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Advances and Challenges in Tumor- and Stroma-Targeted Theranostic Nanoparticles for Treating Therapy-Resistant Cancer

Lily Yang*

Department of Surgery, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA 30322

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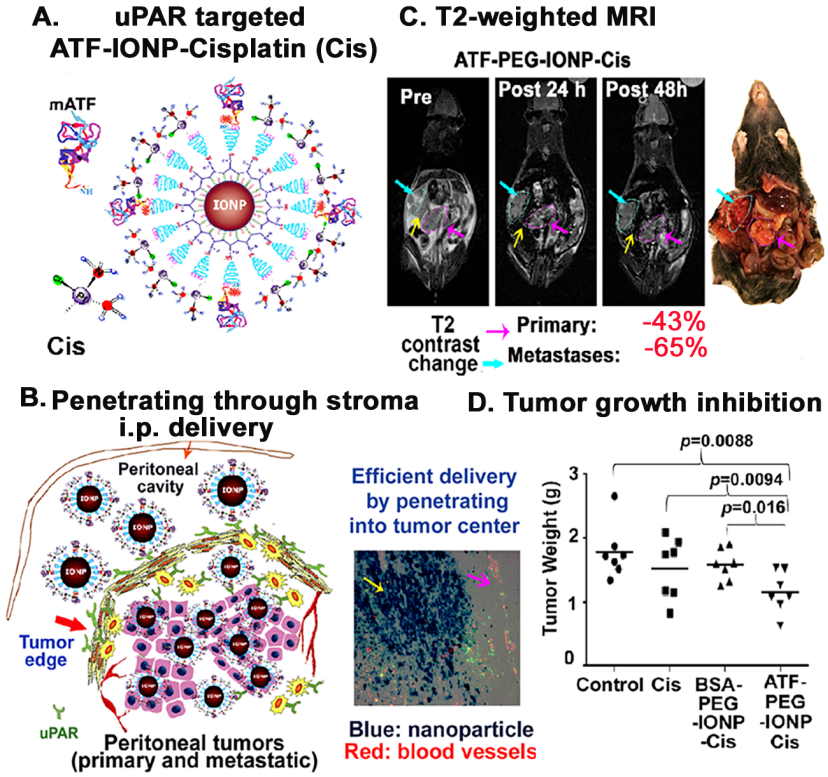
Graphical Abstract



Abstract

Emerging nanomedicine strategies, particularly theranostic nanoparticles integrating imaging and therapeutic capabilities, have been developed to overcome stromal barriers, improve drug penetration, and enable real-time monitoring of treatment response. Here, we summarize several approaches developed in our group on the production and evaluation of tumor and stroma co-targeted theranostic nanoparticles. We will discuss rationales for target/ligand selection and highlight examples of preclinical studies and the potential applications for precision oncology to improve the outcome of treatment of therapy-resistant human cancers.

Keywords: Theranostic nanoparticles, tumor and stroma targeting, Image-guided therapy, targeted drug delivery

Introduction

The tumor microenvironment plays a decisive role in cancer progression and therapeutic resistance. Malignant transformation of epithelial cells causes a complex interplay with surrounding stromal components, resulting in infiltration of immune cells and proliferation of

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tumor-associated fibroblasts and macrophages, as well as the extracellular matrix(ECM) [1, 2]. While stromal responses initially restrain tumor growth by limiting invasion and promoting immune clearance, tumor cells with genetic mutations and dysregulated signal pathways produce growth factors, cytokines, and extracellular vesicles that hijack stromal cells and evade immune response[3-6]. Increasing evidence supports the notion that the tumor stroma contributes significantly to aggressive tumor biology and resistance to therapy[1, 3]. The presence of extensive stroma creates a physical barrier that traps tumor-imaging and therapeutic agents within the stroma, reducing the accuracy of biomarker-specific imaging probes and decreasing drug delivery into tumor cells[7]. As stromal cells transform their biological properties within the tumor microenvironment, they secrete growth factors and cytokines to enhance tumor cell proliferation and invasion, and angiogenesis [8]. Tumor-associated fibroblasts, macrophages, and tumor cells produce extracellular matrix and upregulate matrix metalloproteinases (MMPs) that lead to remodeling of the tumor stroma to facilitate tumor cell invasion and metastatic spread [6, 9]. The tumor stroma also modulates the immune response by recruiting regulatory T cells and myeloid-derived suppressor cells, as well as tumor-promoting M_2 macrophages, leading to an immunosuppressive tumor stroma microenvironment [6, 10-12]. Those tumor-promoting effects form a biological barrier in cancer treatment.

