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 elicit 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. Adaptively 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

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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