611 EXPLOITING T CELLS AS VEHICLES OF LIPOSOMAL SHP2I TO ENHANCE ADOPTIVE CELL THERAPY

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Background Adoptive T cell therapy (ACT) is often accompanied by supporting immunomodulatory drugs to protect T cells from the suppressive tumor microenvironment (TME) [1]. However, systemic administration of these immunomodulators can cause serious side effects and fail to distribute optimally to exert sufficient lymphocyte stimulation within the tumor and lymphoid compartments. Loading T cells with adjuvant drugs or cytokines prior to cell transfer provides a solution to this issue, showing the potential to use T cells as vehicles to carry immunomodulatory molecules to target sites [2]. SHP2 is an important hub connecting several intracellular oncogenic signaling pathways including PD-1/PD-L1, representing a notable target for cancer immunotherapy. SHP2 inhibition has been shown to elicited tumor regression by improving CD8+ T cells activity [3]. Herein we present a lipid nanoparticle system encapsulating an SHP2 inhibitor (SHP2i) that allows high T cell loading capacity and enhances their therapeutic activity.

Methods Remote-loading gradients were used to achieve high encapsulation efficiency of SHP2i into the lipid nanoparticle platform. Mouse cytotoxic T cells were loaded with SHP2i, and loading efficiency and release rates from the T cells were evaluated in vitro. Flow cytometry was used to assess T cell viability, proliferation, and phenotype. In vivo biodistribution of loaded T cells was evaluated by labeling lipid nanoparticles with gadolinium and T cells with Cell-trace-marker, which were measured with ICP-MS and Flow respectively. The therapeutic anti-tumor efficacy of the loaded T cells was demonstrated on EG.7-OVA tumor-bearing mice.

Results The developed formulation allowed high T cell loading efficiency of SHPi and extended-release over 5 days. Loading T cells with lipid formulated SHP2i did not compromise cell viability and proliferation and resulted in T cells retaining a central memory phenotype than unloaded counterparts. Adoptively transferred T cells loaded with lipid nanoparticles showed the same distribution and proliferation behavior as the unloaded T cells in vivo, accumulating into tumor tissue three days post cell infusion. Loaded OT.I T cells significantly improved tumor growth inhibition and overall survival than OT.I T cells alone, with 5 out of 6 mice completely tumor-free, resulting in durable long-term responders.

Conclusions Loading T cells with liposomal SHP2i before ACT allowed specific and controlled delivery of immunomodulatory drugs by T cells. The loaded T cells showed improved anti-tumor efficacy. The developed lipid formulation allows the loading of a variety of immunomodulatory drugs to T cells, which serve both as a drug delivery vehicle and enhance the tumor efficacy of the transferred cells.

REFERENCES

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Ethics Approval The study has been approved by the Danish Animal Experiments Inspectorate with the permit number 2020-15-0201-00482. The participants gave informed consent before taking part.

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