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A secondary site *rpoB* mutation restricted to a multidrug-resistant outbreak strain restored the fitness defect of BCG harboring the rifampicin-conferring mutation, S531L

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Multidrug-resistant tuberculosis (MDR-TB) outbreaks represent the most successful example of a naturally-occurring compensatory evolution. Acquisition of multidrug resistance generally incurs a fitness cost leading to reduced transmissibility and virulence. Therefore, MDR-TB strains that evolve into outbreaks are likely to have accumulated mutations that not only restored their fitness defect, but could also have contributed to their epidemic phenotype.

An MDR-TB outbreak due to a Haarlem3-ST53 genotype strain emerged in Tunisia since year 2000. As of June 2011, it involved 45 HIV-negative, no institutionalized, young patients (mean age 29.7 yrs), 9 of which have died. Hence, one can reasonably argue that such an MDR strain has benefited of a successful compensatory evolution.

A hallmark of the MDR outbreak strain was the presence in its *rpoB* sequence of a secondary site mutation, V615M, in addition to the rifampicin-conferring mutation S531L. Comparative genomics involving 7 outbreak-associated strains, revealed no mutations in *rpoC* and *rpoA*, which could be involved in fitness restoration, thus suggesting a compensatory role for the V615M mutation. To address this hypothesis, we engineered BCG strains harboring either the S531L mutation or the double mutation S531L and V615M. Individual and competitive in vitro growth assays firmly established the compensatory effect of V615M. Structural modeling mapped the V615M mutation in a region that is compatible with its compensatory role.

In conclusion, we here provide a direction proof that a secondary site *rpoB* mutation associated with a severe outbreak strain efficiently compensates the fitness cost incurred by the rifampicin resistance-conferring mutation, S531L.

Biography

Helmi Mardassi obtained his doctorate in veterinary medicine(1988) at the Tunisian National School of Veterinary Medicine. After that, he moved to the university of Montreal (Canada) where he completed a master degree in Microbiology and Animal Pathology. In 1996, he obtained his PhD degree in Molecular Virology at the Institut Armand-Frappier (University of Quebec, Canada), and next joined the Biotechnology Research Institute of Montreal for a post-doctoral training. Actually he is leading a research unit focusing on molecular epidemiology, evolution and genetics of Mycobacterium tuberculosis. He has published more than 26 papers in reputed journals.

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