Theranostic Imaging in Cancer

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• Located at the interface of diagnosis and therapy, theranostic imaging is a rapidly expanding aspect of molecular imaging that is creating exciting new possibilities for personalized precision medicine in cancer.
• A critical need in cancer treatment is to minimize damage to normal tissue. Molecular imaging can be applied to identify targets specific to cancer with imaging, design agents against targets and visualize their delivery, monitor response to treatment, and minimize collateral damage to normal tissue.
• Because of the complex characteristics of cancer, genomic and proteomic profiling can provide an extensive 'fingerprint' of each tumor.
• With this cancer fingerprint, theranostic agents can be designed to personalize treatment for precision medicine of cancer, and minimize damage to normal tissue.
• The purpose of this talk is to provide insights into the capabilities and applications of this exciting new field in cancer treatment.
• The effective implementation of theranostic agents may achieve cancer cures, a goal that remains elusive for many cancers despite the technological advances available in the 21st century.

The field of theranostic imaging can be broadly categorized based on different imaging modalities and the different aspects of cancer being targeted. Since theranostic imaging requires the delivery of therapeutic cargo to cancer-specific targets that can be noninvasively imaged, receptors and antigens expressed specifically by cancer cells provide the most direct targets. As an example, 20-30% of breast cancers express the human epidermal growth factor receptor (Her-2). Trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of Her-2 has provided a breakthrough in the treatment of Her-2 positive metastatic breast cancer [1]. Patients with Her-2/neu overexpressing cancers respond well to antibody targeting of Her-2/neu with Trastuzumab or with the dual tyrosine kinase inhibitor lapatinib that inhibits EGFR/ErbB1 and Her-2/ErbB2, but a large percentage develop resistance due to adaptation of signaling pathways [2], making it an attractive target for theranostic imaging of antibody resistant tumors. Another example that is being exploited for theranostic imaging is prostate-specific membrane antigen (PSMA), a type II integral membrane protein that is abundantly expressed on the surface of androgen-independent, advanced prostate cancer [3, 4]. CD44 is a transmembrane glycoprotein that is important in metastasis and in stem-like breast, prostate, pancreatic, ovarian and colorectal cancers [5], making it an excellent target for theranostic imaging.

Most tumors do not express cancer cell specific receptors and antigens, creating a critical need to mine other aspects of the tumor such as metabolism, angiogenesis, inflammation, the tumor microenvironment (TME), and stromal cell receptors for theranostics. Physiological environments in tumors that are characterized by hypoxia, acidic extracellular pH, and substrate deprivation, and the TME that consists of the extracellular matrix (ECM), cancer associated fibroblasts (CAFs), adipocytes, pericytes, multiple immune cells such as tumor associated macrophages (TAMs), and vascular and lymphatic endothelial cells, provide opportunities for theranostic imaging [6].

Several imaging modalities with a bench to bedside span such as magnetic resonance imaging/spectroscopy (MRI/S), positron emission tomography (PET), single photon emission computerized tomography (SPECT), as well as optical imaging that is increasingly being explored for intra-operative imaging, are available for theranostic imaging. There is a rapid expansion of innovative nanoplatforms for theranostics that are being developed based on the imaging modality, the therapeutic cargo, and the target [7]. These nanoplatforms are typically liposomes, nanoparticles, micelles and viral vectors that are decorated with imaging reporters and deliver conventional therapy or molecularly targeted medicine such as complementary DNA (cDNA) or small interfering RNA (siRNA). There is an increasing trend to combine imaging modalities and, as a result, the nanoplatforms are decorated with multi-modal imaging reporters. Innovative strategies such as pH-responsive micelles that show pH-dependent demicellization at pH below 6.5 have been developed [8].

We have designed and developed targeted nanoplexes carrying multimodality imaging reporters together with siRNA/cDNA and a prodrug enzyme for cancer theranostic imaging. In prodrug enzyme therapy, a drug-activating enzyme is delivered to the tumor followed by the administration of a non-toxic prodrug administered systemically. The ability to image the delivery of the prodrug enzyme can be exploited to time prodrug administration to minimize damage to normal tissue. We synthesized a prototype agent consisting of the prodrug enzyme cytosine deaminase (CD) labeled with multimodal MR and optical imaging reporters [9]. CD converted a non-toxic prodrug 5-fluorocytosine (5-FC) to 5-fluorouracil (5-FU) that was detected by ^{19}F MRS. We extended this approach to develop a prototype targeted nanoplex that delivers a prodrug enzyme together with multiple siRNA for theranostic imaging of metastatic disease [10]. We have incorporated a low molecular weight PSMA binding agent in the nanoplex to target the nanoplex to prostate cancer cells [11]. Since choline kinase (Chk) is significantly upregulated in aggressive cancer cells [12] we have used siRNA against Chk in the nanoplex. Chk downregulation can be detected using ^{1}H MRS.
Down-regulation of specific pathways using small interfering RNA (siRNA) provide strategies that can be expanded to down-regulate multi-drug resistance pathways, or repair enzymes, to increase the efficiency of chemo- or radiation therapy.

A major challenge is the ability to rapidly translate and implement the most promising of these agents in the clinic. Quantitative image analyses, cost of synthesizing theranostic agents, solving immunogenicity problems associated with these agents, challenges with cGMP synthesis, obtaining FDA/IRB approval, and the costs of clinical trials are some of the challenges in this field. Despite these challenges, the exciting opportunities in theranostic imaging that are occurring at the interface of chemistry, molecular biology, and imaging provide tangible advances in finding effective treatments against cancer.

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