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Scientists target spermidine production to combat emerging drug resistance in Salmonella

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Spermidine is crucial for Salmonella to protect itself from oxidative stress inside the macrophages



Food-borne diseases like typhoid, caused by Salmonella Typhimurium, are a severe threat to public health, especially in India. The indiscriminate use of antibiotics has allowed this bacterium to become resistant, posing a major hurdle in treating infections.

Scientists at the Department of Microbiology and Cell Biology (MCB), Indian Institute of Science (IISc), Bengaluru have pinpointed how the bacterium uses a key molecule called spermidine to shield itself from the onslaught of the host's defence machinery. They also find that an existing US FDA-approved drug can reduce spermidine production, weakening the bacterium's ability to cause infection.

The researchers found that spermidine is crucial for Salmonella to protect itself from oxidative stress inside the macrophages. Spermidine specifically regulates the expression of an enzyme called GspSA, which causes spermidine to bind strongly to a protein called Glutathionyl (GSH). This conjugate forms chemical bonds with various bacterial proteins, strengthening and shielding them during oxidative stress. Mice infected with mutant Salmonella lacking the ability to import and produce spermidine showed higher survival rates compared to the ones infected with normal Salmonella.

The team focused on D, L-alpha-difluoromethylornithine (DFMO), an FDA-approved drug used widely for treating human African trypanosomiasis. They found that DFMO irreversibly blocks ornithine decarboxylase, an enzyme involved in a key step of the spermidine biosynthesis pathway in the host, reducing its levels and making the bacteria more vulnerable. Mice which were administered the drug showed better survival rates. DFMO is, therefore, a promising candidate for treating salmonellosis, the researchers say.