MedicalXpress

Researchers identify a new mechanism of TB drug resistance

June 12 2013

Pyrazinamide (PZA)—a frontline tuberculosis (TB) drug—kills dormant persister bacteria and plays a critical role in shortening TB therapy. PZA is used for treating both drug susceptible and multi-drug resistant TB (MDR-TB) but resistance to PZA occurs frequently and can compromise treatment.

A recent study, led by researchers at the Johns Hopkins Bloomberg School of Public Health and Huashan Hospital, Fudan University, has identified a new mechanism for PZA-resistance, which provides new insight into the how this mysterious drug works. The study is available online June 12 in the journal *Emerging Microbes and Infections*.

Previously, the Johns Hopkins group identified mutations in the pncA gene and the rpsA gene as the primary causes for PZA resistance. According to the study authors, resistance to PZA is most commonly caused by mutations in the pncA gene encoding enzyme nicotinamidase/pyrazinamidase, which converts the prodrug PZA to the active form pyrazinoic acid (POA), and sometimes associated with mutations in the drug target RpsA (ribosomal protein S1). The active form of PZA, POA, interacts chemically with RpsA to block the trans-translation process, which is essential for bacterium's survival under stress conditions.

However, for unknown reasons, some PZA-resistant TB bacteria lack mutations in pncA or rpsA. The current study suggests that mutations in the panD gene may also be involved. PanD encodes aspartate

decarboxylase, which is involved in synthesis of the amino acid β-alanine, a precursor for pantothenate (which is vitamin B5) and co-enzyme A biosynthesis. The panD mutations were identified not only in mutants isolated from in vitro but also in clinical isolates such as in the naturally PZA-resistant bacterium M. canettii strain and in a PZA-resistant MDR-TB strain.

"There is significant recent interest in understanding PZA, since it is the only TB drug that cannot be replaced without compromising the efficacy of the therapy. It's indispensible," said Ying Zhang, MD, PhD, senior author of the study and professor in the Bloomberg School's W. Harry Feinstone Department of Molecular Microbiology and Immunology. "The process of identifying the correct resistance mutations was quite tedious and took about two years to complete. However, the work led to the identification of a potential new mechanism of PZA resistance."

While more study is needed, Zhang and his colleagues believe panD could be a potential target for new antibiotic therapies.

The study was conducted in collaboration with researchers Wenhong Zhang and Jiazhen Chen from Fudan University. The authors of "Mutations in panD encoding aspartate decarboxylase are associated with pyrazinamide resistance in Mycobacterium tuberculosis" are Shuo Zhang, Jiazhen Chen, Wanliang Shi, Wei Liu, Wenhong Zhang, and Ying Zhang.

Provided by Johns Hopkins University Bloomberg School of Public Health

Citation: Researchers identify a new mechanism of TB drug resistance (2013, June 12) retrieved 9 April 2024 from https://medicalxpress.com/news/2013-06-mechanism-tb-drug-resistance.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.