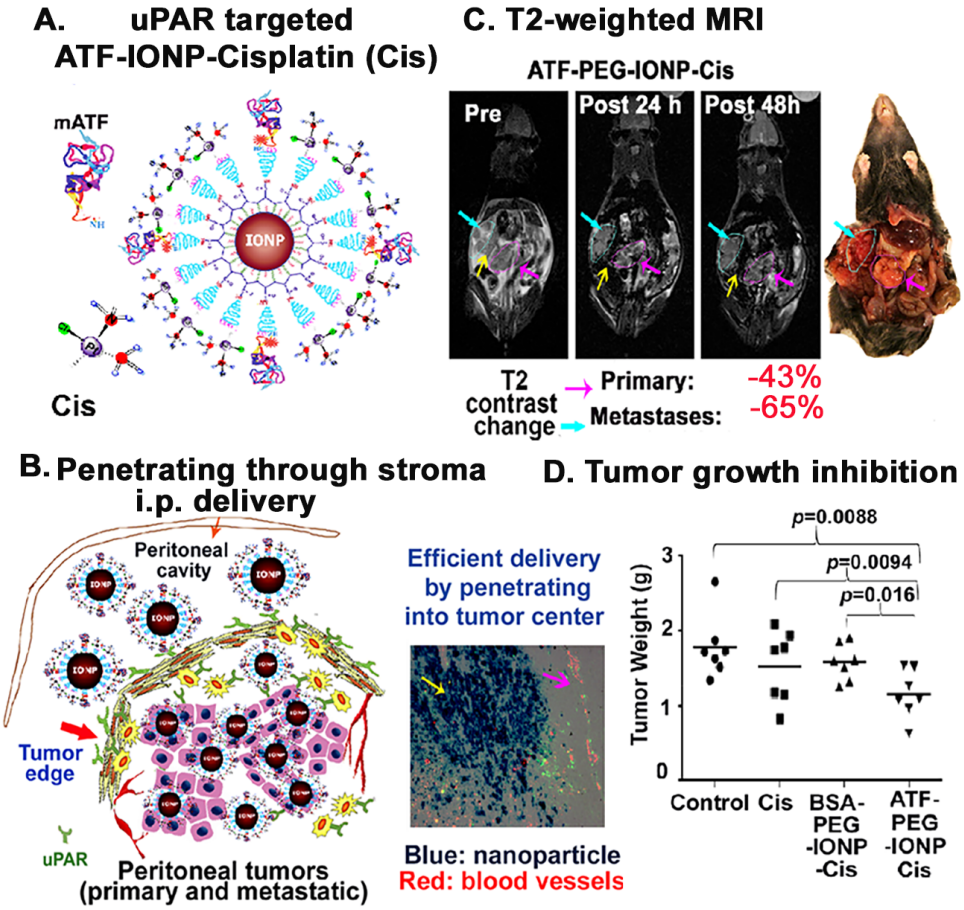

Figure 1: Tumor penetrating theranostic nanoparticles for enhancement of targeted and image-guided drug delivery into peritoneal pancreatic tumors following intraperitoneal delivery
A&B. Intraperitoneal (i.p.) delivery of uPAR-targeted theranostic nanoparticles carrying cisplatin (Cis) mediates enhanced drug delivery into primary and metastatic peritoneal tumors (Prussia blue staining positive tumors, yellow arrow) by penetrating through the dense stroma of the tumor edge, not through tumor vessels (pink arrow). C. MRI detected targeted delivery of ATF-PEG-IONP-Cis into a large primary and small peritoneal metastatic lesions in a mouse pancreatic tumor model after i.v. delivery. D.I.P. administrations of ATF-PEG-IONP-Cis significantly reduce tumor burden in the peritoneal cavity.

