【Science and Engineering（Chemistry）】

Design, Synthesis and Biological Application of Chemical Probes for *in vivo* Imaging

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【Outline of survey】

One of the great challenges in the post-genome era is to clarify the biological significance of intracellular molecules directly in living animals. If we can visualize a molecule in action, it is possible to acquire biological information, which is unavailable if we deal with cell homogenates. One possible approach is to design and synthesize chemical probes that can convert biological information to chemical output.

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.

【Expected results】

A novel design strategy for ^{19}F-MRI probes to detect protease activities is proposed. 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. T_2 is a parameter that can be used to generate contrasts in MR images. Using this probe as a positive contrast agent, the probe could detect enzyme activity spatially from a phantom image using ^{19}F MRI.

【Reference by the principal investigator】

S. Mizukami, R. Takikawa, F. Sugihara, Y. Hori, H. Tochio, M. Wälchli, M. Shirakawa & K. Kikuchi: “Paramagnetic Relaxation-based ^{19}F MRI Probe to Detect Protease Activity”, *J. Am. Chem. Soc.*, **130,** 794-795 (2008).

【Term of project】 FY2008－2012	**【Budget allocation】** **81,500,000 yen** (direct cost)

【Homepage address】

http://www-molpro.mls.eng.osaka-u.ac.jp/mlsmpwww/toppageenglish.html