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An Attenuated Quadruple Gene Mutant of Mycobacterium tuberculosis Imparts Protection against Tuberculosis in Guinea Pigs

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Abstract : Mycobacterium tuberculosis, the causative agent of human tuberculosis, is a major cause of mortality. Bacillus Calmette-Guérin (BCG), the only licensed vaccine available for protection against tuberculosis confers highly variable protection ranging from 0%-80%. Thus, novel vaccine strains need to be evaluated for their potential as a vaccine against tuberculosis. We had previously constructed a triple gene mutant of M. tuberculosis (MtbΔmms), having deletions in genes encoding for phosphatases mptpA, mptpB, and sapM that are involved in host-pathogen interaction. Though vaccination with MtbΔmms strain induced protection in the lungs of guinea pigs, the mutant strain was not able to control the hematogenous spread of the challenge strain to the spleens. Additionally, inoculation with MtbΔmms resulted in some pathological damage to the spleens in the early phase of infection. In order to overcome the pathology caused by MtbΔmms in the spleens of guinea pigs and also to control the dissemination of the challenge strain, MtbΔmms was genetically modified by disrupting bioA gene to generate MtbΔmmsb strain. Further, in vivo attenuation of MtbΔmmsb was evaluated, and its protective efficacy was assessed against virulent M. tuberculosis challenge in guinea pigs. Our study demonstrates that MtbΔmmsb mutant was highly attenuated for growth and virulence in guinea pigs. Vaccination with MtbΔmmsb mutant generated significant protection in comparison to sham-immunized animals at 4 and 12 weeks post-infection in lungs and spleens of the infected animals. Our findings provide evidence that deletion of genes involved in signal transduction and biotin biosynthesis severely attenuates the pathogen and the single immunization with the auxotroph was able to provide significant protection as compared to sham-immunized animals. The protection imparted by MtbΔmmsb fell short in comparison to the protection observed in BCG-immunized animals. This study nevertheless indicates the importance of attenuated multiple gene deletion mutants of M. tuberculosis in generating protection against tuberculosis.

Keywords : Mycobacterium tuberculosis, BCG, MtbΔmmsb, bioA, guinea pigs
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