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“Combination of a Strategy to Prolong Dendritic Cell Survival and a Strategy to Bypass Antigen Processing Enhances DNA Vaccine Potency”

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Background: Intradermal vaccination via gene gun efficiently delivers DNA vaccines into dendritic cells (DCs) of the skin, resulting in the activation and priming of antigen-specific T cells *in vivo*. We have previously demonstrated that intradermal delivery of DNA vaccine encoding a single-chain trimer (SCT) composed of the most immunogenic epitope of the human papillomavirus type 16 (HPV-16) E6 protein (aa49-57), β 2-microglobulin, and MHC class I heavy chain (SCT-E6) can bypass antigen processing and lead to stable cell-surface presentation of E6 peptides. In addition, we have shown that co-administration of DNA vaccines with DNA encoding anti-apoptotic proteins can prolong the survival of DNA-transduced DCs, resulting in significant enhancement of antigen-specific CD8⁺ T cell immune responses.

Design: In the current study, we hypothesized that combining the SCT strategy and antiapoptotic strategy may further enhance DNA vaccine potency by augmenting antigen-specific CD8⁺ T cell immune responses and antitumor effects in vaccinated mice.

Results: Here we show that C57BL/6 mice vaccinated with SCT-E6 DNA in combination with DNA encoding the antiapoptotic protein BCL-xL generated significantly higher E6-specific CD8⁺ T cell responses compared to mice vaccinated with SCT-E6 DNA and a non-functional mutant BCL-xL (mBCL-xL). Furthermore, mice treated with SCT-E6 and BCL-xL DNAs generated a better anti-tumor effect against E6-expressing tumor cells (TC-1/Lucif) than mice treated with SCT-E6 and mBCL-xL DNAs. Our long-term bioluminescent kinetic observations also indicated significant reduction of tumor load in mice treated with SCT-E6 and BCL-xL DNA vaccines.

Conclusion: We conclude that the combination of a strategy to bypass antigen processing and presentation mechanisms and a strategy to prolong the life of DCs can lead to significant enhancement of DNA vaccine potency.