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Scientists explain unique activity of TB drug pyrazinamide

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Pyrazinamide has been used in combination with other drugs as a first-line treatment for people with tuberculosis (TB) since the 1950s, but exactly how the drug works has not been well understood.

Now, researchers have discovered a key reason why the drug effectively shortens the required duration of TB therapy. The finding potentially paves the way for the development of new drugs that can help eliminate TB in an infected individual even more rapidly. The study was supported by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, and published online on August 11 in Science Express.

Unlike most first-line TB drugs, pyrazinamide does not directly kill Mycobacterium tuberculosis, the bacterium that causes TB, grown in a test tube; rather, the drug acts only on latent TB bacteria that exist in an acidic environment in the body. From previous studies, the investigators knew that shortly after pyrazinamide enters latent M. tuberculosis in the body, the drug converts to its active form, pyrazinoic acid (POA). But they did not know how POA then killed the bacteria, thereby shortening the normal 9- to 12-month course of therapy by several months.

In this study, the researchers learned that once formed, POA binds to a vital bacterial cell protein, ribosomal protein S1 (RpsA), blocking RpsA from decoding M. tuberculosis DNA to create other proteins that keep the bacteria alive in the body. The investigators note that their results explain the mechanism of this enigmatic TB drug, which could assist

researchers attempting to develop improved TB drug treatment regimens.

More information: W Shi et al. Pyrazinamide inhibits trans-translation in Mycobacterium tuberculosis. *Science Express*. DOI:10.1126/science.1208813 (2011).

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