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RNAseq Reveals Hypervirulence-Specific Host Responses to M. tuberculosis Infection

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Abstract : The distinguishing factors that characterize the host response to infection with virulent Mycobacterium tuberculosis (M.tb) are largely confounding. We present an infection study with two genetically closely related M.tb strains that have vastly different pathogenic characteristics. The early host response to infection with these detergent-free cultured strains was analyzed through RNAseq in an attempt to provide information on the subtleties which may ultimately contribute to the virulent phenotype. Murine bone marrow-derived macrophages (BMDMs) were infected with either a hyper- (R5527) or hypovirulent (R1507) Beijing M. tuberculosis clinical isolate. RNAseq revealed 69 differentially expressed host genes in BMDMs during comparison of these two transcriptomes. Pathway analysis revealed activation of the stress-induced and growth inhibitory Gadd45 signaling pathway in hypervirulent infected BMDMs. Upstream regulators of interferon activation such as and IRF3 and IRF7 were predicted to be upregulated in hypovirulent-infected BMDMs. Additional analysis of the host immune response through ELISA and qPCR included the use of human THP-1 macrophages where a robust proinflammatory response was observed after infection with the hypervirulent strain. RNAseq revealed two early-response genes (IER3 and SAA3) and two host-defence genes (OASL1 and SLPI) that were significantly upregulated by the hypervirulent strain. The role of these genes under M.tb infection conditions are largely unknown but here we provide validation of their presence with use of qPCR and Western blot. Further analysis into their biological role under infection with virulent M.tb is required.

Keywords : host-response, Mycobacterium tuberculosis, RNAseq, virulence
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