Symposia

[1S03m]Regulation and manipulation of neural stem/progenitor cells in the brain

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*Videos are available throughout the meeting period.

[1S03m-01]Regulatory Mechanism of Neural Stem Cells Revealed by Optical Manipulation of Gene Expressions

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The mammalian brain consists of a complex ensemble of neurons and glial cells. Their production during development and remodeling is tightly controlled by various regulatory mechanisms in neural stem cells. Among such regulations, basic helix-loop-helix (bHLH) factors have key functions in the self-renewal, multipotency, and fate determination of neural stem cells. Here, we highlight the importance of the expression dynamics of bHLH factors in these processes. We propose the multipotent state correlates with oscillatory expression of several bHLH factors, whereas the differentiated state correlates with sustained expression of a single bHLH factor.

It is also now widely accepted that in mammals, including humans, neural stem cells exist in the postnatal/adult brain and newly born neurons are continuously generated and incorporated into the functional neural networks. The active versus quiescent states of neural stem cells are tightly controlled. In active neural stem cells of the adult brain, Hes1 expression oscillates and drives cyclic expression of the proneural gene Ascl1, thereby activating cell proliferation. We found that Hes1 levels are high and sustained while Ascl1 expression is suppressed in quiescent neural stem cells in the adult mouse brain. Inactivation of Hes1 and its related genes up-regulates Ascl1 expression and increases neurogenesis. However, neural stem cells are soon depleted, and neurogenesis ceases prematurely. Conversely, sustained Hes1 expression represses Ascl1, inhibits neurogenesis, and maintains quiescent neural stem cells. By contrast, induction of Ascl1 oscillations activates neural stem cells and increases neurogenesis in the adult mouse brain. Thus, Ascl1 oscillations, which normally depend on Hes1 oscillations, regulate the active state, while high, sustained Hes1 expression and resultant Ascl1 suppression contribute to the quiescent state of neural stem cells.

We also developed a new optogenetic method that can manipulate gene expressions in neural stem cells by light. We used this technology to manipulate the growth and fate-determination of neural stem cells. I also introduce various applications of light-induced control of gene expressions in broad fields of biology.