Identifying regulators of cell morphology.

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Objectives

While the Shroom3-Rock-myosin II signaling module is essential for proper tissue morphogenesis in vertebrates, we hypothesize that other cellular pathways work with Shroom to form tissues of the correct morphology. The following aims will be used to test this hypothesis:

Aim 1: Complete a genome-scale genetic screen in *Drosophila* to identify proteins and pathways that work with Shroom to control tissue architecture.

Aim 2: Determine the functional conservation of the identified pathways using mammalian models of cell morphology.

Project Description

screening cross

♀ *ShroomOEX / ShroomOEX* × ♂ *deficiency (df) / balancer*

↓

ShroomOEX ; df vs *shroomOEX ; balancer*

↓

quantify F1 phenotype:

Enhancer or Suppressor or no effect

↓

identify candidate genes:

Screen smaller *df* or defined mutations in specific genes.

↓

Identify vertebrate orthologs

↓

test conservation

Screen using quantifiable cell-based apical constriction assay

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Pool of candidates for further hypothesis-based inquiry

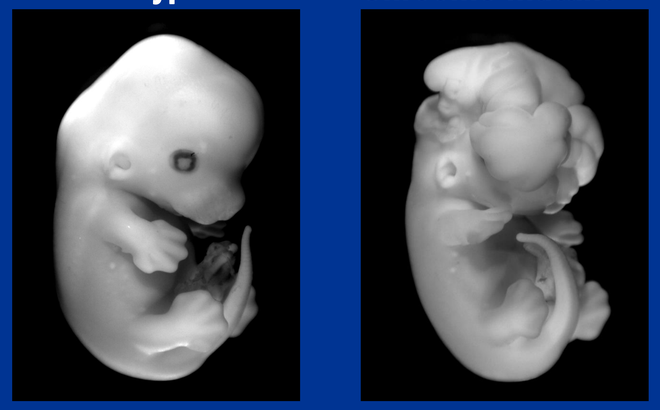
Context

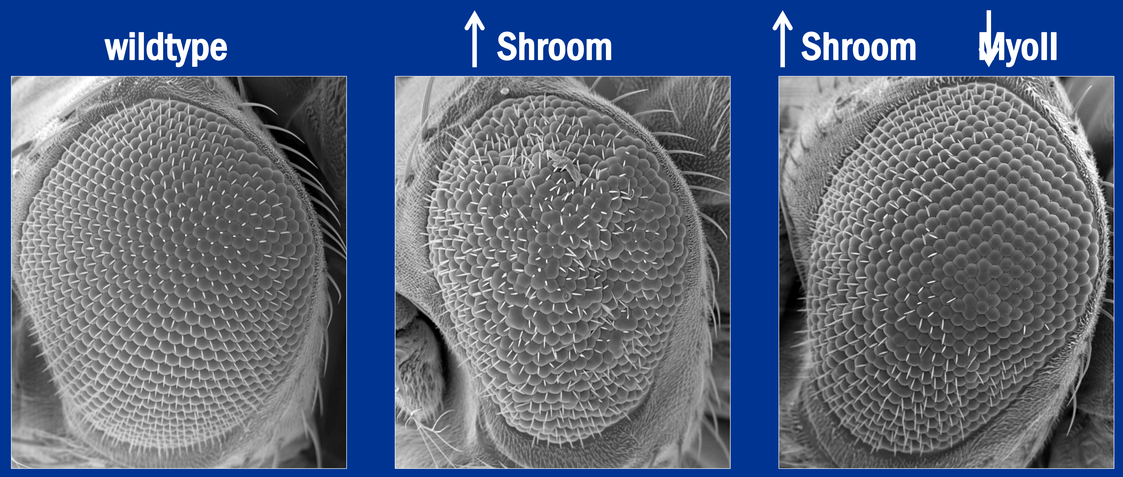
Previous efforts to identify new pathway components in mammalian systems are limited by redundancy and methodology.

These issues can be circumvented in *Drosophila* as they have a simple genome and defects in cell architecture in the embryo/larva are easily observed in adult tissues.

University of Pittsburgh

Identifying the determinants of **cell architecture** as a method to understand the mechanisms of **tissue morphology** and **function**.

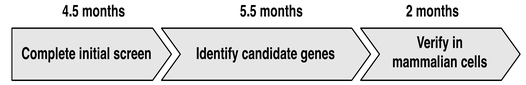




Project Deliverables

This research plan can be divided into three phases, each representing a project milestone, with a timeline below.

- Initial screening
- gene identification
- verification of functional conservation in mammalian cells



This works should provide a comprehensive network of proteins and pathways that participate in regulating cell architecture. This will allow for hypothesis-driven approaches to understanding the molecular and mechanical basis for tissue morphogenesis.

This work will be foundational for applications external funding agencies. These will focus on understanding how the Shroom pathway and other pathways may be integrated to control tissue morphology. This collaborative research would utilize cell biology, biochemistry, and biophysics to specifically define how proteins in these pathways may interact and would focus to elucidate protein-protein interactions, subcellular distributions, and combined influences on cell behaviors.

Significance and Justification

The importance of cell mechanics in human disease has only recently come to light. Shroom3 was one of the first proteins shown to regulate a mammalian developmental process by controlling cell contractility. The ability of cells in tissues to control their individual and collective architecture is a fundamental property of embryonic development and adult homeostasis, and errors in these processes result in birth defects and disease. Understanding how cells interpret intercellular cues to execute changes in cell architecture could be a way to prevent such defects and disease. In addition, the ability to harness these pathways could benefit the areas of tissue engineering and stem cell biology. This project leverages the power of large-scale genetic analysis to identify the pathways that cells use to control tissue morphogenesis during development and employs methods that allow for the transition into mammalian model systems to verify relevance to human disease.

References

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