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Bactericidal auxotrophy as new drug target space to eliminate persistent human pathogen *Mycobacterium tuberculosis*

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Tuberculosis is a dreadful disease caused by a successful human pathogen *Mycobacterium tuberculosis* (*M. tb*). Strict compliance to long chemotherapy, lack of diagnostics and vaccines has led to emergence of MDR (multi drug-resistant) and XDR (extensively drug-resistant) strains. Therefore, better understanding of metabolic relationship and interactions among host and pathogen are of fundamental importance for better design of effective vaccine and drug therapies. Availability of essential nutrients, cofactors, and metabolites are of prime importance for successful survival and proliferation of any pathogen. Many pathogens like *Legionella, Coxiella, Francisella, Salmonella* and Listeria have acquired the ways to sustain them by acquiring nutrients, cofactors and essential metabolites from the host. However *M. tuberculosis* lives autonomic life style and is equipped with its own biosynthetic pathways for most of the nutrients, which along with being boon also makes *M. tb* more vulnerable. Most of the auxotrophs of *M. tb* are not proliferate but they survive and persist. Here, using genetic approach, we have discovered novel bactericidal auxotrophies, which rapidly kill *M. tb* in vitro as well as in vivo without the appearance of any suppressor mutants. *M. tb* auxotrophs in these pathways got rapidly killed in immunocompetent, immunodeficient mouse models and in macrophages, despite recruitment of macrophage amino acid transporter on phagosomes. Time course metabolomic and transcriptomic studies on starved cells showed multifactorial mechanism of death involving perturbances in envelope integrity and redox imbalance leading to oxidative stress followed by rapid cell death. Furthermost excitingly, screening fragment library we have obtained fragment inhibitors which cause allosteric inhibition of enzymes in the pathway. Thus, our findings identify a novel attractive target for antimycobacterial therapy and may be for other pathogens also.

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