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COMBINATION THERAPY USING MALARIA DRUG QUICKLY CLEARS TB

Relevant for: Developmental Issues | Topic: Health & Sanitation and related issues

Potent combination: TB lesions (white patches) are absent in lungs of mice treated with chloroquin plus isoniazid (left) while these can be seen in the lungs of mice treat with isoniazid alone (right) as indicated by arrows.

Researchers from Bengaluru have made an important discovery of the mechanism used by TB bacteria to tolerate TB drugs, which necessitates longer treatment of six-nine months. They have also demonstrated that a drug combination that prevents the bacteria from inducing this mechanism leads to almost complete clearance of the bacteria from the mice lungs in just two months of therapy. If further studies and trials show similar results, a shorter treatment regimen might be sufficient to treat drug-sensitive TB.

The common notion is that only the non-replicating or slowly metabolising TB bacteria become tolerant to anti-TB drugs. But the team led by Amit Singh from the Department of Microbiology and Cell Biology, and Centre for Infectious Disease Research at the Indian Institute of Science (IISc) found a fraction of the bacteria inside the macrophages was able to tolerate anti-TB drugs even when actively multiplying.

The researchers found that using an already approved anti-malaria drug chloroquine in combination with a TB drug isoniazid can almost clear all the bacteria from the lungs of mice and guinea pigs in just eight weeks. In addition, the drug combination also reduces the chances of TB relapse. The results were published in the journal *Science Translational Medicine.*

Reducing the pH to make it acidic is the first-line of defence by macrophages when infected with pathogens. But the researchers found that instead of controlling the TB bacteria, the mildly acidic pH was actually facilitating a fraction of the bacteria to continue multiplying and develop drug tolerance.

“We used a biosensor which we had developed a few years ago to see the amount of oxidative stress inside the TB bacteria during infection. We found that anti-TB drugs induce oxidative stress to kill bacteria inside macrophages. However, the drug tolerant bacteria have a remarkable ability to counter oxidative stress,” says Prof. Singh. “The bacteria used the acidic pH of macrophages as a cue to specifically increase its capacity to deal with oxidative stress.” Also, the drug-tolerant bacteria induce efflux pumps to expel antibiotics as an additional mechanism to reduce antibiotic efficacy.

The drug-tolerant bacteria were found in macrophages that were more acidic (pH 5.8) while the drug-sensitive bacteria were seen in macrophages that were less acidic (pH 6.6).

“We hypothesised that reverting the pH within macrophages to its normal state could probably make the bacteria sensitive to antibiotics,” Prof. Singh says. “The chloroquine drug does just that — it neutralises the pH within the macrophages. This prevented the bacteria from inducing the mechanism to protect themselves from oxidative stress. So no drug-tolerant TB bacteria emerged.” Once the pH is neutralised, the isoniazid drug was able to eradicate TB from animals.

While the two-month treatment was able to completely sterilise mouse lungs, a near-complete eradication was observed from the lungs of guinea pigs. “The combination was shown to reduce

TB bacteria load in both mice and guinea pigs," says Richa Mishra from IISc and the first author of the paper.

In the case of *in vitro* studies using cell lines and mice macrophages, the ability of the combination drug therapy to reduce TB load was found to be three- to fivefold higher than when treated only with TB drugs. "Reduction in bacteria load was more when we combined chloroquine with isoniazid," says Mishra. "We observed threefold reduction when we combined chloroquine with rifampicin and fivefold reduction when we used chloroquine-isoniazid combination."

To determine TB relapse following treatment, mice infected with TB were completely rid of bacteria using the drug combination. Eight weeks later, the immune system of mice was suppressed using a drug. While all the five mice treated with only isoniazid relapsed with high bacterial load, three of the five mice treated with the combination drug showed very little presence of bacteria. "This shows that the drug combination reduces the chances of TB relapse," says Mishra.

The work was carried out in collaboration with researchers from Bengaluru's National Centre for Biological Sciences and Foundation for Neglected Disease Research.

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