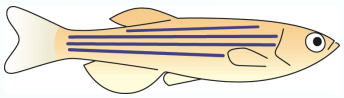

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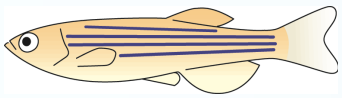

Connecting the eye to the brain: Local apoptotic pathway activation sculpts axonal arbors

Douglas S. Campbell

Institute of Neuronal Cell Biology, Technological University of Munich, Germany

July, 26 (Tue) 13:30-15:00
Room No. A222 School of Science Building A

In addition to being critical for apoptosis, components of the apoptotic pathway, such as caspases, function in local non-apoptotic roles in cells, including neurones. However, very little is known about their role and regulation in non-lethal dynamic processes such as axonal arborisation and synaptogenesis. We are investigating theses processes using the zebrafish retinotectal projection as a model system in which retinal ganglion cell (RGC) growth cones navigate along a highly stereotypical pathway from the retina to their primary target, the optic tectum in the midbrain. Once they have reached the tectum, growth cones dramatically change their behaviour to undergo arborisation and synaptogenesis, key processes in the generation of neuronal connectivity and affected early during degeneration.

In vivo live imaging of RGC arbors expressing a FRET-based reporter of Caspase-3 activity reveals that Caspase-3 is activated locally at branch points of young dynamic arbors, but not at the branch points of older stable arbors, nor in RGC cell bodies or tectal dendrites. Caspase-3 becomes rapidly activated (within 5 minutes) during the processes of developmental branch point addition and additionally globally, at the initiation of axonal degeneration, suggesting the hypothesis that apoptotic pathway activation may be a key regulator of axonal arbor and synaptic stability in the CNS. To test this, time-lapse imaging of RGC axonal arbors was performed in embryos where Caspase-3 and -9 function were inhibited revealing that arbor and presynaptic dynamics were reduced. Since these effects were similar to loss of Slit-Robo signalling on arbor dynamics (Campbell et al., 2007), we tested a role for and observed a genetic interaction between the apoptotic pathway and Slit-Robo signalling, suggesting that local caspase activation lies downstream of a ligand-receptor system, acting as key promoters of axonal branch tip and synaptic dynamics restricting arbor growth *in vivo*. We have now established *in vivo* imaging of cytoskeletal and mitochondrial dynamics in axons to determine where and how caspase activity and potential substrates regulate cytoskeletal stability underlying branch dynamics and its possible upstream pathways.

Our results may also imply that axon arbor and synaptic development require an optimum level of local apoptotic pathway activation which promotes both positive (i.e. branch addition) and regressive (i.e. branch retraction) events, and that abnormal global caspase activation throughout axons might contribute to axon degeneration in the vertebrate CNS.

世話人 ： 名古屋大学生物機能開発利用研究センター 日比正彦（内線5198）