Reducing drug-resistance in ovarian cancer through multiple siRNA encapsulated in lipid nanoparticles.

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Background and Aims: The development of resistance to chemotherapeutics such as doxorubicin is a major hurdle in cancer treatment. There are many mechanisms through which drug resistance can develop, such as upregulation of efflux transporters which reduces the concentration of chemotherapeutics in cancer cells. Pathways underlying the resistance mechanism can be specifically targeted and silenced by small interfering RNA (siRNA), reversing chemoresistance and thereby improving efficacy of the drug. Encapsulating siRNAs in lipid nanoparticles (LNPs) can improve the half-life and protect from degradation, subsequently promoting transfection. Therefore, optimising LNP systems can improve quality of cancer treatment outcomes.
Methods: LNPs encapsulating siRNA were fabricated using the NanoAssemblr and characterised. Effective cell uptake and target gene knockdown was initially optimised using a fluorescent reporter cell line. A mix of siRNAs which target multiple drivers of chemoresistance were packaged using different LNP formulations and delivered to doxorubicin-resistant ovarian cancer cells (A2780ADR). Cell viability was investigated using a MTT assay at a range of doxorubicin concentrations. Additionally, the study explored the inhibition of upregulated pathways through rt-qPCR and apoptosis analyses.
Results: Fabricated LNPs were approximately 55-60 nm in size and effectively reduced mCherry mRNA expression when dosed at 20 nM for 5 hours. A screen for known chemoresistance pathways in ovarian cancer cells identified six highly upregulated genes, which were then selectively targeted with siRNA to provide a synergetic strategy. Pretreatment of these cells with the cocktail of siRNAs encapsulated in LNPs significantly increased doxorubicin-induced cell death compared to cells that were not treated with LNPs.
Conclusions: The research demonstrates a promising approach to overcoming chemoresistance in cancer treatment by using LNPs to deliver siRNAs targeting multiple upregulated drug resistance pathways. This approach could lead to more effective treatment regimens for drug-resistant cancers, ultimately improving patient outcomes. These findings suggest that this cocktail of siRNA and LNP approach holds potential for improving the therapeutic efficacy of chemotherapeutics in chemoresistance.