Source : www.thehindu.com Date : 2019-11-03

STIMULATING WHITE BLOOD CELLS HELPS CLEAR TB BACTERIA

Relevant for: Science & Technology | Topic: Biotechnology, Genetics & Health related developments

Effective: Just two doses of rifampicin, along with the small molecules cleared the TB bacteria, says Javed Agrewala

Instead of using drugs to directly kill TB bacteria, researchers at the Indian Institute of Technology (IIT) Ropar have directly stimulated the immune system to kill the bacteria. This was achieved by using small molecules (ligands) to stimulate two specific receptors (CLEC4E and TLR4) found on the surface of white blood cells (macrophages) to kill the bacteria. The two receptors are copiously expressed on the surface of the macrophages, and activating them help regulate the cell function.

Once activated, the ability of the macrophages to reduce the TB load and eliminate the bacteria gets enhanced through increased autophagy. Autophagy is the body's way of cleaning out damaged cells, in order to regenerate newer, healthier cells.

Through *in vitro* studies, the team led by Javed N. Agrewala from the Biomedical Engineering Department at IIT Ropar first tested the ability of the two receptors to activate the macrophages to kill the bacteria. The macrophages were first infected with TB bacteria and stimulated for 48 hours by activating the receptors using the small molecules. Compared with controls, the stimulated macrophages exhibited increased bactericidal activity. The enhanced bactericidal activity was confirmed using animal models.

Similarly, the enhanced expression of autophagy-related genes in macrophages was first observed in the lab and confirmed in animal models by IIT Ropar researchers in collaboration with CSIR-Institute of Microbial Technology (IMTECH), Chandigarh.

The specificity of the receptors to regulate macrophage function was tested using inhibitors which block the functioning of the receptors. There was increased survival of the bacteria in the macrophages on inhibiting the receptors.

To reconfirm the role of the receptors in inducing autophagy, the researchers abrogated the autophagy in macrophages and tested the ability of the activated receptors to clear the bacteria in mice models. "The ability to clear the bacteria was absent when autophagy was inhibited. This helped confirm that receptor-mediated elimination of TB bacteria in macrophages was through autophagy," says Prof. Agrewala.

Besides *in vitro* studies and mice models, the activated receptors were found to reduce the TB burden when tested on human macrophages too. The results were published in the journal *Autophagy.*

Compared with controls, the potency of anti-TB drugs — isoniazid and rifampicin — to kill the bacteria dramatically improved when the two receptors were also activated. With rifampicin, the ability to kill the bacteria was seen even at one-tenth of the dose. Greater effectiveness at reduced dosage was seen only when rifampicin was used along small molecules that activated the receptors. Also, the ability to clear the bacteria was achieved with just two doses of rifampicin.

The enhanced potency of anti-TB drugs when used along with the small molecules that stimulate the receptors was seen in animal models, too. In mice, there was significant reduction in bacteria load in the lungs, liver and spleen compared with controls. The number of granulomas in the lung too decreased.

Even in Guinea pigs, there was significant decrease in bacterial load and increased efficacy of the drugs to kill the microbes. The lungs and spleen of Guinea pigs treated with small molecules and TB drugs exhibited nearly normal morphology compared with controls.

“The activating the receptors have an immunomodulatory role in reducing both the dose and duration of treatment using anti-TB drugs,” says Prof. Agrewala. “Since the receptors only activate the macrophages and do not directly act on the bacteria, there are fewer chances of emergence of drug-resistant strains of TB bacteria.”

In mouse and Guinea pig models, there was proliferation of certain T cells that offer protection against TB bacteria. Also, there was significant increase in the number of memory T cells that provide long-lasting protection against TB bacteria thus signifying protection from subsequent infection with TB bacteria.

The last confirmed case of WPV3 was recorded in northern Nigeria in 2012.

Researchers have found that immune cells called microglia, which play an important role in reorganising the connections between nerve cells, fighting

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