Abstract 3625: Novel phage-display derived peptides for tumor- and vasculature-targeted therapies in neuroblastoma

Cancer Research

Experimental and Molecular Therapeutics

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DOI: 10.1158/1538-7445.AM2011-3625 Published April 2011

Proceedings: AACR 102nd Annual Meeting 2011-- Apr 2-6, 2011; Orlando, FL

Abstract

Disseminated neuroblastoma (NB) is refractory to most current therapeutic regimens. The therapeutic index of anticancer drugs is increased by liposome encapsulation and further improvements is obtained by coupling tumor-targeting ligands to the surface of the lipidic envelop. Phage display technology is a powerful tool in discovering novel ligands specific to receptors on the surface of tumor epithelial and endothelial cells. Therapeutic targeting to tumor blood vessels combines blood vessel destruction with the expected anti-tumor

activities of the drug, resulting in increased efficacy and reduced toxicity.

To find NB-specific targeting moieties, we established a protocol for the isolation of heterogeneous cell populations by tissue fractionation of primary tumors and metastases from two models of human NB (with tumor cells injected either intravenously, to mimic minimal residual disease, or orthotopically in the adrenal gland of mice, to reflect the growth of advanced NB in children with large adrenal gland tumors and small metastatic lesions) and from stage IV, stroma poor, NB-derived specimens immediately after surgical removal. Cells extracted from corresponding healthy organs from mice and patients were used both in a negative pre-selection step and as a negative control for specific phage enrichment. The NB cell suspensions were subjected to multi-step screenings with the phage-displayed peptide library CX7C (where C = cysteine and X = any aminoacid). We globally isolated 135 NB-binding peptides. Of these, 31 were selected for binding to the primary tumor mass, 16 to the metastatic mass, 63 to tumor endothelial cells, and 25 to endothelial cells of metastases. Several proteins presenting sequence homology with the discovered peptides have been identified by BLAST analysis and were evaluated for their expression in NB tumors, derived from both mouse xenogratfs and patient specimens. Specifically, 5 novel phage display derived-peptides showed specific binding on NB specimens and homing to tumor cells and tumor vasculature, 10 minutes and 24 hours after injection through the tail vein of NB-bearing mice. We are testing the new molecular, tumor- and vasculature-specific peptides for generating novel tumor-specific liposomal therapies against NB. 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 sophisticated liposomal targeted anticancer strategies that exhibit high levels of

selective toxicity for the cancer cells.

Citation Format: {Authors}. {Abstract title} [abstract]. In: Proceedings of the 102nd Annual Meeting of the American Association for Cancer Research; 2011 Apr 2-6; Orlando, FL. Philadelphia (PA): AACR; Cancer Res 2011;71(8 Suppl):Abstract nr 3625. doi:10.1158/1538-7445.AM2011-3625

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Cancer Research Online ISSN: 1538-7445
Cancer Research Print ISSN: 0008-5472
Journal of Cancer Research ISSN: 0099-7013
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