Chemistry of Contrast Media

Basic Considerations about Suitable Modalities and Probes

Nanoparticle-based diagnostics and theranostics: Pharmacokinetic considerations and (pre-) clinical applications

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Learning Objectives:

- Pharmacokinetic properties of nanoparticles
- Applications of diagnostic and theranostic nanoparticles
- Theranostic concepts to individualize and improve interventions

Nanoparticles are extensively used for diagnostic and therapeutic purposes. In this talk, I will discuss how differences in pharmacokinetic properties between nanoparticles and low-molecular-weight agents affect their suitability for functional and molecular imaging purposes, as well as for theranostic drug targeting. The basic features of nanoparticles are: I) a size between 1 and 100(0) nm; II) a longer circulation half-life time than small molecules; III) a smaller volume of distribution as compared to small molecules; IV) accumulation in tumors and inflammatory lesions via the enhanced permeability and retention (EPR) effect; V) high uptake by organs of the mononuclear phagocytic system (MPS; such as liver, spleen and lymph nodes); and VI) low accumulation in healthy organs and tissues. These properties make nanoparticles suitable for several functional imaging purposes, e.g. for angiography, for lymph node and liver imaging, and for monitoring macrophage-rich lesions such as atherosclerotic plaques. The applicability of i.v. administered nanoparticles for molecular imaging purposes, however, is questionable, or should at least be interpreted with caution, because of the high leakiness of blood vessels in tumors and at sites of inflammation. This leads to unspecific EPR-mediated accumulation and/or retention at the pathological site, also in cases in which the target receptor (to which the ligand-modified and 'actively targeted' nanoparticle is directed) is absent, thereby limiting the specificity of the molecular imaging information obtained. This situation is different for activatable probes, which are locally activated (i.e. de-quenched) at the target site upon cleavage by disease-specific enzymes. These formulations are able to provide highly specific and therefore truly molecular imaging information. Unfortunately, however, their physicochemical nature largely limits their applicability to optical imaging, thereby compromising widespread clinical use. Theranostic nanoparticles combine diagnostic and therapeutic properties within a single formulation. Such agents are highly useful for image-guided drug delivery, which can be employed to individualize and improve interventions, in particular in the case of cancer. By preselecting patients presenting with sufficiently high levels of EPR, and by excluding those presenting with no or very low EPR-mediated target site accumulation, responders can likely be discriminated from non-responders, thereby providing a theranostic means to personalize nanomedicine treatments.

Relevant Publications:

1. Kiessling F, Mertens M, Grimm J, Lammers T. Nanoparticles for imaging: Top or flop? Radiology (in press)

2. Lammers T, Rizzo L, Storm G, Kiessling F. Personalized nanomedicine. Clin Cancer Res 18: 4889-4894 (2012)
3. Lammers T, Aime S, Hennink W, Storm G, Kiessling F. Theranostic Nanomedicine. Acc Chem Res 44: 1029-1038 (2011)