Combination of peptides-targeted liposomal chemotherapy against neuroblastoma

Experimental and Molecular Therapeutics

Abstract #3677: **Combination of peptides-targeted liposomal chemotherapy against neuroblastoma**

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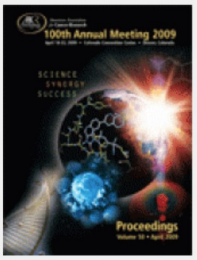
Abstract

Disseminated neuroblastoma (NB) is refractory to most current therapeutic regimens. Previously, we showed that the therapeutic index of anticancer drugs is increased by liposome encapsulation and further improvements have been obtained by coupling tumor-specific ligands to the surface of the lipidic envelop. Phage display technology was used as a powerful tool in discovering novel ligands specific to receptors on the surface of tumor epithelial and endothelial cells. The targeting of therapeutics to tumor blood vessels, using probes that bind to specific molecular addresses in the vasculature, combines blood vessel destruction with the expected anti-tumor activities of the drug, resulting in



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increased efficacy and reduced toxicity. Recently, we demonstrated that doxorubicin (DXR)-entrapped liposomes, targeting the endothelial tumor cell marker, aminopeptidase N (APN), displayed enhanced anti-tumor effects and prolonged survival in NB-bearing mice. In this work, *in vivo* selection of phage display libraries was used to isolate peptides binding specifically to the tumor blood vessel address aminopeptidase A (APA), expressed on perivascular tumor cells. APA-targeted, liposomal DXR, displayed *in vitro* specific binding to APA-transfected cells. After having demonstrated by immunohistochemical (IHC) analyses the APA positiveness of cells within the vascular wall of orthotopically implanted NB tumors in mice, the novel APA-targeted formulation was validated for its anti-tumor effect in clinically relevant animal models of human NB. In this model of NB, preliminary results indicate that APA-targeted liposomal DXR formulations led to an increase in life span compared to control mice, but less than that obtained by using APN-targeted formulation. These results were confirmed by IHC analyses performed in paraffin-embedded tumors derived from mice after 3 and 5 weeks of treatment, which revealed the highest increase of tunel-positive tumor cells in mice treated with the formulation directed to APN. However, combined experiments using APN- and APA-targeted liposomes administered in a sequential manner following the same time schedule at half the dose of DXR for each formulation, led to a significant increase in life span compared to each treatment administered separately. Tunel assay demonstrated statistically significant increased level of apoptosis in tumor of mice treated with the combination therapy and a pronounced destruction of the tumor vasculature with an almost total ablation of endothelial cells and pericytes. In conclusion the availability of novel ligands binding to additional tumor-associated antigens and to targets on both endothelial and perivascular tumor cells will allow to design more

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sophisticated liposomal targeted anticancer strategies that exhibit higher levels of selective toxicity for the cancer cells in a combined setting.

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Footnotes

- 100th AACR Annual Meeting-- Apr 18-22, 2009; Denver, CO

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