MOLECULAR REGULATION OF EPITHELIAL TUBE SIZE

AKADEMISK AVHANDLING

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Avhandlingen baseras på följande delarbeten:

I **Tonning A*, Hemphälä J*, Tång E, Nanmark 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
* These authors contributed equally to this work

II **Tång E*, Moussian B*, Tonning A, Helms S, Schwartz 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 organisation.
Development 133(1): 163-171, 2006
* These authors contributed equally to this work

III **Tång E, Chavoshi TM, Uv A**
Balancing luminal and subapical forces regulate tube size and shape in the *Drosophila* trachea.
Manuscript

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ABSTRACT

MOLECULAR REGULATION OF EPITHELIAL TUBE SIZE

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In nature, epithelial tubes are vital structures in organ design and are required for transport of gases and liquids in organs, such as the vascular system, the vertebrate lung and the kidneys. The tubular epithelium is single layered, but is often reinforced by layers of muscular support. It constitutes an apical side facing the lumen and a basal side that contacts surrounding tissues. To ensure optimal flow, it is critical that the tubes are correctly sized and shaped. Epithelial tube growth depends on apical membrane enlargements, as well as subapical rearrangements, but the mechanisms involved in the regulation of epithelial tubes size and shape are yet to be revealed.

In this thesis the *Drosophila* respiratory (tracheal) system has been used as a model organ to identify essential genes and clarify the mechanisms involved in the making and shaping of tubes. Through genetic and molecular analyses, new biological concepts have been uncovered. The main tracheal tube, the dorsal trunk (DT) expands three-fold during a short interval followed by tube elongation. In this thesis we have dissected the roles of five genes in tube regulation, called *kkv*, *knk rtv*, *dBest2* and *DAAM*. Analysis of *kkv*, *knk* and *rtv* led us to identify an unprecedented need for luminal matrix components in modeling tube shape (Paper I and II). A chitinous luminal matrix is deposited in newly formed tubes and constitutes an expanding cord inside the tube that is required for uniform tube diameter growth. *kkv* is required for chitin synthesis while *knk* and *rtv* are needed for chitin filament assembly. If chitin is missing or fail to form an organized matrix, the expanding tubes develop severe local dilations and constrictions.

The subsequent tube elongation requires dBest2 and DAAM (Paper III). *dBest2* encodes an apical chloride channel and is essential for lumen growth during elongation, suggesting that elongation is driven by an increased luminal osmotic pressure. DAAM has a function in actin organization. In the wild type trachea, actin filaments arrange as subapical rings perpendicular to tube length, thus allowing for lumen elongation, but not diametrical expansion, upon the increase in lumen pressure. In *DAAM* mutants, the actin rings are disorganized, thus lumen elongation is inhibited. The luminal chitin matrix has a second role at this stage by preventing excess tube elongation. Thus, a balance between combinatorial physical forces exerted by the lumen and subapical actin cytoskeleton determines final tube size.

Key words: *Drosophila*, trachea, epithelial tubes, morphogenesis, chitin, luminal matrix, tube shape, chloride channel, subapical actin

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