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NOVEL METHOD FOUND TO KILL DORMANT TB BACTERIA IN STEM CELLS

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

Shielded: The bacteria hide inside lipid droplets and so the stem cells do not kill them, say (from right) Gobardhan Das, Samreen Fatima and Anand Ranganathan

Delhi-based researchers have found that inhibiting lipid synthesis inside stem cells that produce bone cells (mesenchymal stem cells) can help in killing TB bacteria that are found inside the stem cells in a dormant state and safely shielded from the host immune system and TB drugs. While TB bacteria inside the macrophages actively divide, microbes inside stem cells lie dormant and also make the stem cells less likely to replicate thus surviving for an extended period of time. *Ex vivo* studies with human stem cells and work on mice showed that the two cells are programmed very differently to support active and dormant TB bacteria infection.

A team led by Gobardhan Das from the Special Centre for Molecular Medicine at the Jawaharlal Nehru University (JNU) found that TB bacteria are free in the intracellular fluid (cytosol) of the mesenchymal stem cells while they are surrounded by the macrophage cell membrane on being engulfed. This allows the bacteria to promote rapid synthesis of lipids inside the stem cells and hide within the lipid droplets so created.

The results were published in *Journal of Clinical Investigation.*

That mesenchymal stem cells serve as reservoirs of dormant TB bacteria was known but the mechanism by which the bacteria survive for a long period was not known.

“Studies using human mesenchymal stem cells and macrophages and mice model studies helped us understand how TB bacteria hijack the cellular mechanism to stop the stem cells from replicating and turn themselves dormant,” says Prof. Das. “The bacteria instruct the stem cells to synthesise lipids and hide inside them. The stem cells don’t kill microbes that are inside lipid droplets.”

There was sustained expression of genes controlling dormancy in the bacteria isolated from stem cells while genes that promote replication were expressed in bacteria isolated from macrophages. Mouse mesenchymal stem cells and macrophages too showed similar behaviour. *In vitro* studies using human stem cells showed the bacteria inhibiting stem cell replication.

When inhibitors to block lipid synthesis were used, there was reduced expression of genes that regulate dormancy of TB bacteria and replication of stem cells. “This helped confirm that TB bacteria induce lipid synthesis in stem cells and hide inside the lipid cells to escape from anti-TB drugs,” says Samreen Fatima from JNU and the first author of the paper.

“Using a drug that inhibits lipid synthesis will prevent TB bacteria dormancy and make them susceptible to anti-TB drugs,” says Fatima. But killing the bacteria and preventing disease reactivation can be achieved by inducing autophagy (mechanism by which cells removes unnecessary or dysfunctional components) along with anti-TB drugs.

Inhibiting autophagy is one of the ways by which TB bacteria survive inside host cells. The researchers treated human macrophages and stem cells infected with TB bacteria with an anti-TB drug (isoniazid) and/or rapamycin. While isoniazid eliminated replicating bacteria found in

macrophages, rapamycin induced autophagy in stem cells to kill the microbes. Similar results were obtained in mouse models too.

“In mouse models, inducing autophagy led to elimination of TB bacteria from stem cells. Addition of autophagy-inducing drug along with isoniazid led to sterile cure of TB and prevention of disease reactivation,” says Fatima.

“This discovery paves the way for finally getting to grips with the scourge that is tuberculosis in its dormant state, and whose resurgence poses a threat to not only treating TB but also to disease control,” says Anand Ranganathan, a co-author.

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