International Journal of Mycobacteriology xxx (2016) xxx–xxx

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/IJMYCO

Increased expression of efflux pump genes in extensively drug-resistant isolates of *Mycobacterium tuberculosis*

Akbar Kanji [a], *Rumina Hasan* [a], *Ying Zhang* [b], *Wanliang Shi* [b], *Kehkashan Imtiaz* [a], *Kiran Iqbal* [a], *Samreen Shafiq* [a], *Zahra Hasan* [a,*]

[a] *Department of Pathology and Laboratory Medicine, Aga Khan University Hospital, Karachi, Pakistan*

[b] *Department of Molecular Microbiology and Immunology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA*

ARTICLE INFO

Article history:
Received 6 September 2016
Accepted 13 September 2016
Available online xxxx

ABSTRACT

Introduction: Extensively drug-resistant tuberculosis (XDR-TB) is defined as tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) strains that are multidrug resistant (MDR) and also resistant to a fluoroquinolone and to one injectable aminoglycoside or capreomycin. Whilst resistance in MTB has been associated with single nucleotide polymorphisms (SNPs), efflux pumps are thought to play a role in conferring resistance to MTB but little is known about them.

Methods: We studied XDR MTB ($n = 10$) strains characterized by whole genome sequencing (WGS; http://www.ebi.ac.uk/ena/data/view/PRJEB7798). Phenotypic susceptibility testing was performed by the MGIT 960 (Becton, Dickinson and Co., NJ, USA) method. All XDR MTB strains were resistant to at least seven drugs whilst one XDR MTB strain, X54 was resistant to isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol, fluoroquinolones, capreomycin, kanamycin, amikacin, and ethionamide. The mRNA expression of efflux candidate genes *Rv0194*, *Rv2688c*, *Rv1634*, *drrA*, and *drrB* was determined in XDR MTB strains as compared with the ATCC reference strain, H37Rv, and drug-susceptible (DS) MTB ($n = 9$) strains using the relative quantification method normalized to 16S rRNA.

Results: The mRNA expression levels of efflux genes *Rv2688c* ($p = 0.0037$), *Rv1634* ($p = 0.0042$), *drrA* ($p = 0.0078$) and *drrB* ($p = 0.0003$) were upregulated in XDR-TB strains as compared with DS MTB strains.

Conclusion: The differences between XDR-TB and drug-susceptible isolates suggest that the increased expression levels of MTB efflux pump genes may contribute to drug resistance in extensively drug-resistant tuberculosis. Future studies are needed to determine whether combining efflux pump inhibitors to antitubercular drugs would be effective to treat resistant tuberculosis.

Conflicts of interest

All authors have no conflicts of interest to declare.

* Corresponding author.
E-mail address: akbar.kanji@aku.edu (A. Kanji).

Peer review under responsibility of Asian African Society for Mycobacteriology.
http://dx.doi.org/10.1016/j.ijmyco.2016.09.067