Novel lipid-polymer nanocarriers for enhanced γδ T-cell immunotherapy

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INTRODUCTION

Clinical translation of conventional immunotherapy treatments has been underwhelming due to major challenges with immune evasion and suppression by cancer cells. γδ T cells present a promising alternative given their ability to overcome these evasion mechanisms. Unfortunately, commonly used γδ T cell agonists suffer from systemic toxicity and suboptimal cellular uptake. Phosphoantigens offer a viable therapeutic alternative to stimulate populations of γδ T cells more directly hence minimise systemic toxicity; yet in their natural form, suffer from limited cellular uptake and biodistribution[1]. This study compares novel lipid-polymer hybrid nanoparticle (PEI-LNP) and liposomal formulations of these agonists and their ability to induce γδ T cell-mediated lysis against cancer cells *in vitro*.

METHODS

Liposome and PEI-LNP formulations of ZOL and HMBPP were prepared using benchtop microfluidic techniques and optimised for drug loading and cellular uptake. DLS, NTA and FACS were employed to characterise particle size, PDI, surface charge and cellular uptake. Pressure ultrafiltration and HPLC were used to quantify drug encapsulation and *in vitro* release. MTT assays determined cytotoxicity of the drug-free formulations. Co-culture assays assessed the ability of these nanoparticles to induce γδ T cell-mediated cytotoxicity against glioblastoma and breast cancer cell lines.

RESULTS AND DISCUSSION

A library of cationic and neutral liposomes and PEI-LNPs were synthesized and characterised. Their nature and type, size and zeta potential specifically influenced drug encapsulation and release and cellular uptake. Small cationic PEI-LNPs (~95nm and z ~ +13mV) displayed improved cancer cell uptake in comparison to neutral liposomes, reflecting negatively charged cell membranes[2]. PEI-LNP formulations for both HMBPP and ZOL resulted in higher γδ T cell-mediated cytotoxicity against glioblastoma cells than liposomal formulations (Figure 1). The efficacy in stimulating γδ T cell responses at comparable agonist concentrations was dependent on lipid nanocarrier type, agonist type and mechanism of actions.

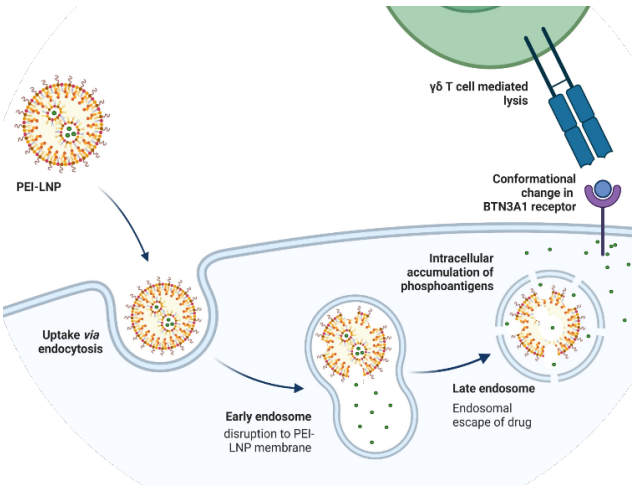

Figure 1. Schematic demonstrating the likely mechanism of action of PEI-LNPs and liposomes. Cationic nanocarriers can interact with negatively charged cancer cell membranes to facilitate the cellular uptake of γδ T cell agonists to induce γδ T cell anti-tumour activity.

CONCLUSION

Due to the potent ability of HMBPP and ZOL to activate γδ T cell-induced cytotoxicity, the optimised development of novel drug delivery systems that improve their cellular uptake is vital for the success of γδ T cell immunotherapies. Given the improved cellular uptake and ability of PEI-LNPs to induce γδ T-cell induced cytotoxicity more potently, these formulations have implications for both *in vivo* and adoptive T-cell based immunotherapies for solid and haematological cancers.

REFERENCES

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