

The Metabolomics of Drug Bioaccumulation in Macrophages: The Story of Clofazimine

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Clofazimine (CFZ) is a riminophenazine antibiotic that is FDA-approved for the treatment of *Mycobacterium leprae* and is used off-label to treat *Mycobacterium tuberculosis*. Chronic administration of CFZ has anti-inflammatory activity that is attributable to a CFZ-induced increase in the production of interleukin (IL)-1 receptor antagonist (RA) and the formation of red intracellular drug crystals (IDC) that exclusively form in tissue macrophages particularly those of the lungs. Since IDC formation is macrophage-targeted, identification of metabolic and physiologic changes that occur in parallel with CFZ accumulation could enhance mechanistic understanding of the role of macrophage drug processing in mammalian immune homeostasis and physiology.

Quantitative proton (^1H)-1-dimensional (1D) nuclear magnetic resonance (NMR) metabolomics generates metabolite data which are useful for identifying metabolic changes associated with phenotype (5, 45). This is because metabolites are the end-products of gene and protein activity and represent the organism's physiological condition (46, 63). As such, it could be a particularly useful approach to delineate potential mechanisms of IDC formation as well as the overall metabolic consequences of CFZ treatment to the host. This principle has been illustrated by a number of studies (46, 51, 58, 62) for which metabolomics has served as a sensitive indicator of phenotype and physiological response. We employed quantitative NMR metabolomics of urine and whole blood (WB) to better understand the metabolic consequences of CFZ administration. We show that prolonged, 8-week oral administration of CFZ to mice is associated with significant changes in host metabolism that lend insight into processes involved in IDC formation.