The dual nature of the stroma, both protective and tumor-promoting, makes it a critical barrier and therapeutic target [12-14]. Stroma-directed therapeutic approaches have been pursued in preclinical studies and clinical trials. Pegylated hyaluronidase aimed to degrade hyaluronic acids in the ECM, decompress blood vessels, and improve drug penetration [15-19]. Sonic pathway inhibitors sought to deplete stromal fibroblasts and reduce desmoplasia [20-23].

Both approaches showed improved chemotherapy drug delivery and slowed tumor growth in pancreatic cancer mouse models. However, for both therapies, clinical trials failed to demonstrate an overall survival benefit[22, 24-26]. Further studies in mouse tumor models revealed that stromal depletion accelerated disease progression by unleashing more aggressive tumor behavior and increasing tumor invasion[27, 28]. These findings underscore the complexity of stromal biology and suggest that a significant reduction of stroma, without effective elimination of tumor cells, may be counterproductive. Instead, strategies that modulate stromal properties without fully abrogating protective elements and improve drug delivery into tumor cells to induce tumor cell death are needed. The development of such a therapeutic approach requires novel multifunctionalities in a single cancer therapy agent, including 1) innovative designs to significantly improve drug delivery not only into tumors but also with the ability to pass through the tumor stroma to reach tumor cells; and 2) to be efficiently internalized into tumor cells with a high drug concentration and potence to induce cell death in resistant tumor cells.

Discussion

Development of urokinase plasminogen activator receptor (uPAR) targeted Theranostic Nanoparticles

Targeted theranostic nanoparticles with the capability of selective drug delivery, tumor imaging, and high drug loading have the potential to enhance the therapeutic effect and to apply image-guided, personalized cancer treatment [29-31]. Selection of cell-surface targets is critical to increasing the efficiency of targeted delivery. Most cell surface targets used for targeting tumors are upregulated in tumor cells, but a low level of expression is also present in normal tissues. Targeting a biomarker only expressed in tumor cells lacks the ability to increase the extravasation of imaging and therapeutic agents into the tumor interstitial areas[29]. A low level of the delivered imaging probes or drug carriers is likely retained in the perivascular stroma and is unable to reach their tumor cell targets. Therefore, cell receptors that are highly expressed in tumor endothelial cells, stromal fibroblasts, macrophages, and tumor cells are excellent targets for the development of targeted theranostic nanoparticles. uPAR is upregulated in many types of human cancer tissues, and its expression level is associated with a poor prognosis[32, 33]. A high level of uPAR is found in tumor vessels, stromal cells, and cancer cells, which offer multi-cell-type targeted drug delivery to improve intratumoral delivery and distribution of imaging and therapeutic agents [30, 34]. An advantage of uPAR-targeted drug delivery is that the ligand-receptor binding induces efficient internalization of ligand-nanodrug/uPAR complexes mediated by interactions with the low-density lipoprotein receptor-related protein (LRP), initiating internalization via clathrin-mediated endocytosis[35]. Following the release of ligand-nanoparticle/drugs into the endosomes/lysosomes, uPAR is recycled to the cell surface to take up more ligand/drugs. uPAR targeted magnetic iron oxide nanoparticles (IONPs) or theranostic IONPs using the amino terminal fragments (ATFs) of human or mouse uPA have been developed. The results showed that uPAR-targeted delivery of IONPs led to selective accumulation of near-infrared dye-labeled ATF-IONP or ATF-IONP carrying chemotherapy drugs, gemcitabine, doxorubicin, or cisplatin, in orthotopic pancreatic cancer xenograft or mouse tumor models [30, 36] (Figure 1). Targeted delivery was detected by dual optical and MR imaging modalities with a high sensitivity and specificity, with 1 mm diameter tumors detectable in the pancreas of mice using T_2-weighted MRI and a clinical 3-T MRI scanner[34]. MRI monitoring therapeutic response and the residual tumors following the treatment with uPAR targeted theranostic IONPs was also demonstrated in a mouse pancreatic cancer model [30, 36].

