Tailoring Nanomedicines aiming at anticancer molecular therapy

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Abstract

The identification of activated oncogenes, as fundamental genetic differences relative to normal cells, has made possible to consider such genes as targets for antitumor therapy. *PLK-1* is a serine/threonine kinase that regulates mitosis entry and progression. It is undetectable in normal tissues but is overexpressed in tumors contributing for the capability of cancer cells to proliferate in an uncontrolled manner. Therefore, effective downregulation of Plk-1 at the tumor level can have a positive impact in the treatment of cancer. Gene downregulation can be efficiently achieved by small-interfering RNAs (siRNAs). However, the clinical use of these molecules has been impaired by their unfavourable pharmacokinetics profile and low intracellular accumulation (1).

A tumor is like an organ encompassing multiple cell types each one contributing to the overall tumor aggressiveness. In this respect, endothelial cells assume a key role in the progression of solid tumors and metastasis formation. Therefore, new therapeutic approaches that preferentially target angiogenesis, in addition to cancer cells, could be tremendously advantageous for the treatment of solid tumors as it compromises the access to oxygen and nutrients impairing tumor survival and proliferation.
The main goal of this work was to design a novel ligand-mediated targeted lipid-based nanocarrier containing an anti-*PLK1* siRNA, aiming at targeting, simultaneously, human cancer cells and endothelial cells from angiogenic vessels.

Conclusions

A novel ligand-mediated targeted lipid-based nanocarrier, containing an anti-PLK1 siRNA, aiming at targeting simultaneously, cancer cells and endothelial cells from the angiogenic blood vessels was developed. This novel ligand-targeted sterically stabilized lipid-based nanoparticle is characterized by high siRNA encapsulation efficiency, efficient protection of siRNA, average size lower than 200 nm, and charge close to neutrality. Overall, these are nanoparticles that present adequate features for systemic administration.
Our results have shown that the covalent attachment of a specific ligand at the extremity of poly(ethylene glycol) chains, brings a major advantage as it significantly improves the internalization of the lipid-based nanoparticle by both human breast cancer cells (MDA-MB-435 and MDA-MB-231), human prostate cancer cells (PC3) and endothelial cells from angiogenic blood vessels (HMEC-1). Moreover, it was not observed a significant internalization by the non-transformed cell line, BJ fibroblasts, indicating the cellular specificity of the developed targeted nanoparticle.
Treatment of PC3 cells with non-targeted liposomes did not have significant effects on cell viability. In contrast, targeted liposomes encapsulating an anti-*PLK1* siRNA resulted in a significant decrease on the cell viability of PC3 indicating that the strategy presented herein may have a truthfully potential in the treatment of solid tumors. Moreover, this decreased on cell viability was a consequence of *PLK1* downregulation as it was observed both at the protein and mRNA levels.

References

[1] Gomes-da-Silva, L. C., Fonseca, N. A., Moura, V., Pedroso de Lima, M. C., Simoes, S., and Moreira, J. N., Acc Chem Res **45** (2012) 1163-1171.

Figures

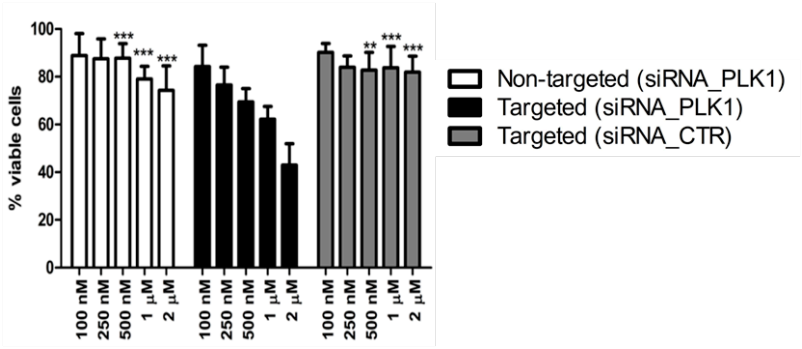

Fig. 1: Impact on the viability of human prostate cancer cells (PC3 cells) after treatment with liposomes containing an anti-*PLK1* siRNA. Cell viability was accessed by the Resazurin reduction assay. ***p<0.001 and **p<0.01.

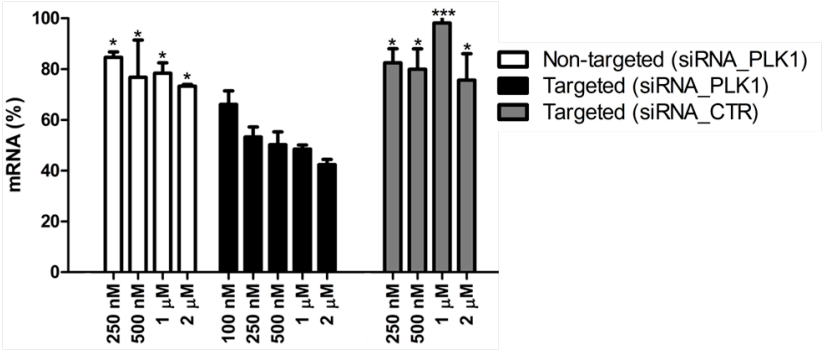

Fig. 2: Quantification of *PLK1* mRNA on PC3 cells after treatment with liposomes containing an anti-*PLK1* siRNA. ***p<0.001 and *p<0.05.