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Enhancing the efficacy of conventional BCG vaccine

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Abstract

The need for an efficacious control of the spread of tuberculosis (TB) disease is urgent and not restricted to the developing world. Protective vaccination is the best and most cost-effective option to prevent the spread of infectious diseases. However, efficacy of the only available TB vaccine (derived from the non-pathogenic mycobacterium *M. bovis* bacillus Calmette-Guérin, or BCG) varies from 0 to 80% in different populations, with a consistently low efficacy in parts of the world where TB control is the most needed. Although the BCG vaccine is generally safe and rarely induces disease in human, it appears to mimic virulent *M. tuberculosis* (Mtb) strains in their capacity to inhibit macrophage (MØ) functions that initiate adaptive immune response. Our investigations have revealed that MØ infection with conventional BCG down-modulates surface expression of mature MHC class II molecules by mechanisms that are in part dependent on the inhibition of Cathepsin S (CatS) expression, a cysteine protease that is required for normal processing and maturation of MHC class II molecules in MØ. BCG also significantly blocks phagosome biogenesis, which is a prerequisite for Ag processing. Therefore inhibition of antigen presenting cell functions may, at least partially, explain its failure to induce efficient immunity to TB. We believe that removing the inhibitory effects could improve the current BCG vaccine. Overcoming even one aspect of MØ activation may improve BCG immunogenicity enough to enhance its protective efficacy. Therefore, we cloned and expressed a secreted form of human active CatS (huCatS) in BCG to generate a novel BCG-derived vaccine. Our in vitro investigations demonstrated that infection with rBCG-huCatS (**i**) restores normal levels of MØ CatS, (**ii**) induces phagosome-lysosome fusion and apoptosis and (**iii**) restores the expression of mature class II molecules as well as their capacity to present mycobacterial Ag to specific CD4 T cells. More recently, we generated a second recombinant BCG expressing a stable chromosomal copy of active CatS (rBCG-muCatS) to examine the efficacy of BCG expressing CatS in the mouse model. Preliminary experiments showed a significant decrease in the number of virulent Mtb in the lung of vaccinated animals. Such findings were consistent with concomitant observations that CatS also stimulates the MHC class I pathway in cells infected with mycobacteria.

Biography

Zakaria received a PhD degree from the University Claude Bernard (Lyon, France) in 1993. He is currently Associate Professor at the University of British Columbia (Department of Medicine) and holds a Scholarship Award from the Michael Smith Foundation of Health Research. Ongoing research in Zakaria's lab focuses on developing novel gene manipulation technologies to upgrade the current BCG vaccine in order to maximize the induction of protective TB immunity. Of equal importance to the vaccine project, a biology-based study of Mtb persistence has revealed important virulence factors that represent attractive drug targets that could be used for TB treatment.