Phage display technology for novel tumor- and vascular-targeted therapies against neuroblastoma

Cancer Research

Experimental and Molecular Therapeutics

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Abstract

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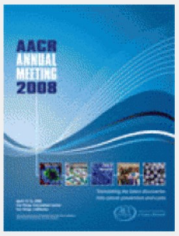
Disseminated neuroblastoma (NB), the most common extra-cranial solid tumor in children, is refractory to most current therapeutic regimens and hence the prognosis remains very poor. Conventional anticancer therapy with chemotherapeutic drugs has been a mainstay for several decades, but the poor selectivity of these agents causes severe dose-limiting side-effects and limits their clinical utility. We recently showed that the therapeutic index of anticancer drugs is increased by liposome encapsulation and further improvements of the intrinsic tumor selectivity of liposomes has been obtained by coupling tumor-specific antibodies and/or peptides to the surface of the lipidic envelop. In this direction, phage display technology, used as a powerful tool in the discovery of ligands specific to receptor on the surface of tumor and tumor endothelial cells, could impact clinical issues including functional diagnosis and cell-specific drug delivery. Moreover, the targeting of



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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 increased efficacy and reduced toxicity. Tumor associated endothelial and perivascular cells either over-express angiogenic markers or express unique epitopes. Targeting cytotoxic antibodies or drugs to these molecular markers leads to destruction of the tumor vasculature and, indirectly, to tumor cell death. Recently, i*n vivo* selection of phage display libraries was used to isolate peptides binding specifically to the tumor blood vessel addresses aminopeptidase N (APN) and A (APA). APN-targeted, doxorubicin (DXR)-entrapped, liposomes displayed enhanced anti-tumor effects and prolonged survival in NB-bearing mice. APA-targeted, liposomal DXR, alone and in combination with the APN-targeted formulation, are under investigation for their effectiveness on inducing tumor regression in clinically relevant animal models of human NB. In the meanwhile, we set up a protocol for the isolation of heterogeneous cell populations by tissue fractionation of primary tumor and metastases from orthotopic NB-bearing mice. We screened these tissues with phage-displayed peptide libraries, obtaining more than 60 single peptides binding to both tumor and tumor parenchyma cells, 10 of which are further validating. The availability of novel ligands binding to additional tumor-associated antigens, and to additional targets on both endothelial and perivascular tumor cells will allow to design more sophisticated liposomal targeted anticancer strategies that exhibit high levels of selective toxicity for the cancer cells. This would improve therapeutic outcome, decrease dose-limiting side-effects and improve patient quality of life.

Footnotes

- 99th AACR Annual Meeting-- Apr 12-16, 2008; San Diego, CA

  American Association for Cancer Research

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