



How to Overcome Biologic Barriers for the Therapy of Neuroblastoma: The Tumor Vascular Targeted Approach

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Abstract

Neuroblastoma is a rare pediatric cancer characterized by a wide clinical behavior and adverse outcome despite aggressive therapies. New approaches with targeted therapies may improve efficacy and decrease toxicity. Nanotechnology offers potential developments in pharmaceutical, medical imaging and diagnosis and cancer treatment. We demonstrated that novel doxorubicin loaded nano carriers functionalized with neuroblastoma-selective peptides increases tumor vascular permeability and perfusion, enhances tumor penetration, leading to a delay of orthotopic tumor growth, and abrogates metastatic spreading through decreased tumor glucose consumption, accompanied by absence of systemic toxicity. Our findings are functional to the design of targeted nanocarriers with potentiated therapeutic efficacy towards the clinical translation and they open the way for developing.

Introduction

Neuroblastoma (NB) is the most common and deadly solid tumor in children arising from the sympathetic nervous system and accounting for 8-10% of all childhood cancer and 15% of deaths from pediatric tumor [1]. The majority of patients have metastatic disease, and most of them progress despite intensive multimodal treatments. Moreover, most anticancer agents are being used at maximally tolerated doses, leading to short- and long-term toxicity in many patients [2]. Recent advances in understanding the molecular pathogenesis of NB have provided considerable insights into the genetic and biochemical mechanisms underlying NB clinical behaviors. These, in turn, allowed to identify genes, proteins and pathways that might represent effective targets for biologically based therapy [3]. Antigens exclusively expressed on the surface of tumor cells provide an excellent opportunity for targeting. However, considering the variety of cell types and of signaling pathways involved in the crosstalk between the tumor and its microenvironment, it is reasonable to expect that a multi-target approach would lead to a substantially increased therapeutic efficacy. Thus, searching for novel targetable receptors is critical for developing innovative therapeutic strategies also in a feasible combinatory point of view.

Screening phage display peptide libraries on intact cells or tissues allows the identification of novel specific peptide ligands to be exploited for systemic targeting throughout the circulation, by interacting with proteins expressed within tumor-associated vessels and homing to neoplastic tissues [4,5].

Nanotechnology offers potential developments in pharmaceutical, medical imaging and diagnosis and cancer treatment. In clinical applications, drug-loaded nanocarriers, like liposomes, have been proven to be mostly useful for their ability to passively accumulate at sites of increased vasculature permeability and for their ability to reduce the side effects from the encapsulated drugs relative to free drugs. This has resulted in an overall increase in therapeutic index (efficacy over toxicity); however, due to a poor liposomal extravasation into solid tumor, the gain in therapeutic index have been more on the side of reduced toxicity than on the side of increased efficacy [6].

At present, efforts have been focusing on further increasing delivery and penetration of liposomal-carried drugs into NB tumors. While the enhanced permeability and retention effect has indeed served as a key rationale for using nanoparticles to treat solid tumors, it does not enable uniform delivery of these particles to all regions of tumors as a result of physiological barriers presented by the abnormal tumor vasculature and interstitial matrix [7,8].

Goals of the work

We hypothesize that a therapeutic strategy based on the use of more penetrating, targeted-

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liposomes, might help drug-loaded nanoparticles to penetrate faster and deeper inside the tumor, thus increasing the therapeutic effects.

Experimental

Some peptides, isolated by using phage display technology, have been used to selectively target neoplastic cells, the microenvironment of primary and metastatic NB tumors and their vasculature [9-11]. We have then validated few peptide sequences as specific ligands for the vasculature of aggressive NB [12,13]. We developed liposomal formulations of doxorubicin, targeted to NB through various peptides to demonstrate increased targeting and penetration of the drug into diseased tissues [14,15]. We tested attenuation of drug-related side effects, paralleled by a possible delay in tumor growth and by abrogation of the metastatic spreading [14,15].

Results and Discussion

In this work, we show that novel doxorubicin- loaded nanocarriers functionalized with neuroblastoma-selective peptides increase tumor vascular permeability and perfusion, enhance tumor penetration, leading to a delay of orthotopic tumor growth, and abrogate metastatic spreading through a decreased tumor glucose consumption, accompanied by absence of systemic toxicity [12-15]. Our findings open the way for developing simultaneous or sequential multi-target approaches for the treatment of NB. The use of peptides (and antibodies) against different receptors expressed on the tumor microenvironment (i.e. the endothelial cell marker Aminopeptidase N [9,11,16, 17], the perivascular cell marker Aminopeptidase A [10], the neuronal pentraxin-2 pathway [18], and on the tumor cells themselves (i.e. GD2 [19]), may promote, in principle, combined and/or synergistic targeting effects [10,12,20], and therefore, might improve the therapeutic response to anticancer drugs [21-23].

Conclusion

Given the clinical experience with targeted agents and the development of drug resistance, it is unlikely that targeting a single cell population (as well as a single molecular target) will lead to durable responses, thus multi-modality therapeutic approaches are needed to overcome biologic barriers for the therapy of cancer.

Our findings are functional to the design of targeted nano carriers with potentiated therapeutic efficacy towards the clinical translation.

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