Pre-Clinical MR of Cancer

Molecular Imaging in Cancer

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Platforms and mechanisms of contrast used for targeted MR molecular imaging in cancer
MRI provides imaging contrast via multiple mechanisms including spin density, relaxation, flow, chemical composition and exchange. MR relaxation times T1 and T2 (T2*) are among the most important parameters that determine imaging contrast. Relaxation times can be shortened by relaxation contrast agents (CA) that are generally divided into two groups: T1- agents and T2-agents. Mechanisms of actions of these classes of CA will be briefly reviewed.

To improve relaxation properties of CA and to enable detection of low-concentration molecular targets a macromolecular platform that can carry large number of paramagnetic ions or iron-oxide based superparamagnetic nanoparticles (SPIO) should be used. Chemical structure, relaxation and delivery properties, and imaging methods used for different platforms will be discussed. Another important class of CA is MR imaging agents that generate contrast using proton exchange between bulk water and exchangeable chemical groups. Potential applications of CEST, ParaCEST, and GlucoCEST for molecular imaging of cancer will be introduced.

Targeting strategies– challenges for *in vivo* applications
Monoclonal antibodies (mAb) and their fragments, affibodies, and synthetic peptide have been developed for specific targeting of cellular molecular epitopes such as extracellular domains of cell-surface receptors. An important concept in the development of targeted agents is the multi-step labeling. Molecular targets are initially labeled with the first component of the CA and the secondary contrast-generating component of the agent is subsequently delivered to prelabeled targets. This technique can improve pharmacokinetic and delivery properties of the agent as well as targeting specificity. Optimization of the secondary binding component that should have high affinity and high specificity is an important challenge and several possible strategies include biotin/avidin systems, secondary antibodies, and *in vivo* click chemistry. Pharmacokinetics and biodistribution of the targeted CA and/or its components, such as clearance of the unbound agent from plasma and nonspecific sites, possible toxicity and immunogenic properties need to be addressed for *in vivo* applications and future translation.

Amplification and activation strategies
MR contrast agents can be designed to change relaxivity by changes in the chemical structure of the probe or by clustering of multiple molecules of CA within a compact nanostructure. This strategy was used to develop highly specific activated imaging agents. A significant amplification of the signal is possible if a reporter enzyme capable of activating of large number of CA molecules is expressed or delivered to the target cells. Specific intracellular accumulation of the imaging agent by the target cell can also be used to increase the number of the CA molecules per cell and to amplify the signal.

Discussion and Perspectives
Current applications of targeted MR contrast agents are limited to preclinical animal studies. There are multiple challenges that need to be resolved before the technology can become feasible for clinical translation including the choice of imaging targets, sensitivity issues, toxicity, and immunogenicity. Development of imaging agents for multimodality molecular imaging technologies such as MRI/PET can also be a very important scientific and clinical goal.