A novel redox-responsive, dual-modality MRI/optical imaging probe

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Introduction

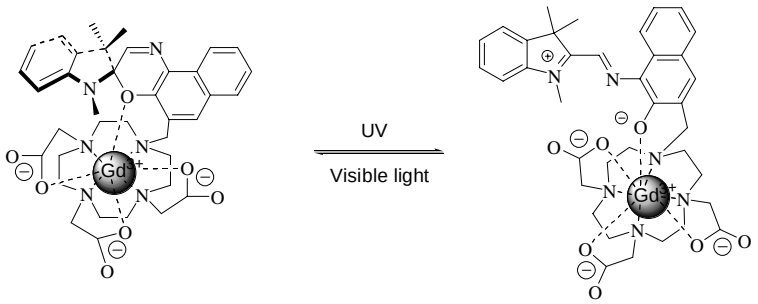
Abnormal cellular redox state has been linked to a number of diseases such as cancer, heart disease, inflammatory conditions, airway disease and is also associated with aging.[1-4] Healthy cells and tissues are usually able to overcome small perturbations in redox conditions and return to their original state through innate repair mechanisms, but severe oxidative stress can lead to destruction of cells and tissues by the production of reactive oxygen species (ROS) such as peroxides and free radicals.[5] Currently, there are no clinical methods to observe cellular or tissue oxidation state even though conditions of oxidative stress have repeatedly been associated with illness and injury. A clinical method to determine cellular or tissue oxidation state would be a beneficial tool in the study of redox environment as it relates to disease evolution. We believe magnetic resonance imaging (MRI) may be the diagnostic tool to provide a solution and have developed an MRI contrast agent that responds to redox conditions.

Methods

The redox response of a magnetic resonance imaging (MRI) probe (spirooxazine-Gd-DO3A) was tested in water using a series of biological redox agents. NADH was found to be an effective reducing agent for the "open" isomer of the probe. The influence of NADH on the MR and optical imaging of the probe was tested in both solution and cells in culture. When in dark, the probe (open form) has a r_1 relaxivity of 4.72 $mM^{-1}s^{-1}$ and gives out strong fluorescence. Upon mixing with NADH, the compound undergoes an isomerization to closed form. The r_1 relaxivity increases by 41% and the brightness in MRI increases immediately and significantly. However, the fluorescence of the probe was almost fully quenched by NADH, which leads to a marked intensity in confocal images.

Conclusions

We hypothesize that the relaxivity properties of the probes are modulated by a conformation change in the molecule that alters the hydration state of the gadolinium center as shown in the figure below. The response of the probe to concentrations of NADH that are comparable to biological values (10^{-5}) suggest that the probe has potential for in vivo use. The potential ability to turn this type of probe "ON" and "OFF" would be a useful addition to the recent reports of biochemical reporter probes. The probe is promising for direct, non-invasive observation of biochemical process *in vivo*.



"closed" isomer "open" isomer