Design Synthesis and Biological Application of Chemical Probes for Molecular Imaging

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Real-time imaging of enzyme activities *in vivo* offers valuable information in understanding living systems and in the possibility to develop medicine to treat various forms of diseases. Magnetic resonance imaging (MRI) is an imaging modality adequate for *in vivo* studies. Therefore, many scientists are interested in the development of MRI probes capable of detecting enzyme activities *in vivo*. However, in the case of ^{1}H-MRI probes, interference from the background signals intrinsic to ^{1}H becomes problematic. Because such a background signal is hardly detectable, ^{19}F-MRI probes are promising for *in vivo* imaging. Despite this potential, few principles exist for designing ^{19}F-MRI probes to detect enzyme activities. We propose a novel design strategy for ^{19}F-MRI probes to detect protease activities and to demonstrate its practical applicability. The design principle is based on the paramagnetic relaxation effect from Gd^{3+} to ^{19}F. A peptide was synthesized, Gd-DOTA-DEVD-Tfb, attached to a Gd^{3+} complex at the N-terminus and a ^{19}F-containing group at the C-terminus. The ^{19}F-NMR transverse relaxation time (T_2) of the compound was largely shortened by the paramagnetic effect of intramolecular Gd^{3+}. The peptide was designed to have a sequence cleaved by an apoptotic protease, caspase-3. When the peptide was incubated with caspase-3, the peptide was cleaved and subsequently the Gd^{3+} complex and the ^{19}F-containing group were separated from each other. $T_{2,}$ after cleavage, was extended to cancel the intramolecular paramagnetic interaction. Using this probe as a positive contrast agent, the probe could detect caspase-3 activity spatially from a phantom image using ^{19}F MRI.