**A Possible Role for Sigma Factor C in *Mycobacterium tuberculosis* Latency.**

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*Mycobacterium tuberculosis* remains the leading cause of morbidity and mortality by a bacterial pathogen. Annually 6.8 million suffer from active tuberculosis leading to 2.4 million deaths globally. It is estimated that 1/3 of the world's population is latently infected with the bacterium, each individual carrying a 10% lifetime risk of developing active tuberculosis or a 10% annual risk if co-infected with the HIV virus. The metabolic fate of the bacilli inside the host during latent infection is unknown. One possibility is that the bacilli enter into a metabolically-inert state to avoid being killed by granulomas that form around infected macrophages to prevent bacterial dissemination. Another possibility is that the pathogen "hides out" by replicating slowly in other cell types such as lung epithelial cells. In either scenario, the mycobacteria persist for months to decades until an immune-compromising event allows the bacilli to emerge from the "latent state" and cause active disease.

Some of the non-primary sigma factors likely enable *M. tuberculosis* to sense and alter gene expression in various host environments. I have created a family of secondary sigma factor knockout mutants in the pathogenic *M. tuberculosis* strain H37Rv and have utilized in vitro and animal models to identify sigma factors required for virulence. Of those examined to date, a mutant defective in the production of sigma factor C possesses phenotypes consistent with SigC functioning as an important regulator of persistent infections. SigC is not required for growth in rich medium, for entry or survival inside of the human macrophage cell line THP1, or for initial replication in the lungs of guinea pigs infected by aerosol. However, a SigC mutant strain is less effective than the parent, H37Rv, at disseminating the infection to the spleen by 6 weeks post-infection. The mutant is less able than H37Rv at maintaining a persistent infection; titers of the mutant strain in the lungs and spleen drop to undetectable levels by 20 weeks post-infection. Animals infected with the SigC mutant also exhibit reduced pathology by possessing fewer and smaller lung granulomas than animals infected with H37Rv. Experiments to identify the SigC-regulated factors that enable *M. tuberculosis* to be a successful pathogen are underway.