Title: Drug resistance leads to significant metabolic alterations in *Mycobacterium tuberculosis*

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Abstract:

Tuberculosis is an infectious disease of high medical relevance and is one of the leading causes of death provoked by a single infectious agent worldwide. Despite this, tuberculosis can be easily treated through antimycobacterial drug therapy. However, resistance to antibiotics is becoming increasingly common, leading to treatment failure and making the control of this disease challenging. Therefore, the determination of drug susceptibility profiles is routinely performed in diagnostic laboratories. However, such tests take time, and treatment often needs to be initiated before results are available, which may result in treatment failure and the development of drug resistance. For this reason, the development of new techniques that can quickly determine drug susceptibility profiles of *Mycobacterium tuberculosis* is imperative. This study aimed to characterize the metabolic alterations of drug-susceptible, multidrug-resistant and extensively drug-resistant *M. tuberculosis* strains by metabolomics using mass spectrometry, in order to determine if the analysis of metabolic profiles can be used as an alternative to traditional methods of drug susceptibility testing. This proposal is based on the principle that strains with different levels of resistance are metabolically distinct, thus allowing metabolic biomarkers to be associated with patterns of resistance and used as diagnostic tools. Our findings demonstrated that resistance profiles of *M. tuberculosis* can be predicted through metabolic analyses. In addition, we observed that susceptible strains show higher levels of molecules directly involved in fatty acid synthesis, an important facet of *M. tuberculosis* metabolism, in their metabolic profiles when compared to resistant strains. Furthermore, two amino acids were also found in different levels when comparing susceptible and resistant strains and therefore represent biomarker candidates. This study represents a significant advance in the current understanding of the effect of drug resistance on bacterial metabolism and opens new avenues for the detection of drug resistance-specific biomarkers. In the future, the results presented herein may support the development of tools for the rapid detection of resistance, contributing to better informed decisions by health care providers concerning the appropriate treatments for each patient, aiding in the success of tuberculosis control measures.

Keyword: tuberculosis; drug susceptibility; metabolic alterations; diagnostic tools.

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