optimize them from the start to behave best under low-oxygen conditions. This work is already proceeding in the laboratory at NIAID and in partnership with collaborators from the Novartis Institute for Tropical Diseases in Singapore as well as with scientists from the Genomics Institute of the Novartis Research Foundation in San Diego.

Because humans have neither the bacterial cofactor nor any enzymes equivalent to Ddn, PA-824 has no effect on human cells. Conversely, many bacteria have enzymes in the same family as Ddn. Thus, says Dr. Barry, it is possible to envision new kinds of NO-generating drugs designed to interact with enzymes associated with other disease-causing bacteria as well.

Source: National Institute of Allergy and Infectious Diseases