Lipid nanoparticles encapsulating multiple siRNAs to reverse chemoresistance in breast cancer cells.

Nikita Parekh[1], Clive Prestidge[1], Cameron Bracken[2] and Kristen Bremmell[1]
[1]University of South Australia, UniSA Clinical and Health Sciences, Adelaide, South Australia 5000, Australia
[2] University of South Australia, Center for Cancer Biology, Adelaide, South Australia 5000, Australia
nikita.parekh@mymail.unisa.edu.au

INTRODUCTION

Resistance to pharmacological treatment is common in breast cancer and reduces the efficacy of doxorubicin, a clinically important chemotherapeutic in treatment regimens. Acquired resistance results from the upregulation of genes associated with such processes as drug metabolism and drug transport[1]. These genes can be specifically targeted and silenced by small interfering RNA (siRNA), thus reversing chemoresistance and improving drug efficacy. Furthermore, using combinations of siRNAs to target multiple genes in drug resistance pathways may provide a synergetic effect. Encapsulating the siRNAs in nanoparticles can improve half-life, protect the molecule from degradation and achieve accumulation in cancer cells in tumors through both passive and active targeting.[2]

METHOD

Doxorubicin resistance in the MCF-7 breast cancer cells was induced by treating with increasing concentrations of doxorubicin. The initial concentration applied to the cells was 200 nM (the IC_{50}). Once the cells were able to grow and reached 70-80% confluency, the concentration was increased 1.2-fold until reaching a final concentration of 345 nM. Resistance was confirmed by analysing intracellular accumulation of doxorubicin using fluorescent microscopy. Resistant and drug-sensitive parental cells were screened by RT-qPCR, analysing genes previously reported to play a role in chemoresistance. Based on these results, siRNAs to target upregulated genes with reported roles in drug resistance were encapsulated into lipid nanoparticles (LNPs). LNPs were fabricated using a microfluidic device and their physicochemical properties and biological uptake characterised. mRNA and protein expression of the targeted genes were investigated via RT-qPCR and western blot, before and after siRNA-LNP treatment.

RESULTS AND DISCUSSION

Doxorubicin resistant MCF-7 cells exhibited decreased intracellular doxorubicin as determined by fluorescent microscopy and increased IC_{50} compared to sensitive MCF-7 cells. LNPs encapsulating siRNA targeted to efflux transporters, including ABCB1, decreased their respective protein and mRNA expression in doxorubicin resistant MCF-7 cells.

CONCLUSION

Lipid nanoparticles can facilitate the delivery of siRNAs to decrease expression of key chemo resistant vectors in breast cancer resistant cells.

REFERENCES

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