

Genetic and molecular regulation of epithelial tube morphogenesis

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av

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Avhandlingen baseras på följande delarbeten:

- I. **Tonning, A.**, Hemphälä, J., Tång, E., Nannmark, U., Samakovlis, C. and Uv, A.
A transient luminal chitinous matrix is required to model epithelial tube diameter in the *Drosophila* trachea.
Developmental Cell 9: 423-430, 2005
- II. Moussian, B., Tång, E., **Tonning, A.**, Helms, S., Schwarz, H., Nüsslein-Volhard, C. and Uv, A.
Drosophila Knickkopf and Retroactive are needed for epithelial tube growth and cuticle differentiation through their specific requirement for chitin filament organization.
Development 133(1): 163-171, 2006
- III. **Tonning, A.**, Helms, S., Schwarz, H., Uv, A. and Moussian, B.
Hormonal regulation of *mummy* is needed for apical extracellular matrix formation and epithelial morphogenesis in *Drosophila*.
Development 133(2): 331-341, 2006
- IV. **Tonning, A.**, Wikström, J., Tång, E., Nannmark U. and Uv, A.
The novel protein Humongous is required for tubular epithelial barrier function in *Drosophila*.
Manuscript

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Networks of epithelial tubes, such as the vertebrate lung, kidney and vascular system, enable transport of gases and nutrients to all tissues in the body. These tubes are built up by a single layer of polarized epithelial cells, with the apical membrane facing the lumen. For optimal organ function it is critical that each tube in the network attains correct size and shape, as constricted or dilated tubes will affect the flow rate and impede organ function. When tubes form during organ development, they often have a narrow lumen that must expand to attain the typical mature length and diameter. Both apical (luminal) membrane growth and rearrangements of the subapical cytoskeleton are central to tube growth, but the mechanisms that coordinate these events across the tubular epithelium to ensure uniform tubes with functional dimensions have remained unknown.

We have used the respiratory organ (trachea) of the fruit fly *Drosophila melanogaster* as a model system to gain insights into the molecular mechanisms that control tube size and shape. This thesis includes the analyses of five new tracheal tube size genes, which mutational analyses have revealed a new biological principle to ensure uniform functional tubes: newly formed tracheal tubes deposit a broad luminal chitin filament around which the tubular epithelium can rearrange. After tube expansion and before the tubes become functional in transport, the luminal filament is cleared. Four of the genes (*krotzkopf verkehrt*, *knickkopf*, *retroactive* and *mummy*) are required to build the luminal chitin filament, and their loss of function result in severe diameter constrictions and dilations in the expanding tubes. A fifth gene, which we have called *humongous*, encodes a novel protein required for formation of the septate junctions (SJs), which are analogous to vertebrate tight junctions. Many previously identified tracheal tube size genes encode SJ components, but their role in tube expansion has been unclear. We find that intact SJs are essential for correct assembly of the chitin filament, thus reinforcing the central role of the luminal chitin filament in tube size regulation.

Keywords: epithelial tube morphogenesis, trachea, *Drosophila*, chitin, chitin synthase, apical extra cellular matrix, paracellular diffusion barrier, tube expansion, septate junctions

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