Polyanhydride particle vaccine platform enhances antigen-specific cytotoxic T cell responses

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Statement of Purpose: A critical feature of next generation vaccines is the need to develop safe and efficacious vaccine delivery platforms that are capable of enhancing antigen-specific cell-mediated immunity, resulting in the development of long-lived immunologic memory. Subunit vaccines are a viable alternative to live-attenuated or killed vaccines due to the purity of the immunogen and relative ease in production of recombinant antigens. However, recombinant proteins are often poorly immunogenic, leading to the need for multiple immunizations that incorporate adjuvants to enhance immune functions. Nanoparticles based on polyanhydride copolymers of sebacic acid (SA), 1,6-bis(*p*-carboxyphenoxy) hexane (CPH), and 1,8-bis(*p*-carboxyphenoxy)-3,6-dioxaoctane (CPTEG) have been shown to provide adjuvant activity along with sustained release of the immunogen and to induce long-lived and protective serum antibody responses [1, 2]. Induction of cytotoxic $CD8^+$ T cells necessary for mediating immune responses against virally infected cells, intracellular bacterial pathogens, or tumor cells is often difficult to achieve with purified subunit vaccines. Here, we expand our analysis of cell-mediated immune responses elicited by polyanhydride particle vaccination. Our results demonstrate that encapsulation of antigen within polyanhydride nanoparticles enhances antigen specific $CD8^+$ T cells in high and low frequency adoptive transfer models.

Methods: Transgenic naïve OTI $CD8^+$ $Thy1.2^+$ T cells were adoptively transferred into Thy 1.1^+ mice to assess expansion of and induction of antigen-specific T cell phenotypes. Mice were immunized with 1.75 mg of soluble ovalbumin (sOVA) in combination with CPH:SA and CPTEG:CPH nanoparticle formulations (20:80 C:S, 20:80 C:C, and 50:50 C:C) that contained 250 µg of OVA. Separate groups of mice received 2.0 mg sOVA adjuvanted with Alum or monophosphoryl lipid A (MPLA) or 2.0 mg sOVA alone. Flow cytometric analysis (FACS) was used to examine expansion of and induction of antigen-specific, effector populations of $CD8^+$ T cells post-immunization.

Results: Vaccine regimen using OVA-containing 20:80 C:S and 20:80 C:C nanoparticle formulations induced significantly greater expansion of antigen-specific $CD8^+$ T cells at 7 days post-immunization as compared to Alum-sOVA, MPLA-sOVA and sOVA alone (Fig. 1). The OTI $CD8^+$ T cells recovered from the mice immunized with the nanoparticle formulations were phenotypically characterized as central memory precursor cells ($CD44^{high}$ $CD62L^{high}$) and memory precursor effector cells ($KLRG1^{low}$ $CD127^{low}$). The number of central memory OT I $CD8^+$ T cells ($CD44^{high}$ $CD62L^{high}$ $CCR7^+$) was also increased but not significantly.

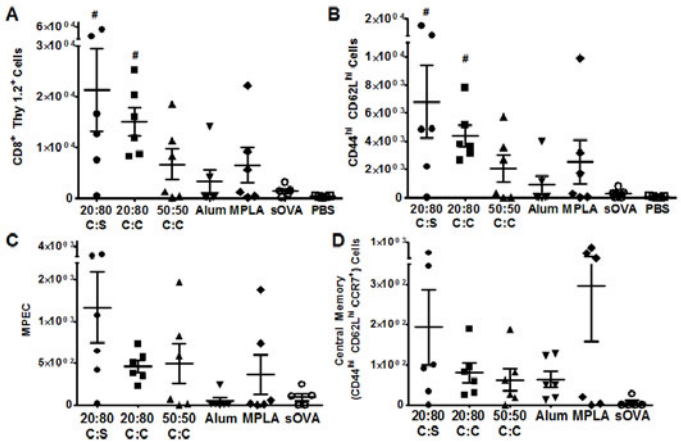

Figure 1. Polyanhydride nanoparticle-based vaccines enhanced antigen specific $CD8^+$ T cell expansion and created larger numbers of central memory precursors and central memory cells early after immunization. Quantified expansion of donor OTI $CD8^+$ Thy 1.2^+ T cells at 7 days post immunization (A). Quantified cell populations of precursor central memory phenotype analysis showing gating of $CD44^{high}$ $CD62L^{high}$ or $KLRG1^{low}$ $CD127^{low}$ donor OTI T cells (B and C). Quantified numbers of the central memory ($CD44^{high}$ $CD62L^{high}$ $CCR7^+$) populations (D). n =5-6 with # indicating $p < 0.05$ from PBS.

Conclusions: Polyanhydride nanoparticle-based vaccines were able to expand antigen-specific $CD8^+$ T cells resulting in the induction of short term effector cells as wells as expanding the central memory precursors within seven days post-immunization. The ability to design vaccine formulations that induce balanced adaptive immune responses (cellular and humoral) following immunization with recombinant proteins will be key characteristic of efficacious vaccines used to maintain healthy populations.

References:

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