Fluorescent Protein-based Optogenetic Technology for the Study of Brain Functions and Diseases

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Abstract

Genetically encoded fluorescent biosensors based on fluorescent proteins (FPs) are powerful technology for the study of brain functions and diseases. First, fluorescent biosensors can be applied to monitor neurotransmission for the study of brain function. In particular, we recently developed multicolor fluorescent sensors for dopamine receptor subtypes, DRD1 and DRD2, which can sensitively and selectively visualize dopamine transmission. These multicolor biosensors further allowed the investigation of receptor functional crosstalk between DRD1-DRD2 heterodimers, and discovered the differential crosstalk in the DRD1-DRD2 heterodimers upon different dopamine levels.

Additionally, fluorescent biosensors and live-cell imaging techniques can be applied to investigate new pathological mechanism of brain diseases. In particular, we investigated the role of focal adhesion kinase (FAK) in Huntington's disease (HD), and found that the activity of FAK is severely reduced in HD cell line, animal models, and HD patients. In addition, we discovered that the neurotransmitter-induced FAK activation and FA dynamics are impaired, causing the abnormally increased number of immature neurites in HD. We further investigated the molecular mechanism of FAK inhibition in HD, and surprisingly discovered that mutant huntingtin strongly associates with phosphatidylinositol 4,5-biphosphate, altering its normal function for the FAK activation. Therefore, our results provide a novel molecular mechanism of FAK inhibition in HD along with its pathological mechanism for synaptic dysfunctions during the progression of HD.