Elimination of therapy-resistant cancer stem cells by combination targeting of uPAR and Wnt receptor for drug delivery

Resistance to therapy is the major clinical issue in the treatment of cancer patients. There is

a close association between the presence of cancer-stem-like cells and drug resistance. The Wnt ligand/receptor signaling pathway is a crucial cell communication cascade that regulates fundamental processes like cell proliferation, differentiation, and migration of cancer stem cells. A short peptide derived from Wnt inhibitory DKK-1 protein (iWnt) was conjugated to IONPs encapsulated with DOX[37]. Systemic delivery of iWnt-IONP/DOX led to targeted delivery into doxorubicin-resistant breast cancer patient-derived xenograft (PDX) tumors. However, Wnt receptor-targeted delivery alone did not yield a significant effect on tumor growth in this resistant model. Tumor growth inhibition was observed only when treated with the IONP/DOX co-conjugated with ATF and iWnt peptides [37]. Thus, co-targeting uPAR and Wnt receptor (LRP5/6) is necessary to induce internalization of ATF/iWnt-IONP/DOX, leading to the induction of cell death in resistant tumor cells (Figure 2).

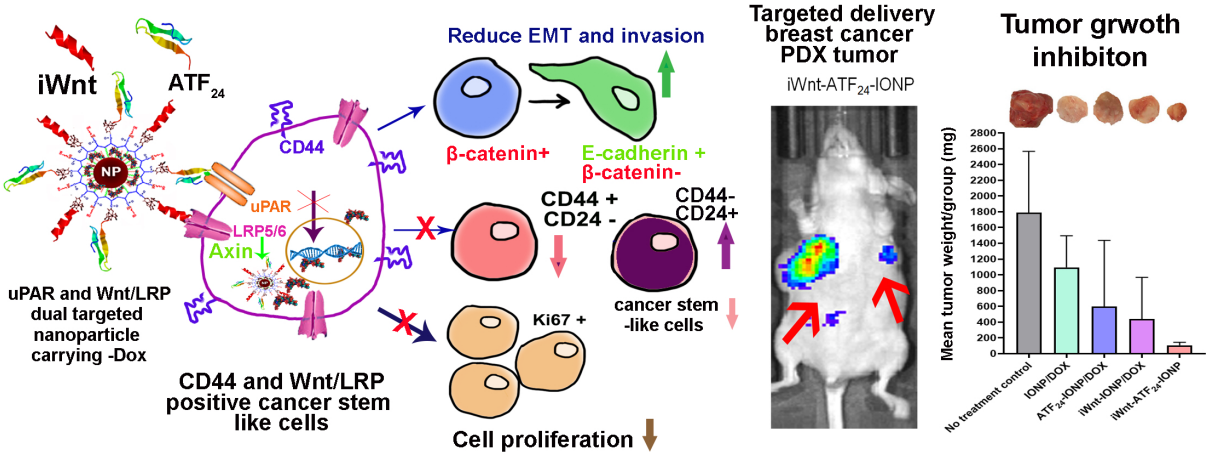

Figure 2 Therapeutic effect of systemic delivery of uPAR and Wnt dual-targeted IONP-carrying Dox on tumor growth in a human breast cancer PDX model
iWnt, a Wnt receptor targeted peptide derived from DKK1, and ATF24, engineered from the uPAR binding domain of human uPA, were conjugated to magnetic iron oxide nanoparticles (IONPs). Dual receptor targeting leads to efficient internalization of IONP/DOX into cancer cells, especially CD44-expressing cancer stem cells, leading to the inhibition of cell proliferation and invasion. Optical imaging of near-infrared dye-labeled targeted-IONPs detected a high level of imaging signal following intravenous delivery into a nude mouse bearing an orthotopic breast cancer PDX tumor (arrows). Systemic administration of the dual-targeted iWnt/ATF-IONP/DOX significantly inhibited tumor growth in the breast cancer PDX model derived from a DOX-resistant breast cancer tissue.

