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Epigenetic Alteration of *M. tuberculosis* Strains during Exposure to Cholesterol Reveal Unique Methylome Motifs

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ABSTRACT

Mycobacterium tuberculosis is the causative agent of Tuberculosis (TB), which has raised concern worldwide due to the high mortality rates of this disease. Many studies have revealed that lipids are a crucial carbon source utilized by *M. tuberculosis* and contribute to infection and pathogenesis. The members of the *Mycobacterium tuberculosis* complex (MTBC) are genetically very similar however, differ significantly regarding host range, transmission and pathogenicity. Therefore, the aim of the current study is to investigate the epigenomic changes within genes associated with cholesterol metabolism, which could provide insight into novel targets for treatment development. The clinical MTBC strains were cultured in Middlebrook 7H9 and minimal media supplemented with cholesterol. The growth curve analysis revealed that 85 (L2), 88 (L2) and 92 (L4) strains were fast growers in cholesterol-supplemented media, suggesting the ability to better utilize cholesterol as carbon source, while 91 (L3), 94 (L4) and 87 (L2) strains were slow growers in the cholesterol-supplemented media. The differences in growth rates between clinical strains of the same lineages confirm that *M. tuberculosis* exhibits strain-specific characteristics. DNA was extracted in the Cetyltrimethylammonium bromide (CTAB) method and cleaned up using the Zymo DNA concentrator kit. Whole genome sequencing was performed using the PacBio SMRT sequencer and the methylome was characterized using the RS Modification and Motif Analysis protocol and annotated further using DistAMo by selecting methylated genes with a significant z score (≥2 or ≤-2). The highest significantly methylated motifs, CTCCAG, CTGGAG and VNCYGVNYR coding for *Rv2060*, *rseA* and *Rv1175* genes, respectively, were detected in H37Rv grown in normal 7H9 broth while an additional CYGVNYR motif was detected during growth in cholesterol-rich media. This was in contrast to RNCYGVNYR motif detected in the *Rv3632* gene for Lineage 8 strain during grown in 7H9 broth compared to CBBV, CTACCCGVC, GATNNNNRTAC, GNCTACSCA, GTAYNNNNATC, GVGGYMVCR and CACGCAGHNH motifs detected for *pks8, Rv2459, PE_PGRS16, vapC22, fadD2, sseA, ackA* genes, respectively. This suggests that the clinical MTBC strains have distinct epigenetic regulations compared to H37Rv. The complete characterization of the MTBC methylation profiles in the presence of cholesterol-rich environments could provide insight into the development of novel treatment methods.

Keywords: *M. tuberculosis*, Cholesterol, SMRT sequencing, Methylome, Epigenetics

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