Molecular Imaging
Title: Imaging of nucleic acid-based therapies
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Highlights

- Nucleic acid-based therapies represent a promising platform for therapy and imaging of various human pathologies (cancer) and infection
- Major drawback in wide-spread application of these therapies is our inability to deliver active molecule to the target side and to monitor its delivery
- Various methods of nucleic acid delivery and imaging are discussed including theranostic probes

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 various human pathologies.

Objectives:

Nucleic acid therapies have emerged in recent years to yield extremely promising candidates for drug therapy to a wide range of diseases, including cancer, infectious diseases, diabetes, etc. The unresolved issues hampering a widespread application of nucleic acid therapies include nuclease sensitivity, off-target effects and efficient delivery. For efficient delivery to the target tissue nucleic acids have to be protected in the blood stream by a carrier. Various carries proposed for this purpose will be discussed. Nucleic acid conjugated or complexed to a carrier in combination with an imaging reporter (theranostic probe) is the best-suited combination to ensure delivery and monitor this delivery using non-invasive imaging. In many cases theranostic probes allow for targeted delivery of therapeutic nucleic acids efficiently decreasing the injected dose and reducing systemic toxicity and induced cytokine response. Most importantly, theranostic probes enable the delivery of nucleic acid therapies that could not be delivered in their native state due to their fast degradation in the bloodstream. This presentation will discuss various methods for delivery of nucleic acid therapies and for monitoring the delivery by non-invasive imaging including step-by-step development of targeted theranostic probes.

Summary:

Nucleic acid therapies comprising of DNA- and RNA-based therapies have tremendous potential for inhibiting gene expression at either the transcriptional or posttranscriptional level. They include plasmids, antisense oligonucleotides, aptamers, small interfering RNAs (siRNA), microRNAs etc. Regardless of the formulation, nucleic acid therapies are prone to degradation in the blood stream, which severely limits their bioavailability at the target site. Various strategies have been proposed for protecting nucleic acids from degradation that include covalent and non-covalent complexing with scaffolds, nano-sized carriers and protective shielding. An essential element in the development and optimization of a nucleic acid delivery method is the ability to measure the bioavailability and functionality of the molecule after administration into the body. Noninvasive imaging provides the necessary set of tools to accomplish this in authentic physiologic environments and across time. Most protective carriers could be modified to include an imaging reporter for optical, nuclear or magnetic resonance imaging. In certain cases as with magnetic nanoparticles, a carrier could serve as an imaging reporter. In general, combination probe that include a carrier, a therapeutic drug and an imaging reporter is called a theranostic probe. A theranostic probe can also be modified with a ligand targeting a specific cellular marker.

Theranostic probes have recently become an integrated part of nanomedicine because of their ability to diagnose, deliver targeted therapy and monitor the response to therapy (1). Among

other features that are characteristic to theranostic probes, the important are: (a) the ability to target specific disease marker and deliver therapy simultaneously; (b) the ability to target multiple disease 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 cells; (d) theranostic probes can provide early feedback of therapeutic efficacy.

In application to nucleic acid therapy theranostic probes proved their utility for delivery and monitoring of various molecules in pre-clinical and clinical settings.

While this presentation will cover various strategies for nucleic acid delivery and imaging, specific consideration will be given to siRNA and miRNA therapies, which showed promising results in treating cancer.

RNA interference mechanism is 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. To facilitate siRNA delivery to tumors and enable in vivo imaging of the delivery, theranostic nanoparticle probes, which allowed for visualization by non-invasive/multimodal imaging have been employed.

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 describe targeting miRNAs implicated in breast cancer metastasis using targeted magnetic nanoparticles. These nanoparticles 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-targeted used for gene silencing will be discussed. Examples of their use in pre-clinical models and in clinic will be presented. Future applications 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.