Background Our group has investigated plasmid DNA (pDNA) vaccines encoding tumor-associated antigens for the treatment of cancer. However, DNA vaccines as monotherapies have generally been perceived as being less immunogenic in patients than some other vaccine approaches. Messenger RNA (mRNA) vaccines have recently gained interest for infectious disease prophylaxis, and have been demonstrated to generate robust and safe immune responses against SARS-CoV-2. Due to the recent advancements in delivery and stabilization techniques using lipid nanoparticles (LNPs) that have enabled mRNA vaccines, we sought to determine whether there were differences in immunological outcomes between mice receiving pDNA or mRNA vaccines encapsulated in LNPs, and whether the immune response from pDNA might be increased by LNP encapsulation.

Methods B6 female mice were immunized intradermally two times, one week apart, with 3ug, 15ug, or 30ug mRNA encoding ovalbumin (sOVA) encapsulated in LNP (ALC-0315; ‘mRNA-LNP’) or 3ug, 30ug, or 100ug pDNA encoding sOVA encapsulated in LNP (ALC-0315; ‘pDNA-LNP’) or a negative control (PBS). In separate studies, low dose (3ug) naked pDNA or mRNA encoding sOVA were administered as above with or without LNP encapsulation. Mice were euthanized 5 days after the second immunization, spleens were harvested into single-cell suspensions, and cells were assessed for CD8+ T cell phenotype and checkpoint receptor expression by flow cytometry.

Results Mice receiving mRNA-LNP immunizations at any dose had significantly higher percentages of antigen-specific CD8+ T cells in the spleen by tetramer staining. mRNA-LNP immunization led to antigen-specific CD8+ T cells that were predominantly of an effector memory (Tem, CD44+, CD62L-) phenotype. Furthermore, antigen-specific CD8+ T cells from mice receiving mRNA-LNP immunizations exhibited increases in expression of PD-1 and TIGIT immune checkpoint receptors in comparison to mice immunized with pDNA-LNP. In contrast, antigen-specific CD8+ T cells from mice receiving pDNA-LNP immunizations primarily displayed a central memory (CD44+, CD62L+) phenotype and exhibited increases in expression of CD69 and VISTA. Surprisingly, antigen-specific CD8+ T cells from mice receiving low dose pDNA encapsulated in LNP exhibited an increase in the percentage of cells expressing Ki67 and an increase in the percentage of Tem cells in comparison to mice receiving naked pDNA immunizations.

Conclusions These findings indicate pDNA and mRNA vaccines lead to differences in immune responses. This could potentially be due to differences in cell uptake and antigen presentation between pDNA and mRNA, or activation of different toll-like receptors. Furthermore, immune responses from pDNA vaccines may be enhanced by encapsulation in novel LNP formulations.

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