Hybrid nanoparticle leveraging cell-cell interactions for immunotherapy

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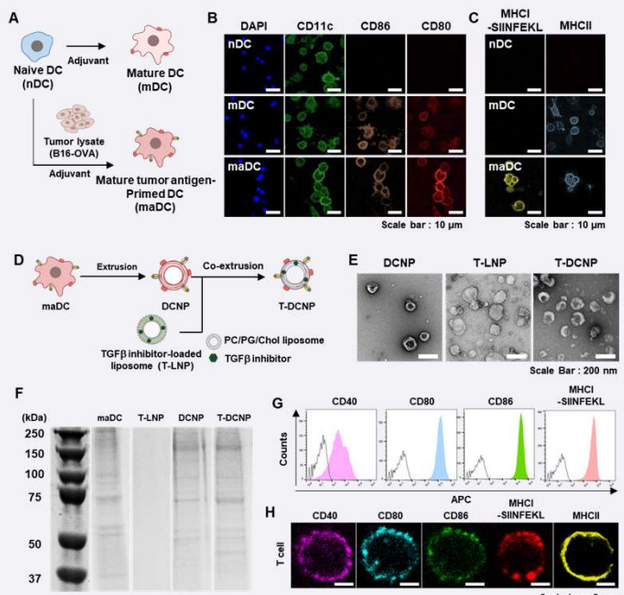
Introduction

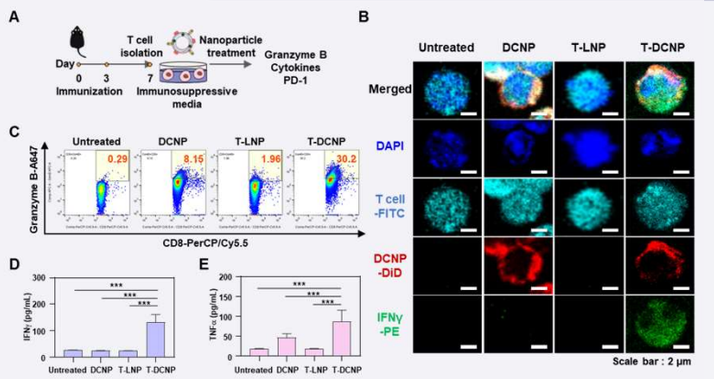
Surgical resection is a cornerstone treatment for solid tumors, but postoperative immunosuppression and microscopic residual disease often lead to recurrence and metastasis. Current adjuvant therapies like chemotherapy and checkpoint inhibitors have limitations in targeting heterogeneous tumor antigens or modulating the immunosuppressive tumor microenvironment. Dendritic cell (DC)-based immunotherapy offers a promising strategy by enhancing antigen-specific T cell responses and inducing immune memory. However, DC function is frequently impaired by immunosuppressive factors such as TGF-β. To address these challenges, we developed a hybrid lipid nanoparticle platform (T-DCNP) integrating tumor antigen-primed dendritic cell membranes and a TGF-β inhibitor to activate cytotoxic T cells and prevent postoperative tumor relapse.

Hybrid lipid nanoparticle



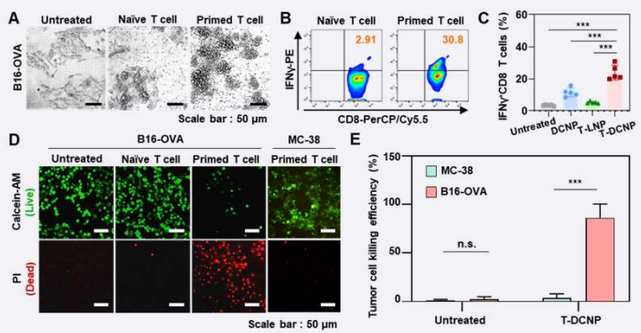
Nanoparticles reflected the characteristics of their parent cells. When DCs were treated with an immune adjuvant and tumor antigens (A), they matured from a naïve to a mature state, as indicated by representative markers (B, C). Co-extrusion of maDCs with T-LNP produced T-DCNPs (D). Similar to DCNPs, T-DCNPs exhibited a homogeneous spherical morphology (E) with an average size of 105 ± 8 nm. The merged nanoparticles retained their original membrane properties, T-DCNPs showed similar membrane protein patterns to those of maDCs (F). The membrane proteins of T-DCNPs include CD40, CD80, CD86, MHCI, and MHCII, which are key receptors for immune responses (G, H).

T cell activation in immune suppressive environment



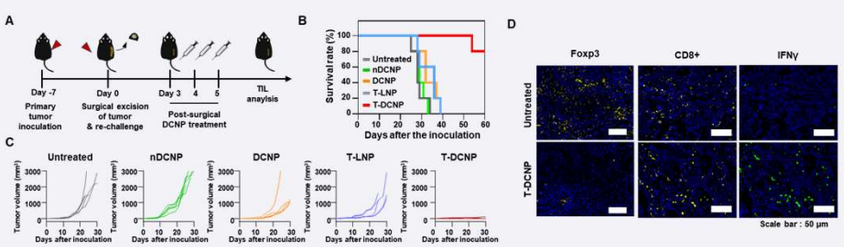
(A) Schematic illustration of the immune modulatory effect of nanoparticles on B16-OVA-immunized T cells cultured in immunosuppressive media. (B) The confocal laser scanning microscopy images display IFNγ expression in T cells following binding with T-DCNP. (C) Representative scatterplots and proportion of granzyme B-positive CD8+ T cells. (D-E) Quantification of pro-inflammatory cytokines in T cell supernatants. IFNγ (D) and TNFα (E) concentrations were measured by ELISA. (***p < 0.001)

T-DCNP promote autologous tumor specific T cell priming



(A) Microscopy images show B16-OVA after co-incubation with B16-OVA-specific T-DCNP-primed T cells for 24 h. (B, C) Flow cytometry analysis presents IFNγ-positive CD8+ T cells. (D) Representative live-cell images show tumor cells and T cells co-cultured for 24 h. Live cells are represented in green, and dead cells are represented in red. (E) Cell-killing efficiency of T-DCNP-primed T cells against B16-OVA or MC-38 tumor cells is demonstrated (n = 5 per group). (n.s.= not significant; ***p < 0.001)

In vivo therapeutic effect in post-surgical model



(A) The therapeutic regimen and sampling schedule for post-operative B16-OVA melanoma tumor models. (B) survival curves (n=5 mice per group). (C) The individual tumor growth curves (D) Foxp3 expression in tumor tissues was visualized. (E) CD8+ T cell infiltration and IFNγ expression were visualized to evaluate T cell activation.

Reference: Hybrid lipid nanoparticles with tumor antigen-primed dendritic cell membranes for post-surgical tumor immunotherapy. J. Control. Release. 2025 Mar 10;379:537–548.