

## **DBT-THSTI study paves way for a drug against TB**

New Delhi, June 30 As scientists ventured out to search for effective drugs for both drug-susceptible and drug-resistant Mycobacterium tuberculosis, they cracked open what is Pandora's box of Mtb system. The search resulted in the accumulation of knowledge about Mtb physiology, genetics, and biochemistry.

The discovery of toxin-antitoxin (TA) systems was one of the results (a rather significant one!). It happened 30 years ago. The Mtb has 80 TA systems, with 30 of them functional. As is inherent to scientific research, the story of TA systems is still being written, particularly since it is a potential target for TB drugs. The Tuberculosis laboratory of the Department of Biotechnology's Translational Health Science and Technology Institute (DBT-THSTI) led by Dr. Ramandeep Singh is writing the section on the VapBC TA system of Mtb.

Toxin-antitoxin systems are small genetic elements that compose of a stable toxin and an antitoxin that neutralizes the toxin activity . They are widely distributed in prokaryotes in multiple copies and have been shown to contribute to stress adaptation, persisters, biofilm formation, or pathogenesis . The toxins are invariably translated into a protein, whereas the antitoxin can either be a protein or RNA.

TA modules have been classified into six different types based on the nature of antitoxin and the mechanism by which antitoxin negates toxin activity. In type II TA systems, the most well-characterized family, the antitoxin negates the activity of the cognate toxin by forming a tight complex through direct interactions. The antitoxins belonging to type II TA systems have inherently disordered regions, which makes them susceptible to cleavage by cellular proteases. This proteolytic degradation results in the release of toxin that subsequently interferes with various cellular processes such as transcription, translation, DNA replication, cell wall synthesis, and cell division.

The conservation of these TA systems in species belonging to the *M. tuberculosis* complex suggests that they regulate metabolic pathways that are essential for bacterial pathogenesis. Mostly, the *M. tuberculosis* systems belong to type II TA systems such as VapBC, MazEF, ParDE, RelBE, and HigBA .

The team at DBT-THSTI has found that regulation of the VapBC22 TA system is essential for *M. tuberculosis* to establish infection in the host. This means that compounds that could target VapC22 might be good candidates for therapy against both drug-susceptible and drug-resistant *M. tuberculosis*. Virulence-associated protein B and C toxin-antitoxin (TA) systems are widespread in prokaryotes. Filling up the gap in understanding the role of these systems

in physiology, the team delineated the functions of the VapBC22 TA system of *Mycobacterium tuberculosis*.

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