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Coexpression network analysis-based identification of critical genes and regulatory factors driving inter-individual variation in response to Mycobacterium tuberculosis infection.

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Background/Introduction: Worldwide, tuberculosis (TB) is the second leading infectious killer after COVID-19 and above HIV and AIDS. Inter-individual variation in M.tb infection presents both challenges and opportunities in understanding, diagnosing, treating, and preventing the disease. However, the substantial inter-person variability in response to a single M.tb strain in the lungs remains poorly understood. In this study, RNA sequencing expression data from interactions of a virulent M.tb strain (H37Rv) with freshly isolated human alveolar macrophages from 28 healthy adult donors (GSE189996) and 11 healthy donors (GSE223863) over 72 hours were pooled for weighted gene coexpression network analysis (WGCNA) to reveal dysregulated biomarkers, correlated regulatory motifs, and transcription factors associated with M.tb infection.

Results: Our exploration implicated 303 genes that drive inter-individual variation in response to M.tb infection. Specifically, matrix metallopeptidase 14 (MMP14), TNF superfamily member 13 (TNFSF13), and neutrophil cytosolic factor 1 (NCF1) were revealed as hub genes mediating inter-individual variation in response to M.tb infection. Elucidation of the regulatory motifs of these molecular signatures revealed short DNA sequences representing promoter and enhancer elements and binding sites for transcription factors including C2H2 zinc finger factors, Homeo domain factors, T-Box factors, and High-mobility group (HMG) domain factors.

Discussion and Conclusion: Significant changes in key host factors were observed to potentially drive inter-individual variation in response to M.tb infection, affecting collagen degradation, extracellular matrix organization, monocyte migration, IgA production, and detoxification of reactive oxygen. This study highlights these elements as central to TB pathogenesis, offering insights into the variability in disease response that could inform targeted and personalized TB therapies and vaccine strategies

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Conflicts of Interest
None