Battling persistence in tuberculosis bacteria

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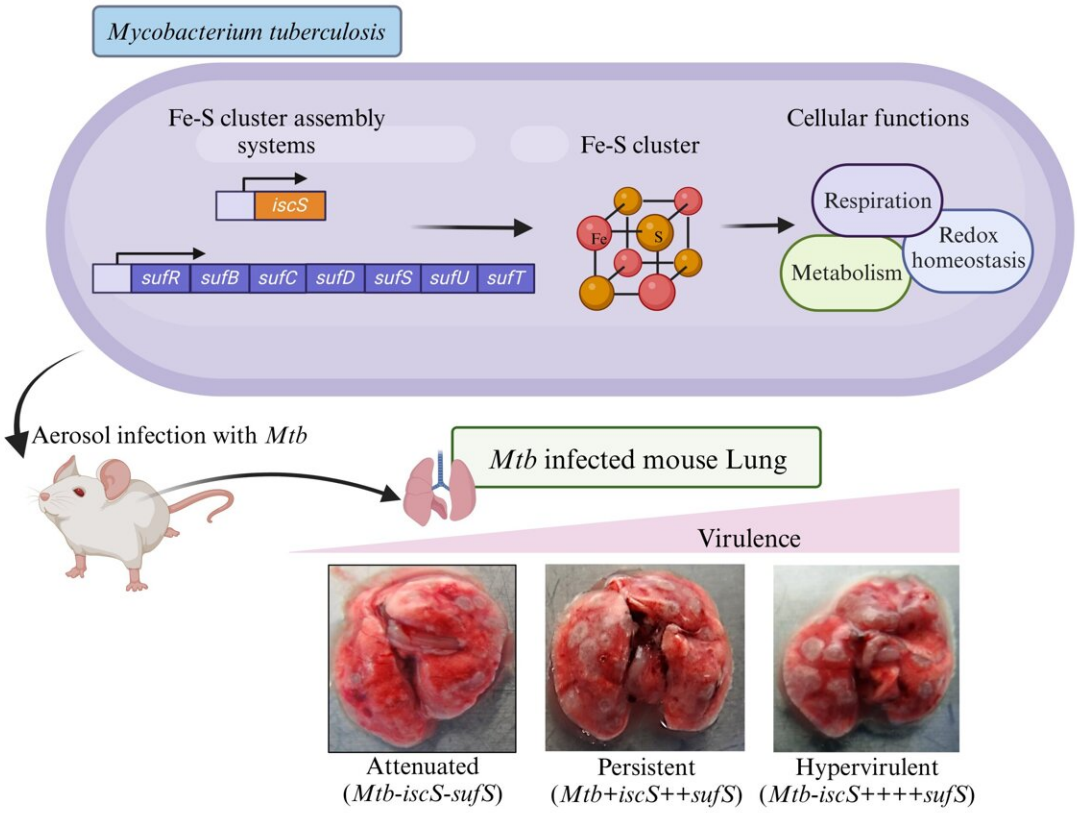

IscS and SUF-mediated Fe-S cluster biogenesis controls persistence of Mtb. Credit: Mayashree Das (created using Biorender)

Researchers at the Indian Institute of Science (IISc), in collaboration with NCBS and InStem, have uncovered an important mechanism that allows the tuberculosis (TB) bacterium to persist in the human host for

decades. They found that a single gene involved in the production of iron-sulfur clusters could be crucial for the persistence of the TB bacterium. The study was published in *Science Advances*.

Tuberculosis (TB) is caused by the bacterium Mycobacterium tuberculosis (Mtb), which can be present in the human body for decades without any symptoms. "Mtb needs humans to survive. In many cases of Mtb infection, the immune system can detect the bug and clear it out," explains Mayashree Das, first author and Ph.D. student at the Department of Microbiology and Cell Biology (MCB), IISc.

However, in several asymptomatic individuals, Mtb hides within deep oxygen-limiting pockets of the lung and enters a state of dormancy in which it does not divide and is metabolically inactive. In doing so, it successfully hides from the immune system and TB drugs.

"Due to persistence, there is a bacterial reservoir in a subset of the human population at any point which can reactivate and cause infection. Unless we understand persistence, we will not be able to eradicate TB," says Amit Singh, Associate Professor at MCB and corresponding author of the study.

Singh's team grew Mtb in liquid cultures containing special supplements needed for its growth in a state-of-the-art Bio Safely Level-3 facility at the Center for Infectious Disease Research (CIDR), IISc. Several proteins in Mtb depend on iron-sulfur clusters for functioning. These clusters consist of iron and sulfur atoms organized in various configurations like chains or cuboids. The iron atoms in the cluster can pass on electrons from one site of a protein complex to another in cellular reactions such as respiration and carbon metabolism.

"The iron-sulfur cluster-containing proteins are important for essential processes such as energy production by respiration, enabling the bacteria

to survive harsh conditions of the lungs and causing infection. So, we wanted to study the mechanisms that Mtb uses to build these iron-sulfur clusters," explains Singh.

Iron-sulfur clusters are mainly produced by the SUF operon in Mtb, a set of genes that get switched on together. However, there is another single gene called IscS that can also produce the clusters. So why would the bacterium need both?

To solve this mystery, the researchers generated a mutant version of Mtb that lacked the IscS gene. They found that under normal and oxygen-limiting conditions, iron-sulfur clusters are produced mainly by the action of the IscS gene. However, when the bacterium faces a lot of oxidative stress, the iron atoms of the clusters become oxidized and released, damaging the clusters. Therefore, there is an increased demand for producing more clusters, which switches on the SUF operon.

The researchers then sought to find out how the IscS gene contributes to disease progression. They infected mice models with the mutant version of Mtb lacking the IscS gene. The absence of the IscS gene led to severe disease in the infected mice rather than a persistent, chronic infection typically seen in TB patients. This is because, in the absence of the IscS gene, the SUF operon is highly activated—albeit in an unregulated fashion—leading to hypervirulence. Depleting both IscS and the SUF system dramatically reduced the persistence of Mtb in mice. Therefore, the team found that the IscS gene keeps the activation of the SUF operon in check, causing persistence in TB.

The researchers also noted that bacteria lacking the IscS gene were more likely to be killed by certain antibiotics. "It becomes sensitive to some antibiotics and resistant to some. We would also like to explore this further," says Das. The team suggests that combining antibiotics with drugs targeting IscS and SUF might be more effective. Singh is hopeful

that a better understanding of the IscS and SUF systems in Mtb can eventually pave the way for eradicating persistence of TB.

More information: Mayashree Das et al, Cysteine desulfurase (IscS)–mediated fine-tuning of bioenergetics and SUF expression prevents Mycobacterium tuberculosis hypervirulence, *Science Advances* (2023). DOI: 10.1126/sciadv.adh2858

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