

Identification of non-homologous isofunctional and species- specific enzymes in *Mycobacterium abscessus* as possible therapeutic targets

Fernanda Cristina Medeiros de Oliveira, Philip N Suffys, Solange Alves Vinhas, Moisés Palaci, Pedro Henrique Campanini Cândido, Elizabeth Andrade Marques, Tania Folescu, Rafael Silva Duarte, Marcos Paulo Catanho de Souza, Ana Carolina Ramos Guimarães

Fundação Oswaldo Cruz, Instituto Oswaldo Cruz, Laboratório de Genética Molecular de Microrganismos, Rio de Janeiro, Brazil

Abstract

The genus *Mycobacterium* is composed of several pathogenic species. Many organisms belonging to this group are responsible for diseases, such as tuberculosis, leprosy and other serious infections. *Mycobacterium abscessus* (MABSC) is responsible for severe infections that are becoming common all over the world. Outbreaks caused by MABSC have already been reported in several countries, including Brazil. Treatment of infections caused by MABSC remains ineffective due to antibiotic resistance, justifying the search for potential new therapeutic targets. The identification of non-homologous isofunctional (analogous) and species-specific (taxonomically restricted) enzymes in these parasites compared to the human host might be a relevant approach to disclose potential new therapeutic targets, as we already demonstrated in previous works. Although catalysing the same reaction, non-homologous isofunctional enzymes have distinct evolutionary origin as well as significantly distinct fold topologies and three-dimensional structures. On the other hand, species-specific enzymes are those found only in one organism in relation to others, therefore comprising the most evident targets. In this work, eleven *M. abscessus* genomes were annotated with three distinct tools to identify and characterize encoded proteins with predicted enzymatic activity: RAST, Argot2.5, and BLASTKOALA. A computational pipeline developed by our group (AnEnPi) was used to predict genes encoding putative non-homologous isofunctional enzymes in enzymatic activities shared between those mycobacteria and the human host, as well as species-specific enzymes encoded in *M. abscessus* genomes. We identified events of evolutionary convergence in 11 enzymatic activities comprising 11 metabolic pathways, shared by *M. abscessus* and *H. sapiens*, involving 153 enzymes in total. Five enzymatic activities (EC 5.3.3.2 - terpenoid biosynthesis, EC 2.3.1.1 - arginine biosynthesis, EC 2.7.7.4 - purine metabolism, EC 4.1.1.19 - arginine and proline metabolism, and EC 4.2.2.1 - nitrogen metabolism) are candidates to be further investigated as new therapeutic targets for drug development against *M. abscessus*. On the other hand, 1, 592 species-specific enzymes (compared to the human host), shared among the eleven isolates of *M. abscessus*, were also identified in this process, belonging to 105 distinct enzymatic activities acting on 96 metabolic pathways of *M. abscessus*. The predicted non-homologous isofunctional instances were confirmed based on structural folding and protein signatures assigned to the implicated enzymes. Mapping these non-homologous isofunctional and species-specific enzymes in *M. abscessus* metabolism revealed potential new therapeutic targets to control infections caused by MABSC.

Funding: CAPES, PAPES-FIOCRUZ, CNPq, FAPERJ, Plataforma de Bioinformática Fiocruz
RPT04A/RJ