文部科学省特別経費プロジェクト
脳と末梢の機能連関に関する戦略的研究の推進

“脳と末梢”

第14回“脳と末梢”セミナー/第41回脳科学セミナー

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Wnt/ß-catenin Signaling in Zebrafish: a Neurodevelopmental and a Cell Biological View.

【日時】　平成25年3月28日（木）　16:00～17:30

【場所】　理学部　8番教室

＜要旨＞

Wnt/β□Catenin signaling is one of the most important paracrine pathways during development, tissue regeneration and stem cell regulation. During brain development, Wnt/ß-catenin signalling is increased in local brain organizers such as the mid-diencephalic organizer (MDO) in the forebrain or at the isthmus organizer at the midbrain-hindbrain boundary. Here we show that canonical Wnt signaling is required for the induction of the Shh-secreting MDO. Knock-down of Wnt3 and Wnt3a leads to a loss of the MDO, which can be rescued by parallel pharmacological stimulation of the Wnt/ß-catenin pathway. Wnt/ß-catenin signaling is needed to maintain the organizer primordium during somitogenesis and subsequently for regionalization of the thalamus in zebrafish.
In an in vivo analysis we addressed the question how the activation of the Wnt signaling cascade is regulated in zebrafish. After activation by Wnt ligands, a multiprotein complex assembles at the plasma membrane joining active receptors and intracellular signal transducers to the so-called signalosome. We find that the m1 subunit of the Clathrin adaptor complex Ap2 can activate Wnt/ß-catenin signaling ligand-independently while knock-down of Ap2m1 reduces signaling in early zebrafish embryos. Our live imaging studies show indeed that Ap2m1 induces signalosome formation via direct binding to Dishevelled2 (Dvl2) at the cytoplasmic membrane. Knock-down studies reveal that Ap2m1 is required for the stabilization of Dvl2. We find that Ap2m1 mediates endocytosis of the signalosome and is responsible for the sequestration of signalosome components including the □-catenin phosphorylating enzyme Glycogen Synthase Kinase 3ß (Gsk3ß) into multi vesicular bodies (MVBs). Interestingly, Wnt is still able to form Ap2m1/Dvl2-depleted signalosomes at the plasma membrane, however, signalosome endocytosis and consequently signaling is decreased.
Our results demonstrate the importance of Wnt/ß-catenin signaling in brain development and link signal initiation by cell-surface signalosomes with signal maintenance by the sequestration of signalosome components into MVBs.

問合せ：　理工学研究科生体制御学コース　弥益恭　内線4349