School of Engineering
Bioengineering Seminar

UCMERCED

Molecular Imaging and Cellular Manipulation in Immuno-engineering

Date :

Tuesday,
05/22/2018

Time :

1:30 pm

Location:

SSB 120

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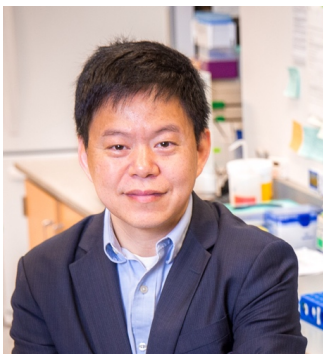
UCSD



Abstract:

Genetically-encoded biosensors based on fluorescence proteins (FPs) and fluorescence resonance energy transfer (FRET) have enabled the specific targeting and visualization of signaling events in live cells with high spatiotemporal resolutions. Single-molecule FRET biosensors have been successfully developed to monitor the activity of a variety of signaling molecules, including tyrosine/serine/threonine kinases. We have a developed a general high-throughput screening (HTS) method based on directed evolution to develop sensitive and specific FRET biosensors. We have first applied a yeast library and screened for a mutated binding domain for phosphorylated peptide sequence. When this mutated binding domain and the peptide sequence are connected by a linker and then concatenated in between a pair of FRET FPs, a drastic increase in sensitivity can be achieved. It has also been increasingly clear that controlling protein functions using lights and chemical compounds to trigger allosteric conformational changes can be applied to manipulate protein functions and control cellular behaviors. In this work, we first engineered a novel class of machinery molecules which can provide a surveillance of the intracellular space, visualizing the spatiotemporal patterns of molecular events and automatically triggering corresponding molecular actions to guide cellular functions. We have adopted a modular assembly approach to develop these machinery molecules. As a proof-of-concept, we engineered such a molecule for the sensing of intracellular tyrosine phosphorylation based on fluorescence resonance energy transfer (FRET) and the consequent activation of a tyrosine phosphatase (PTP) Shp2, which plays a critical and positive role in various pathophysiological processes. We have further integrated this machinery molecule to the "don't eat me" CD47 receptor SIRPα on macrophages such that the engagement of SIRPα and its activation of naturally negative signals will be rewired to turn on the positive Shp2 action to facilitate phagocytosis of red blood cells and target tumor cells, initiated by the specific antigen-targeting antibodies and their interaction with Fcγ receptors. Because of the modular design of our engineered molecule, our approach can be extended to perform a broad range of cell-based imaging and immunotherapies, and hence highlight the translational power in bridging the fundamental molecular engineering to clinical medicine. We have also integrated with lights and ultrasound to manipulate the molecular activation of genes and enzymes, which allowed us to control the cellular functions of immunocells with high precision in space and time. As such, we can integrate fundamental science and engineering principles for biomedical and clinical applications.

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