BMC Proceedings

ORAL PRESENTATION Open Access

Targeting non-viral vectors to tumor cells and the tumor microenvironment

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From 16th International Charles Heidelberger Symposium on Cancer Research
Coimbra, Portugal. 26–28 September 2010

Targeted therapy towards tumor cells has been regarded as a promising strategy, since it offers the possibility of directing and concentrating the therapeutic agent only at the desired target site, increasing therapeutic efficacy through increased tumor cell death and decreased incidence of side effects in healthy tissues. Nonetheless, choosing only one cellular target within the tumor microenvironment is an approach with low probabilities to succeed. In this respect, we aim at designing a non-viral vector that targets, simultaneously, tumor cells and endothelial cells from tumor blood vessels. It is hypothesized that such nanoparticle, with this dual targeting ability, will present an active tumor accumulation. Specific intracellular release of the encapsulated payload will strongly contribute to improve the therapeutic outcome.

Our results show a substantial increase in the levels of association for ligand-targeted nanoparticles, on a ligand- and cell-specific manner, both *in vitro* and *ex vivo* (in breast tumor cells removed from patients, after mastectomy or tumorectomy). Cytotoxicity studies show that targeted nanoparticles containing doxorubicin are more cytotoxic than the non-targeted formulation (4 to 180-fold), against tumor and endothelial cells, indicating that internalization of the former is contributing to a more efficient delivery of the payload to the target cells. Experiments with tumor-bearing mice report a higher tumor accumulation of the radiolabeled targeted nanoparticle over the non-targeted counterpart. Overall, these results represent a novel and a valuable contribution for delivery strategies targeting tumor cells and the tumor microenvironment.

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Published: 24 September 2010

doi:
Cite this article as: Moura *et al.*: Targeting non-viral vectors to tumor cells and the tumor microenvironment. *BMC Proceedings* 2010 **4**(Suppl 2): O26.