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Direct quantification of myelination in multiple sclerosis-from benchtop to bedside

Yanming Wang
Department of Radiology, Case Western Reserve University, USA

Background: Myelination is one of the most fundamental biological processes, providing a unique myelin sheath structure in the vertebrate nervous system that fosters rapid and efficient conduction of impulses along axons. Clinical diagnosis and therapeutic treatments in multiple sclerosis and related neurological disorders are intimately dependent on the capability to selectively detect and monitor myelin damages in the brain. Currently, MR is the primary imaging modality to detect brain lesions. However, the lesion load detected by conventional MRI with or without contrast is often dissociated from disease progression and clinical outcome. All of the existing contrast agents exhibit no affinity for myelin and can only provide lesion enhancement that is solely indicative of disruption of the blood-brain barrier. Lack of myelin-specific contrast agents hampers use of MRI in efficacy evaluation of novel myelin repair therapies currently under development.

Objective: To meet this long-standing challenge, we plan to develop myelin-targeted MR contrast agents that will exhibit characteristic MR properties capable of in vivo detection of demyelinated lesions. The regional distribution and relaxation of the contrast agents will be consistent with myelin neuropathology.

Results: To date, we have developed some prototypical myelin-binding contrast agents with promising MR relaxometric properties. In this presentation, we will discuss 1) the design and synthesis of a selected array of Gd-based MR contrast agents that bind to myelin with high affinity and specificity; 2) characterization of the in vitro MR relaxometric properties and the tissue stability of selected agents in brain tissues; 3) evaluation of the in vivo MR relaxometric properties, pharmacokinetic profiles, metabolism, toxicity.

Conclusion: Myelin-specific MR contrast agents can be developed that will allow us to further determine the pharmacokinetics and define the optimal MR parameters for future clinical studies.

Biography

Dr. Yanming Wang is an Associate Professor of Radiology, Chemistry, and Biomedical Engineering at Case Western Reserve University. He received a PhD in Chemistry in 1995 from the Swiss Federal Institute of Technology in Zurich followed by postdoctoral research at Duke University. Since 1998, Dr. Wang's research has been focused on the development of molecular probes for image-guided diagnosis and efficacy evaluation of therapeutic treatments in neurological diseases and cancer, which are based on a variety of imaging modalities including positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), multiphoton microscopy (SPECT), and near-infrared fluorescent imaging (NIRF). He has developed several imaging agents that target critical pathological processes such as amyloid plaque deposition in Alzheimer's disease and aging, myelin damage and repair in multiple sclerosis, and DNA damage and repair in cancer. He is one of the joint inventors of PIB, an amyloid-imaging agent that has now been widely used in clinical trials worldwide. He is also noted for his work on longitudinal imaging of demyelination/remyelination based on multiple imaging modalities. In addition, Dr. Wang is Director of Radiopharmaceutical Research at Case Western Reserve University and provides imaging agents for many clinical and preclinical studies.

yxw91@case.edu