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DISSERTATION SUMMARY

The novel *Drosophila* formin dDAM regulates the actin cytoskeleton in the tracheal system and the CNS

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Proteins of the formin family plays key roles in the regulation of the actin cytoskeleton. They can nucleate new actin filaments directly, and regulate the polymerization of the growing actin bundle. The formins are multidomain proteins containing several important homology domains: the FH1, FH2, and FH3 formin homology domains, an N-terminal RBD domain, and a C-terminal DAD autoinhibitory domain. The FH2 domain has been shown to be both necessary and sufficient for actin nucleation and polymerization *in vitro*, the FH1 domain is able to bind the G-actin-binding protein profilin, while the FH3 domain has been implicated in the regulation of the subcellular localization of the protein (Evangelista et al. 2003). The largest subclass of formins, called diaphanous-related-formins (DRFs) are activated upon Rho-GTP binding to their RBD domain. This binding alleviates the intramolecular autoinhibitory interaction between the RBD and the DAD domain (Evangelista et al. 2003).

Recent studies have led to the identification of a novel subtype of formins, DAAM that has been implicated in planar signaling during *Xenopus* gastrulation. These results suggested that DAAM might function as a bridging factor between the signaling molecules Dsh and RhoA because Daam1 binds to both Dsh and RhoA, and Wnt/Fz activation of RhoA depends on Dvl (a Dsh homologue) and Daam1 (Habas et al. 2001). However, contrasting to this model, much of previous work provided evidences that formins are Rho effectors that act downstream of the Rho GTPases.

To begin the genetic analysis of *dDAM*, first we have isolated a set of *dDAM* mutant alleles by P-element excisions. We found evidences that *dDAM* is involved in the regulation of the actin cytoskeleton in several different tissues. Below we consider the trachea and the CNS function of *dDAM*.

During the first phase of tracheal development the primordial cells invaginate from the epidermis and form the primary branches. Subsequently, some tracheal branches fuse with an adjacent branch to build up a continuous tubular network. Finally, tracheal cells secrete a cuticle on their apical surface that protects the larvae from dehydration. Interestingly, the tracheal cuticle is distinguished from the epidermal cuticle by the presence of cuticle ridges often called taenidial folds. In the absence of *dDAM*, the taenidial folds fail to organize into parallel running cuticle ridges leading to the collapse of the tube. Our results demonstrate that in tracheal cells apical actin is also organized into parallel running rings just as the overlaying cuticle ridges, and *dDAM* severely impairs actin organization. Taking it together, it appears that *dDAM* directs cuticle secretion in the tracheal system by polymerizing and organizing apical actin into parallel running bundles.

Additionally, we have analysed the CNS function of this formin and found that *dDAM* is required for axon elongation in the embryonic CNS. Interestingly, the vertebrate homologues of *dDAM* are also expressed in the CNS raising the possibility that the regulation of axon growth is an evolutionary conserved function of the DAAM subfamily of formins.

In order to understand the regulation of *dDAM*, we have identified genetic ineractors and collected evidences that suggest that *dDAM* acts together with *RhoA*, and two members of the SRC family of kinases to regulate the actin cytoskeleton in the trachea.

References

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