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Microbiology

Tuberculosis drug discovery: an in-house toxin blocks pathogenic bacterial growth

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Tuberculosis causes more deaths worldwide every year than any other infectious disease, except COVID-19. Today, its treatment is getting increasingly challenging due to the rise of antibiotic-resistant variants of disease-causing bacteria. We discovered an in-house toxin that blocks pathogenic bacterial growth, offering potential clues for future drug design.

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Infectious diseases rank among the greatest threats to human health. While the world stumbles through the current COVID-19 pandemic, a vast array of viral, fungal, parasitic, and bacterial pathogens continue to threaten people's lives. Before the rise of the pandemic, tuberculosis was the world's deadliest infectious disease, killing around 1.5 million people per year with 1.7 billion global infections.

Tuberculosis is caused by the pathogenic bacteria *Mycobacterium tuberculosis (Mtb)*. The bacteria spreads among humans by aerosol droplets and primarily infects the respiratory system. Tuberculosis is curable. However, its treatment is getting increasingly challenging due to the rise of antibiotic-resistant *Mtb* variants, which can survive existing drug treatments. These bacterial variants can exploit "tools" to tolerate external stresses such as those from antibiotics. Extending our understanding of these anti-stress tools will help develop more targeted and effective drugs.

Toxin-antitoxin systems are one such bacterial anti-stress tool. These systems consist of a toxic molecule (toxin) and its antidote molecule (antitoxin), both of which are naturally present within bacterial cells. But why would bacteria produce a toxin that may expose themselves to danger? The antitoxin is the trick — it can specifically associate with the toxin to inactivate its function, fitting together like pieces of a jigsaw

puzzle. Under normal conditions, the toxin remains inactive and harmless as it is neutralized by the antitoxin. However, under certain conditions, the toxin becomes free to target essential cellular processes, which eventually stalls bacterial growth and likely puts them into a dormant state that is stress-tolerant. This suggests that if such a system is found in the disease-causing bacteria, we may be able to block their growth by selectively disrupting the toxin-antitoxin balance.

In this study, we investigated a new family of possible toxin-antitoxin systems in the pathogenic bacteria *Mtb*. Firstly, we asked whether these systems are indeed functional. To our delight, we found that a toxin called $MenT_3$, the strongest in the family, was able to stop bacterial growth. This stalling of bacterial growth was restored by its antitoxin $MenA_3$. We thus discovered a new functional toxin-antitoxin system in the *Mtb* bacteria, which can potentially help them tolerate stress.

To better understand how the $MenT_3$ toxin molecularly behaves to inhibit *Mtb* bacterial growth, we uncovered its 3D structure. This allowed us to identify other molecules structurally similar to $MenT_3$: those involved in a cellular process called protein biosynthesis. Proteins are molecular machinery essential for life, and therefore their biosynthesis is indispensable. Finding the structural resemblance prompted us to hypothesize that $MenT_3$ might stop bacterial growth by interfering with this core biological process. As protein biosynthesis is a complex process in which many different components are involved, we set out to identify which molecule the $MenT_3$ toxin specifically targets. We found that $MenT_3$ interacted with molecules called transfer RNAs — known as key actors in protein biosynthesis. Indeed, this molecular interaction allowed $MenT_3$ to switch off transfer RNA's function by altering its structure.

Overall, we revealed how the in-house toxin $MenT_3$ blocks the growth of the tuberculosis-causing bacteria by interfering with protein biosynthesis. While it is still unknown whether the $MenT_3$-$MenA_3$ toxin-antitoxin system contributes to bacterial infection and stress tolerance, we expect that future studies will answer these questions. If the $MenT_3$-$MenA_3$ system is indeed important for infection in humans, it could present a potential new drug target. This study puts a milestone in developing a new strategy to treat this severe infectious disease.