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Novel non-genetic approach to improve the tuberculosis vaccine BCG

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The global persistence of tuberculosis (TB) epidemic and the current spread of drug resistant *M. tuberculosis* (Mtb) strains have stimulated an unprecedented rush to develop novel efficient vaccines. An important strategy toward this goal remains improving the efficacy of current BCG vaccine based upon its remarkable safety record during almost 100 year of massive human immunization. Current strategies to improve BCG attempt to over-express genes encoding specific Mtb antigens and/or regulators of antigen presentation function, which indeed have the potential to reshape BCG in many ways. However, these approaches often face serious difficulties, in particular the efficiency and stability of gene expression via nucleic acid complementation and safety concerns associated with the introduction of exogenous DNA, in particular antibiotic resistant genes, into human cells and tissues. As an alternative, we developed a novel non-genetic approach for rapid and efficient display of exogenous proteins on bacterial cell surface. The technology involves expression of proteins of interest in fusion with a mutant version of monomeric avidin that has the feature of reversible binding to biotin. Fusion proteins are then used to decorate the surface of biotinylated BCG. Chimeric proteins corresponding to a surrogate antigen derived from ovalbumin and to a fusion of Mtb antigens ESAT6/TB10.4 were generated and tested for immunogenicity functions. We found that modified BCG strains displaying ovalbumin antigen or ESAT6/TB10.4 induce an immune response in the mouse similar to that induced by BCG genetically expressing the same antigens. This novel technology, therefore, represents a practical and effective alternative to DNA-based gene expression for upgrading the current BCG vaccine.

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