Preclinical Cancer Imaging
Title: Theranostic probes for cancer imaging and therapy
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Highlights

- Theranostic approach represents a versatile platform for cancer therapy and imaging
- Magnetic nanoparticle platform demonstrated its utility for primary tumors and tumor metastasis
- Modular design of theranostic probes provides a potential for individualized treatment protocols

Title: "Theranostic Probes for siRNA and microRNA Therapies"
Targeted audience: This presentation is intended for graduate students, postdoctoral scientists, and physicians (radiologists) who are either new to the field of Molecular and Cellular Imaging or wish to be updated on the current state-of-the-art in its applications to cancer imaging and therapy.
Objectives:
Theranostic probes could be used not only for delivery of therapy but also for monitoring of this delivery non-invasively using imaging. In many cases they allow for targeted delivery of therapeutics efficiently decreasing the injected dose and reducing systemic toxicity of cancer drugs. Furthermore, theranostic probes enable the delivery of therapies that could not be delivered in their native state due to their fast degradation in the bloodstream. This presentation will focus on the overall concept of "theranostic probes" and step-by-step development of targeted theranostic probes for delivery of oligonucleotides for siRNA and microRNA therapies. The unresolved issues hampering a widespread application of theranostic probes will be also discussed.

Theranostic nanomedicine is an integrated nanotherapeutic system, which can diagnose, deliver targeted therapy and monitor the response to therapy (1). Among other features, the important are: (a) the ability to target tumor marker and deliver therapy simultaneously; (b) the ability to target multiple tumor markers and deliver multiple agents simultaneously; (c) nanoparticle platform for theranostics can be engineered to provide controlled release of cytotoxic drugs upon targeted delivery to cancer cells; (d) theranostic probes can provide early feedback of therapeutic efficacy.

Theranostic nanoparticles consist of a (targeted) imaging agent conjugated/complexed to therapeutic drug. This presentation will focus on the development of a theranostic probes where (targeted) magnetic nanoparticles serve as imaging agents, while the role of therapeutics is played by oligonucleotides exerting silencing effect on oncogenes.

Development of magnetic nanoparticles capable of targeting cancer cells has been demonstrated in various models of cancer. One of the first publications in this area investigated the utility of the underglycosilated mucin 1 tumor antigen (uMUC1) for in vivo tumor imaging. uMUC1 is overexpressed and underglycosilated in over 50% of human cancers and correlates with poor prognosis, which makes it an excellent biomarker with broad utility in many types of cancer. Targeting was done using novel multi-modal (MR and optical) uMUC1-specific magnetic nanoparticles for tumor detection (2). These nanoparticles were also used for *in vivo* imaging of tumor response to therapy (3). For monitoring purposes it is important to have the target stably expressed on tumor cells. Magnetic nanoparticles targeting uMUC1 antigen demonstrated downregulation of uMUC1 after conventional chemotherapy in breast cancer (4). Aiming at translational potential of this biomarker, these targeted nanoparticles were used to

monitor breast tumor progression and therapeutic response in a human uMUC1-expressing transgenic mouse model (5). Full characterization of the targeting antigen by in vivo imaging using magnetic nanoparticles allowed for their further utilization as a component of theranostic probes.

Silencing of the genes responsible for various pathologies including cancer is possible using RNA interference mechanism, an innate cellular mechanism for post-transcriptional regulation of gene expression in which double-stranded ribonucleic acid inhibits the expression of genes with complementary nucleotide sequences. Its potential as a therapy tool is indisputable, considering that one can use this mechanism to silence virtually any gene with single-nucleotide specificity. Major obstacles in applying RNA interference in vivo are presented by the short circulation half-life of the siRNA molecule, its vulnerability to degradation by nucleases (elimination half-life 2-6 min), and the need to translocate the siRNA into the cytosol, where the RNA interference process takes place.
An essential element in the development and optimization of a siRNA delivery method is the ability to measure the bioavailability and functionality of the siRNA molecule after administration into the body. Noninvasive imaging provides the necessary set of tools to accomplish this in authentic physiologic environments and across time. To facilitate siRNA delivery to tumors and enable in vivo imaging of the delivery, theranostic nanoparticle probes, which allowed for visualization by magnetic resonance imaging/multimodal imaging have been employed (6). The next generation of uMUC1-targeted nanoparticles containing therapeutic siRNA to the gene encoding anti-apoptotic protein surviving was used for cancer treatment and resulted in regression of tumor growth (7).

MicroRNA are a class of post-transcriptional regulators that have been implicated in various cell functions including metastatic potential. Several microRNAs that mediate the process of tumor cell migration and tissue invasion have been identified. This presentation will focus on the study describing targeting miR-10b implicated in breast cancer metastasis using theranostic nanoparticles decorated with locked nucleic acid oligonucleotides as a therapeutic moiety (8, 9). The results of this study demonstrated virtually complete prevention of lymph node metastasis formation in breast cancer and arrest of further metastatic dissemination even if lymph node metastases had already formed (8).

Theranostic probes have an inherent capacity for noninvasive imaging and obtaining semi-quantitative information about nanoparticle bioavailability in target tissues. This information could be invaluable in a clinical setting for determining the need for re-treatment on a patient-by-patient basis, opening up the possibility for designing individualized therapeutic regimens.

Composition of various theranostic nanoparticles both targeted and non-targetes used for gene silencing will be discussed. Examples of their use in various pathologies in pre-clinical models and in clinic will be presented. Future application of this class of molecular imaging probes will be evaluated in conjunction with conventional therapies. Limitations of these probes for in vivo applications will be highlighted.

References

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