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Multiple Mutations Often Needed to Make TB Bacteria Drug Resistant

NEWARK, N.J. -- Tuberculosis (TB) drug resistance is not an all-or-none phenomenon, according to new research from Rutgers, The State University of New Jersey. Rather, TB-causing bacteria often accumulate mutations in a step-wise fashion, with the initial mutation having minimal impact but poising the bug to later develop high-level resistance upon acquisition of other mutations. The study appears in *Nature Genetics* on September 1st.

The anti-TB drug ethambutol blocks bacterial genes required for synthesis of the bug's protective cell wall. Several mutations in these bacterial genes (collectively called the embCAB operon) have been identified in drug-resistant strains of TB, and single mutations are widely thought to confer resistance in one fell swoop. But not all bugs carrying embCAB mutations become ethambutol-resistant and not all resistance strains contain these mutations, suggesting that the story is much more complicated.

David Alland, director of the Center for Emerging and Re-Emerging Pathogens at Rutgers New Jersey Medical School, and colleagues had previously shown expressing single embCAB mutations in drug sensitive bugs rendered them only slightly more drug resistant than normal and failed to explain full-blown resistance. The group now identifies new mutations that contribute to drug resistance, with the level of resistance depending on the unique combination of mutations in a given bacterial isolate.

One of the newly identified mutations—in a bacterial gene called Rv3806c—ramps up production of a substrate used by the embCAB-encoded enzymes to generate the bug's cell wall. This excess substrate then binds to the enzymes, potentially limiting the amount of drug that can bind. However, the Rv3806c mutation alone only modestly increased drug resistance. But when combined with other mutations, it generated high-level ethambutol resistance. Surprisingly, they also discovered "synonymous" DNA mutations (ones that don't change the amino acid sequence of the resulting protein) in a related protein called Rv3792 that also contributed to drug resistance.

Alland's group suggests that bugs with single mutations, for example those in Rv3806c and Rv3792, represent a pre-resistant state, in which the bug is poised for full-blown drug resistance upon the acquisition of a 'second hit' mutation. Identification of patients infected with 'pre-resistant' bugs may allow doctors to increase drug dosages or alter treatment strategies before full-scale drug resistance develops.

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Established in 1766, Rutgers, The State University of New Jersey, is America's eighth oldest institution of higher learning and one of the nation's premier public research universities. Serving more than 65,000 students on campuses, centers, institutes and other locations throughout the state, Rutgers is the only public university in New Jersey that is a member of the prestigious Association of American Universities.

Rutgers Biomedical and Health Sciences (RBHS) is the health care education, research, and clinical division of Rutgers University, comprising nine schools and their attendant faculty practices, centers, institutes and clinics; New Jersey's leading comprehensive cancer care center; and New Jersey's largest behavioral health care network.

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