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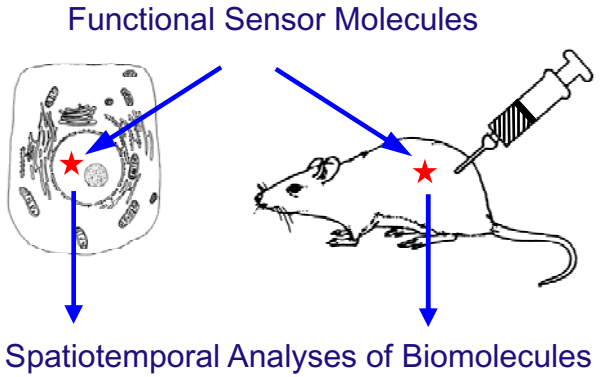

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One of the great challenges in the post-genome era is to clarify the biological significance of intracellular molecules directly in living cells. If we can visualize a molecule in action, it is possible to acquire biological information, which is unavailable if we deal with cell homogenates. One possible approach is to design and synthesize chemical probes that can convert biological information to chemical output. For this purpose, fluorescent sensor molecules based on modulation of coordination space for intracellular messengers have been developed and successfully applied to living cells.

Luminescent lanthanide complexes (Tb3+, Eu3+, etc.) have excellent properties for biological applications, including extraordinarily long lifetimes and large Stokes shifts. However, there have been few reports of lanthanide-based functional probes, because of the difficulty in designing suitable complexes with a luminescent on/off switch. A series of complexes which consist of three moieties were synthesized, those three are a lanthanide chelate, an antenna, and a luminescence on/off switch. This approach to control lanthanide luminescence makes possible the rational design of functional lanthanide complexes, in which the luminescence property is altered by a biological reaction. To exemplify the utility of this approach to the design of lanthanide complexes with a switch, a novel protease probe was developed, which undergoes a significant change in luminescence intensity upon enzymatic cleavage of the substrate peptide. This probe, combined with time-resolved measurements, was confirmed in model experiments to be useful for the screening of inhibitors, as well as for clinical diagnosis.

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. Because background signal is hardly detectable, 19F-MRI probes are promising for in vivo imaging. A novel design strategy for 19F-MRI probes to detect protease activities is proposed. The design principle is based on the paramagnetic relaxation effect from Gd3+ to 19F. A peptide was synthesized, Gd-DOTA-DEVD-Tfb, attached to a Gd3+ complex at the N-terminus and a 19F-containing group at the C-terminus. The 19F-NMR transverse relaxation time (T2) of the compound was largely shortened by the paramagnetic effect of intramolecular Gd3+. 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 Gd3+ complex and the 19F-containing group were separated from each other. T2, after cleavage, was extended to cancel the intramolecular paramagnetic interaction. T2 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 caspase-3 activity spatially from a phantom image using 19F MRI.

URL

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