Role of the Dihydrofolate Reductase DfrA (Rv2763c) in Trimethoprim-Sulfamethoxazole (Co-Trimoxazole) Resistance in Mycobacterium tuberculosis

We thank Wang et al. for clarifying the role of the dihydrofolate reductase DfrA (Rv2763c) in isoniazid (INH) resistance (16). Concerning potential candidates for the unknown INH resistance mechanism(s), we would like to point out that the aldC (Rv2858c) T21A mutation is also present in Mycobacterium tuberculosis strains C (GenBank accession no. AAKR00000000) and CDC1551 (7), both of which belong to lineage 4, X-type (4). Given that strain CDC1551 is INH susceptible (11), another mutation in strain 5297 must be responsible for drug resistance. In contrast, G285V has been previously identified as the sole mutation in an INH-resistant isolate (2). In addition, the same codon is mutated in other INH-resistant strains (1), suggesting that G285V is likely responsible for INH resistance in strain 5324.

Forgacs et al. showed that M. tuberculosis is sensitive to the drug combination of trimethoprim-sulfamethoxazole (co-trimoxazole) (TMP-SMX) (8). In response to this report, Ong et al. found that SMX on its own is active against M. tuberculosis (14). In contrast, Suling et al. had previously reported that TMP on its own was not (15). Furthermore, it should be noted that the recently developed microscopic observation drug susceptibility (MODS) assay contains 4 μg/ml TMP in its 7H9-oleic acid-albumin-dextrose-catalase (7H9-OADC) medium (5, 12). However, given that the studies described above used different methodologies, there remains some uncertainty whether synergy exists between the two compounds, as discussed by Forgacs et al. (14).

Wang et al. have shown that the overexpression of dfrA leads to TMP resistance in M. smegmatis, as is the case for other bacteria (10, 16). Using their pMV261::dfrA plasmid, they could investigate whether the overexpression thereof also alters the MIC for TMP-SMX in M. tuberculosis. In fact, it would be most interesting if they could test their plasmid with TMP and SMX individually as well as together, using the same methodology for each drug. This experiment would not only clarify the question of drug resistance but would also address the open question of synergy.

A clear understanding of the resistance mechanisms of TMP-SMX in M. tuberculosis is urgently needed since the WHO has renewed its call for the widespread use of this drug combination for the prophylactic treatment of patients with HIV (6), many of which also suffer from tuberculosis (9). Given that the supply of these drugs is known to be erratic, this raises the possibility of increased background rates of resistance in M. tuberculosis (6, 9, 13). This should be considered carefully when evaluating the prospect of TMP-SMX for treatment of tuberculosis (8, 14, 17).

REFERENCES


3. Reference deleted.


Author’s Reply

We thank Köser et al. for their interest in our recent publication in Antimicrobial Agents and Chemotherapy. This short letter provides additional information on the different mutations identified during whole-genome sequencing of drug-resistant M. tuberculosis strains. This letter also raises an interesting point about the possible synergy between TMP and SMX. We agree with the authors that a better understanding of how this drug combination works is warranted. Our data match previously published work in that we did observe that M. tuberculosis is resistant to TMP, but we did not test the TMP-SMX combination. We are following the authors’ suggestion and are testing this drug combination against wild-type M. tuberculosis and the M. tuberculosis strain overexpressing dfrA.

Claudio U. Köser*
David K. Summers
Department of Genetics
University of Cambridge
Cambridge, United Kingdom

John A. C. Archer
Computational Bioscience Research Center
King Abdullah University of Science and Technology
Thuwal, Kingdom of Saudi Arabia

*Phone: (44) 1223-333999
Fax: (44) 1223-333992
E-mail: cuk21@cam.ac.uk

William R. Jacobs, Jr.
Department of Microbiology and Immunology
Albert Einstein College of Medicine
1300 Morris Park Avenue
Bronx, New York 10461

Phone: (718) 678-1075
Fax: (718) 678-1085
E-mail: jacobsw@hhmi.org