Using *Drosophila melanogaster* to study the regulation of kinesin-based anterograde axonal transport *in vivo*

by Tobias Rasse

Synaptic Plasticity, Hertie-Institute for Clinical Brain Research
University of Tübingen

Abstract:

Impairments in intracellular transport are the hallmark of many neurological diseases.
Interestingly typically long axons –with a length of up to one meter- are selectively affected. This suggests that perturbations in long-range, tubulin based transport might be a common pathological mechanism. The synapses of human motor neurons are located at a distance of up to one meter from the respective cell body. As the axon spanning this enormous distance contributes little toward the synthesis of proteins or membranes, these components need to be transported from cell body to the synapses. In addition axons have typically a rather small diameter, which limits passive, diffusion driven transport. Thus, both the maintenance of the axons as well as synaptic function critically depend on efficient anterograde and retrograde axonal transport.
The Kinesin-1 family is one major anterograde motor complex. Mutations in a member of the Kinesin-1 family, KIF5A (kinesin heavy chain) cause SPG10. SPG10 is a autosomal dominant form of hereditary spastic paraplegia (HSP). HSP is a genetically heterogeneous neurodegenerative disorder causing spastic weakness of the lower extremities. On the cellular level the disease is characterized by distal axonpathy that affects the longest axons in the cortospinal tract. Axonal degeneration is observed both in the longest axons of the ascending dorsal columns as well as in the descending pyramidal tract. To further probe the pathological mechanisms involved in SPG10 pathology we generated a *Drosophila model* for SPG10 and will present first results.
The Kinesin-3 family plays a vital role in the axonal transport and delivery of synaptic building blocks. In particular, the FHA domain of IMAC's vertebrate homolog, KIF1A, has been implicated in the regulation of this process. Utilizing a screen for impairments in *Drosophila melanogaster* synaptogenesis we identified fluglotse (*imac*^{flg}), a point mutation in the FHA domain of the Kinesin-3 family member IMAC. Thus, we plan to address the specific impact of *imac*^{flg} on controlling IMAC activity and the delivery of cargo to synapses. I will present a brief outlook on how we plan to use atomic force microscopy to address *in vitro* changes in the intramolecular forces exerted between the FHA domain and other domains implicated in the auto-inhibition of IMAC. Next, I will discuss how we plan to use a novel, *in vivo* imaging technique to shed light on the effects of *imac*^{flg} on cargo transport in intact, living fruit fly larvae.

Friday, May 6th, 2011, 13:00
Room PH 127

Contact:
Dr. Günther Woehlke, guenther.woehlke@ph.tum.de , phone: -12486