IGIB find ways to reduce TB's tissue-damaging effects

Foamy macrophages show more inflammatory response than normal ones, say Sheetal Gandotra (left) and Neetika Jaisinghani.

It is generally believed that TB bacteria make the host cells accumulate triglyceride and become lipid-rich as bacteria prefer lipids for their nutrition. Now, using human macrophage cells researchers at the Institute of Genomic and Integrative Biology (CSIR-IGIB) have shown that when TB-infected macrophages undergo necrosis (where the cell ruptures when it dies) lipids and bacteria contained in the cells are released. The neighbouring cells — both healthy and TB-infected — take up the lipids thus leading to lipid accumulation.

"Our study brings a new facet to the way the field has been thinking about pathogenesis where it was believed that because the bacteria prefer lipids for their nutrition, they make the host cell become lipid-rich. Our work points to the relevance of the incident pathology — necrosis in a granuloma result in the development of lipid-rich foamy macrophages [presence of cells with large lipid-filled vacuoles]," says Dr. Sheetal Gandotra from the Cardio Respiratory Disease Biology Unit at IGIB and corresponding author of a paper published in the journal *Frontiers in Immunology.*

The ability to induce necrosis is peculiar to virulent TB bacteria. The avirulent *Mycobacterium bovis* strain used in BCG vaccine is unable to cause necrosis; it triggers a programmed cell death (apoptosis) instead. Like the BCG strain, TB mutants that lack the capacity to induce necrosis also lack the associated capacity to induce necrosis-induced triglyceride accumulation in neighbouring cells.

When macrophages encounter TB bacteria they mount an inflammatory response wherein certain factors are secreted to help recruit other cells of the immune system to kill the bacteria. "For the first time we reported that foamy macrophages showed more inflammatory response than normal macrophages," says Dr. Neetika Jaisinghani from IGIB and first author of the paper. As a result of the inflammatory response more macrophages are recruited to the site of infection thus exposing them to infection.

"So it sets off a positive feed-forward loop such that the inflammatory response gets amplified," says Dr. Gandotra.

To understand the role of excess lipids in host defence strategies, the researchers added uninfected necrotic cells to macrophages that were not infected with TB bacteria. Even these healthy macrophages stored lipids from the dying cells in the form of triglycerides. The macrophages were foamy but not infected. "These macrophages did not show any inflammation till such time they were infected with TB bacteria," says Dr. Gandotra.

Human blood monocyte-derived macrophages, too, showed increased inflammatory response when triglyceride accumulation was increased. Central to the storage of triglycerides in macrophages is the DGAT1 enzyme (diacylglycerol o-acyltransferase). When the DGAT1 gene is silenced in the macrophage cell lines, the macrophages' ability to accumulate triglycerides is compromised.

"Our studies show that macrophages made to store triglyceride in response to necrosis are able to mount a higher level of the inflammatory response, and if we deplete the levels of the DGAT1 enzyme, the inflammatory response of these macrophages to infection is suppressed," Dr. Gandotra says. "Inhibitors are available against this enzyme and we plan to undertake preclinical studies."

While the ability of the host to inhibit TB infection might not be compromised, the tissue-damaging effects of inflammation may be reduced by inhibiting the ability of the macrophages to accumulate lipids. “The work brings out the importance of the role of host lipid metabolism in increasing inflammation by foamy cells during infection, thereby bringing metabolism into perspective as a potential target for TB therapy,” Dr. Gandotra says.

“Currently, all anti-TB drugs are antimicrobials and don’t help in improving the respiratory health of TB patients, which is compromised. We are hoping that our research may help in finding a promising target to reduce inflammation in TB patients,” says Dr. Jaisinghani.

The role of lipids in altering the immune state in non-infectious metabolic disorders such as obesity is well known. But this study for the very first time reports the role of triglyceride metabolism in altering the immune state during infection.

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