Organic compound found in red wine boosts the body's ability to fight drug-resistant tuberculosis

May 31 2017

Credit: CC0 Public Domain

An organic compound found in grape skins can stimulate the mouse immune system to fight even the most persistent tuberculosis strains.

Such immune-based therapies, commonly used to treat cancer, could be the only hope against the spread of drug-resistant tuberculosis, says Amit Singhal, who led the study at the A*STAR Singapore Immunology Network.

Tuberculosis (TB), known in the old days as 'consumption', has plagued mankind for centuries and killed hundred of millions of people. Antibiotics have been the standard treatment since penicillin became widely available in the 1940s, but the emergence of drug-resistant strains of Mycobacterium tuberculosis have led to a resurgence of the disease.

"TB is making a comeback; it is now the largest killer among communicable diseases affecting people at an age when they are most productive," says Singhal. In 2015, an estimated 10.4 million people were infected with tuberculosis, and 1.4 million died of the disease. "The global TB elimination program might not meet its targets unless we come up with new therapeutic and diagnostic strategies."

In search of alternatives, in 2014 Singhal and his team screened FDA-approved drugs for their anti-tuberculosis activity and discovered that the common anti-diabetic drug, metformin, targets an immune protein, leading to reduced inflammation and lung tissue damage in tuberculosis-infected mice. He is now collaborating with clinicians to test metformin therapy in clinical trials.

His search didn't end there. Several other immune proteins can be targeted by drugs in the same way as metformin, and Singhal wanted to test their efficacy as well. His next target was sirtuin-1, an enzyme known to regulate metabolic function and important in aging and inflammation. Sirtuin-1 activators are naturally found in grape skins and red wine, and have been sold as nutritional supplements for their anti-aging benefits.

Mouse models in which sirtuin-1 activity was blocked had tuberculosis spreading much more than the controls. The opposite happened when sirtuin-1 activity was enhanced: the virulent and stubborn tuberculosis colonies in the lungs and spleens of infected mice began to shrink. The antibacterial effect was even more pronounced when sirtuin-1 treatment was combined with a standard antibiotic.

Closer examination of the lung tissue revealed less damage and inflammation under sirtuin-1 enhancement, as compared with untreated controls. Gene expression analysis found that the enzyme worked by inducing the tuberculosis bacteria to devour themselves, a process known as autophagy.

Singhal is now testing sirtuinin-1 activators on monkey models of tuberculosis. He is also looking into whether they can be combined with metformin for a more powerful therapy.

"We now have two candidates to further expand our studies and we may even find something else."

More information: Catherine Y. Cheng et al. Host sirtuin 1 regulates mycobacterial immunopathogenesis and represents a therapeutic target against tuberculosis, *Science Immunology* (2017). DOI: 10.1126/sciimmunol.aaj1789

Provided by Agency for Science, Technology and Research (A*STAR), Singapore