A pH-Responsive Nanoparticle Platform for Improving Immunogenicity of Cancer Vaccines

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Background

- Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of many cancers by enhancing durable anti-tumor responses.
- However, only a minority of patients respond to ICIs.
- Resistance is in part due to a lack of pre-existing tumor infiltrating T cells that recognize tumor antigens.
- Cancer vaccines can increase the magnitude and breadth of tumor infiltrating antigen-specific CD8+ T cells and improve overall ICI responses.
- Cancer vaccines are typically composed of tumor antigens and immunostimulatory adjuvants.
- Activation of CD8+ T cells depends on three signals:
  1. Signal 1: T cell receptor (TCR) engagement to peptide/MHC complexes
  2. Signal 2: expression of co-stimulator molecules
  3. Signal 3: Production of pro-inflammatory cytokines

Results

Nanoparticle Vaccine Fabrication and Characterization

- A pH-responsive diblock copolymer, poly(PDMA-co-DMAA) (PP-DMA) (A), was synthesized via RAFT polymerization.
- Self-assemblies into micelles in aqueous solutions were formed (B).
- Chemical composition of poly(PDMA-co-PDMAA)-block-DMAA-co-PDMAA (PDMA-co-PDMAA) (PP-DMA) (A), polymeric material loaded with I mg poly(lys)
- Representative number-average size, distributions of NP alone or formulated with CCA was measured by DLS (B).
- Schematic representation of polymeric micelles (C).
- Nanoparticle uptake by cancer cells (D).
- Flow cytometry analysis of medium fluorescence intensity (MFI) of DD2, cells treated with indicated formulations and stained with SIINFEKL-H2-α,β-dinitrophenyl (E).
- Polymeric micelles with siRNA conjugated to polylysine via NHS-ester linkages (F).
- Polymeric micelles with siRNA conjugated to polylysine via NHS-ester linkages (G).
- Polymeric micelles with siRNA conjugated to polylysine via NHS-ester linkages (H).

NP Vaccine Enhances Magnitude and Functionality of the CD8+ T Cell Response

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Conclusions

- Developed a novel NP vaccine platform for optimized co-delivery of protein antigens and the nucleic acid adjuvant polyIC.
- Elucidated the importance of achieving cytosolic delivery to activate intrinsic signaling pathways in DCs that will shape the adaptive immune response.

Future Direction

- Demonstrate the impact of NP vaccines in augmenting responses to ICB.

Acknowledgments