10.06 An Unorthodox Phenomena: Dexamethasone reduces glycolysis in *Mycobacterium tuberculosis* infected human macrophages but improves bacillary killing.

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Background: Tuberculosis (TB), a transmissible endemic disease caused by *Mycobacterium tuberculosis* (Mtb) is a huge cost of burden globally especially with the increasing emergence of drug resistant Mtb. There is an urgent need for the exploration of Host Directed Therapies (HDT).

Dexamethasone, a synthetic glucocorticoid (GC) recently gained much attention as the first drug to be clinically approved to treat COVID-19 patients. Presently, the role of GC as an adjunctive treatment in TB is limited and debatable.

Methods: Human Alveolar Macrophages (AM) were purified from bronchoalveolar lavage. Monocyte derived macrophages (MDM) were differentiated from PBMC isolated from the blood of healthy individuals. Human macrophages were treated with dexamethasone and subsequently infected with Mtb. Macrophages were then assessed for cytokine secretion, gene expression, metabolic flux, cell viability, and bacillary killing.

Results: In both AM and MDM, dexamethasone significantly reduced glycolysis and both pro and anti-inflammatory cytokines. Despite this, a reduction in the colony forming units (CFU) was observed. Furthermore, co-treating macrophages with an autophagy inhibitor (bafilomycin) prevented a decrease in CFU suggesting that dexamethasone likely enhances autophagy in human macrophages. Co-treatment with rapamycin (mTOR inhibitor) did not lead to a synergistic effect on CFU, suggesting that dexamethasone also inhibits mTOR.

Conclusion: This study demonstrates the potential of dexamethasone as a HDT against Mtb highlighting the need for more studies and clinical trials to fully evaluate the benefits of GC.

Disclosures: None

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