Targeted drug delivery mediated by IGF-1R for the treatment of pancreatic cancer

It has been shown that drug-resistant tumors upregulate IGF-1 receptor (IGF-1R) levels in tumor cells, stromal fibroblasts, and macrophages [38]. The IGF-1R-targeted drug delivery system has the potential to improve drug delivery into resistant tumor cells, given the very high levels of IGF-1R in these cells. Recombinant human IGF-1 was conjugated to IONP/DOX for targeted drug delivery into pancreatic cancer[38]. The binding of IGF-1-conjugated nanoparticle/drug did not activate the IGF-1 signal. In contrast, endocytosis of the IGF-1-IONP/DOX-bound IGF-1R resulted in down-regulation of the IGF-1R signal. The results showed that IGF-1-IONP/DOX was efficiently delivered into orthotopic pancreatic PDX tumors in nude mice and significantly inhibited tumor growth. MRI was able to monitor nanoparticle/drug delivery in PDX tumors [38]. Histological analysis revealed that IGF1-IONP/DOX targeting the tumor and stroma resulted in efficient delivery of the nanoparticle/drug into tumor cells to induce cell death, while non-targeted IONP/DOX accumulated in the stromal area and had a low level of apoptotic tumor cells.

HER2-directed multimodule theranostic nanoparticles for targeted therapy of heterogeneous tumors

Tumor heterogeneity remains a major challenge for targeted therapy. HER2 is a well-established biomarker in breast and ovarian cancers, but many HER2+ tumors harbor subpopulations with low expression, contributing to resistance[39]. For example, pathological diagnosis of a HER2+ tumor is the detection of strong membrane staining in over 10% of cells by immunohistochemistry or HER2 gene amplification by *in situ* hybridization[40]. Theranostic IONPs with multi-imaging modalities offer promising precision oncology strategies to apply targeted therapy for heterogeneous and therapy-resistant human tumors. The development of HER2-targeted theranostic nanoparticles with near-infrared (NIR) optical and MR imaging capabilities allows targeted drug delivery into HER2+ tumor cells and MR imaging of the level and location of nanoparticle/drug delivery in tumors and therapeutic response[41]. Since NIR dye-labeled theranostic IONPs are retained in resistant tumor cells and stroma for several weeks after the treatment, intraoperative optical imaging can be used to detect and remove residual tumor lesions. In an orthotopic human ovarian cancer xenograft model, systemic delivery of HER2-affibody-conjugated IONPs carrying cisplatin inhibited the growth of primary tumors and peritoneal and lung metastatic lesions [41]. Residual resistant tumors were detectable by T_2-weighted MRI. Furthermore, small residual tumors had strong optical signals that could be identified by Spectroscopic and NIR fluorescence imaging, indicating the feasibility of removing those drug-resistant tumors by intraoperative optical imaging[41]. Therefore, targeted delivery of theranostic IONPs in combination with MRI monitoring, drug delivery, and therapeutic responses, followed by intraoperative optical imaging, has the potential to improve therapeutic response and reduce tumor recurrence.

Conclusion and future directions

Collectively, these studies highlight that targeting receptors shared between the stromal and tumor compartments is a promising approach to improve drug delivery in stroma-rich tumors. Multifunctional theranostic nanoparticles with multimodal imaging capability not only improve intratumoral drug distribution but also enable real-time monitoring of delivery, therapeutic response, and residual disease. Looking forward, rational integration of stromal-modulating strategies with tumor/stroma-targeted nanoplatforms offers a compelling avenue to overcome therapy resistance and improve clinical outcomes in stroma-rich cancers. Rather than eliminating stroma, future therapies should focus on modulating stromal density and structure to allow nanoparticle/drug penetration while preserving protective functions. Examples include temporary softening of extracellular matrix fibers or modulating the density and structure of tumor-associated fibroblasts. With continued refinement, multifunctional theranostic nanoparticles hold strong potential to overcome stromal barriers and deliver precision oncology solutions for therapy-resistant cancers.

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