CDB SEMINAR

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14:00 – 15:00 Auditorium C1F

Genetically encoded light-sensitive amino acids uncover allosteric regulations in neuronal receptors

Summary

Description of allostery is fundamental to understanding most processes involving biological macromolecules. Site-specific incorporation of photo-responsive unnatural amino acids (Uaas) into proteins by the genetic code expansion technology adds unprecedented photochemical properties to varieties of proteins. Although there is a long history to engineer light-activatable proteins, for example ion channels and kinases, the development of light-induced allosteric modulations of pharmacological importance – is a more recent phenomenon. In this talk, I will summarize our findings of light-sensitive NMDA receptors (NMDARs), a type of glutamate-gated ion channels mediating fast synaptic transmission mediating learning and memory. Light-sensitive Uaas have been incorporated at specific sites of the receptors. Targeting sites within heterodimer interfaces led us to identify a series of robust light-sensitive receptors of GluN2A and GluN2B subtypes, two major subtypes playing distinct functional roles. Through heterologous expression in *Xenopus laevis* oocytes and mammalian cells, we have characterized their photochemical properties by using electrophysiology measurements in combination with online-light stimulation. Biochemical analysis has been used to confirm light-induced inter-subunit crosslinking. Characterizations of light-induced allosteric modulations in the presence of inhibitors (Zn^{2+} and ifenprodil) and potentiators (spermine) have provided a unified view of how the same N-terminal domains of both subtypes, distant to the agonists binding domains, bidirectionally modulate receptors functions. Our works are important for neuropharmacology because the NMDARs are promising drug targets for the development of therapeutic compounds to treat neuronal diseases including depression and the Alzheimer's.

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