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Copper Related Toxicity of 1-Hydroxy-2-Thiopyridines

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Abstract : With the emergence of primary resistance to the current drugs and wide distribution of latent tuberculosis infection, a need for new compounds with a novel mode of action is growing steadily. Copper-mediated innate immunity and antibacterial toxicity propose novel strategies in TB drug discovery and development. Transcriptome of M. tuberculosis was obtained by RNA-seq, intracellular copper content was measured by ISP MS and complexes of 1-hydroxy-2-thiopyridines with copper were detected by HPLC.1-hydroxy-2-thiopyridine derivatives were found to be highly active in vitro against both actively growing and dormant non-culturable M. tuberculosis. Transcriptome response to 1-hydroxy-2-thiopyridines revealed signs of copper toxicity in M. tuberculosis bacilli. Indeed, Cu was found to accumulate inside cells treated with 1-hydroxy-2-thiopyridines. These compounds were found to form stable charged lipophylic complexes with Cu^{2+} ions which transport into mycobacterial cell. Subsequent metabolic destruction of the complex led to transformation of 1-hydroxy-2-thiopyridines into 2-methylmercapto-2-ethoxycarbonylpyridines, which did not possess antitubercular activity and releasing of free Cu^{2+} in the cytoplasm. 1-hydroxy-2-thiopyridines are a potent class of Cu-dependent inhibitors of M. tuberculosis which may control M. tuberculosis infection by impairment of copper homeostasis. Acknowledgment: This work was financially supported by the Ministry of Education and Science of the RussianFederation (Agreement No 14.616.21.0065; unique identifier RFMEFI61616X0065).

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