STRESS RESPONSE FACTOR SIGH MODULATES THE INTERACTION OF MYCOBACTERIUM TUBERCULOSIS WITH HOST PHAGOCYTES.


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Abstract

BACKGROUND & AIMS: Tuberculosis (TB) pathogenesis is governed by the interaction between the host and the pathogen (Mycobacterium tuberculosis - Mtb). SigH (σH), encoded by the Mtb sigH gene, is the central regulator of an extensive transcriptional network responsible for this pathogen’s response to oxidative, heat, acidic and nitrosative stresses. σH is induced upon the phagocytosis of Mtb by host macrophages, and is required for full virulence in animal models of TB. Transcriptional regulation by σH is now known to influence such diverse bacillary functions such as enduring hypoxia, cell-envelope damage, mammalian cell entry, sulphate acquisition and Clp proteolysis. σH is induced in host phagocytes following infection with Mtb. We hypothesized that the interaction of Mtb with host cells during the infection phase may be influenced by σH.

METHODS: Here we present a system-wide comparison of rhesus macaque bone-marrow derived macrophage transcriptome in response to equitable infection with Mtb and its isogenic Δ-sigH mutant (Mtb:Δ-σH). Our microarray results approach was validated by quantitative real-time reverse transcriptase PCR (qRT-PCR), enzyme-linked immunosorbant assay (ELISA) and multilabel immunofluorescence confocal microscopy.

RESULTS: Our results show the infection with tubercle bacilli (both Mtb and the Mtb:Δ-σH mutant) generates a robust response from the host cells. This is characterized by a rapid and significant increase in the expression of molecules from the interferon, TNF and cytokine signaling networks. On the other hand, the expression of several chemokine ligands harboring the C-C motif (CCL2, CCL4, CCL5, CCL7, CCL13, CCL19 etc.), was significantly reduced in phagocytes infected with Mtb, relative to Mtb:Δ-σH. A similar effect was not observed for the several chemokine ligands harboring the C-X-C motif, for which the expression was comparable in phagocytes infected with Mtb and Mtb:Δ-σH. These results show that Mtb, with its full complement of σH, modulates the host response to infection by altering the levels of key macrophage and lymphocyte chemoattractant proteins. Due to its inability to induce σH, the infection by Mtb:Δ-σH of the host cells reveals these alterations.

CONCLUSIONS: These findings will enhance our understanding of the crucial role played by σH in infection and pathogenesis of Mtb for the development of new therapies to cure and prevent TB.

ACKNOWLEDGEMENT: This work was supported in part by awards from Tulane Research Enhancement Fund (DK), Louisiana Vaccine Center (DK) and NIH grants R21RR026006 (DK), P20RR020159 and P51RR164.