Mucin-like proteins in *Drosophila* development

Akademisk Avhandling

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av

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Avhandlingen baseras på följande delarbeten:

I. **Syed ZA**, Härd T, Uv A, van Dijk-Härd IF (2008) A Potential Role for *Drosophila* Mucins in Development and Physiology. PLoS ONE 3(8): e3041.

II. **Syed ZA**, Bougé A-L, Byri S, Chavoshi TM, Tång E, Bouhin H, van Dijk-Härd IF, A Uv (2012) A Luminal Glycoprotein Drives Dose-Dependent Diameter Expansion of the *Drosophila* melanogaster Hindgut Tube. PLoS Genet 8(8): e1002850.

III. **Syed ZA**, Byri S, van Dijk-Härd IF, A Uv. Mesh is a lateral cell adhesion molecule required for apical cell membrane restriction in the *Drosophila* gut epithelium. (*Manuscript*)

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Mucins are large and highly glycosylated proteins and major component of the mucus that coats the lining of epithelial organs. Mucins are characterized by the presence of extended regions rich in the amino acids Proline, Threonine and Serine (PTS domain), where the Serines and Threonines are *O*-glycosylated to form sugar-rich mucin domains. Mucins are classified into secreted gel-forming mucins and transmembrane mucins with possible signaling functions. The amino acid sequence of the PTS domains tends to be poorly conserved between species and different mucins. The goal of this thesis was to identify and study potential mucin-like proteins in *Drosophila melanogaster*. We devised a simple bioinformatic approach and developed a program that can identify PTS domains based on amino acid content. We thereby identified 36 mucins and mucin-related proteins. All proteins appear to be secreted, except for two that harbor a predicted transmembrane domain. Expression analysis at different stages of the *Drosophila* life cycle revealed that many mucins are expressed in the larval gut, consistent with a function in mucosal barrier formation. Interestingly, some of the mucins showed dynamic expression in different tubular organs during embryogenesis. Among these was Mur96B/Tenectin (Tnc) that was further studied to dissect its role in epithelial organ development. We found that Tnc is critical for diameter expansion of the developing hindgut. Tnc forms a transient matrix that fills the hindgut lumen and drives expansion in a dose-dependent manner, presumably by generating a luminal pressure. This study revealed a new mechanism in organ development, whereby the extent of lumen volume expansion can be regulated by the accumulation of single glycoprotein. In parallel to the bioinformatic approach, we identified a *Drosophila* protein that shares conserved domains with human SUSD2 and the non-mucin parts of human MUC4, called Mesh. We aimed to analyze Mesh function as a means to address the roles of these domains. Mesh was found to be is expressed in the digestive tract epithelium from mid-embryogenesis and throughout larval and adult life, localizing to the apical junction belt. Mesh is required for correct organization of the Scribble-complex, a main polarity complex conserved between fly and mammals, to prevent excess expansion of apical cell surface and for microvilli organization. The results demonstrate that mucin-like proteins, containing the PTS domains or other mucin-related domains, are essential for epithelial organ development in *Drosophila*.

Keywords: Mucins, PTS-domain, *Drosophila* development, Tube shape, Hindgut, Midgut, Malpighian tubules, Luminal matrix

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