VACCINES

Protecting against tuberculosis

BRANDX

The only vaccine against *Mycobacterium tuberculosis*, the attenuated *Mycobacterium bovis* strain bacille Calmette–Guérin (BCG), has variable efficacy and generates only partial immunity against *M. tuberculosis*. A possible new vaccine strategy that provides highly protective bactericidal immunity against *M. tuberculosis* in mice is described in a paper in *Nature Medicine*.

M. tuberculosis can evade host innate and adaptive immune responses by exporting effector molecules using specialized bacterial secretion systems. The *M. tuberculosis* genome encodes five potential secretion systems (ESX-1 to ESX-5) but only genes with the *esx-3* locus are highly conserved in all mycobacterial species. So, the authors studied the influence of this locus on the innate and adaptive immune systems. Because inactivation of *esx-3* is incompatible with viability in *M. tuberculosis*, they used *Mycobacterium smegmatis*, a mycobacterium that the authors discovered is able to grow without an intact *esx-3* locus.

Analysis of the cytokines released by mice following infection with *M. smegmatis* lacking the *esx-3* locus (*Δesx-3 M. smegmatis*) suggested that mice elicited a T helper 1 (T_H1) cell-type response, which is known to have a key role in protective immunity. Furthermore, mice infected with *Δesx-3 M. smegmatis* survived and cleared their infections, whereas mice infected with wild-type *M. smegmatis* died within 7 days. In addition, *Δesx-3 M. smegmatis* infection did not kill mice lacking T and B cells, suggesting that infection was controlled by an innate immune response. Furthermore, using a panel of mouse strains deficient in various innate immune response genes it was shown that the adapter protein MyD88 was important in mediating clearance of *Δesx-3 M. smegmatis*.

Next, the authors introduced orthologous genes from *M. tuberculosis* into *Δesx-3 M. smegmatis*, and named this new construct IKEPLUS. To see whether IKEPLUS could be used as a potential vaccine, mice were given IKEPLUS intravenously, then challenged 8 weeks later with *M. tuberculosis*. The average time to death after *M. tuberculosis* challenge was 54 days for sham-vaccinated mice, 65 days for BCG-immunized mice and 135 days for IKEPLUS-immunized mice. IKEPLUS-immunized mice had a reduced bacterial burden in lung, spleen and liver tissue, and in mice that survived for more than 200 days there was evidence of a high level of bactericidal and potentially sterilizing immunity.

To assess the efficacy of IKEPLUS as a vaccine in a more physiological setting, the authors immunized mice subcutaneously and then challenged them 1 month later by low-dose aerosol infection with *M. tuberculosis*. IKEPLUS-vaccinated mice showed a trend towards longer survival than BCG-immunized mice. In addition, IKEPLUS vaccination resulted in reductions in bacterial burden in lung and spleen tissues, which were maintained for 25 weeks after infection, whereas in BCG-immunized mice bacterial burdens were increased by this time.

Further work suggested that the protective immunity elicited by IKEPLUS immunization was dependent on major histocompatibility complex class II presentation, and probably involved responses by $CD4^+$ T cells. Strikingly, transfer of $CD4^+$ T cells from IKEPLUS-immunized mice to host mice conferred immunity against *M. tuberculosis* infection, suggesting the generation of a unique memory $CD4^+$ T cell population. Although further work will be necessary to determine the precise mechanism of action of IKEPLUS, this study suggests that it could be a lead vaccine candidate for providing long-lasting immunity against *M. tuberculosis* infection.

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ORIGINAL RESEARCH PAPER Sweeney, K. A. *et al.* A recombinant *Mycobacterium smegmatis* induces potent bactericidal immunity against *Mycobacterium tuberculosis*. *Nature Med.* 4 Sep 2011 (doi:10.1038/nm.2420)