Universität Basel

Research Project

Investigating organ patterning and growth by the Dpp/BMP morphogen gradient using novel synthetic receptors

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Project title Investigating organ patterning and growth by the Dpp/BMP morphogen gradient using novel synthetic receptors
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Cell-cell communication in developing organs is critical to acquire proper cell fate and organ size. It is therefore not surprising that defects in such communications cause birth defects or disease such as cancer. Despite its importance, it remains largely unknown how cells communicate with each other to build our functional organs. A class of molecules that mediates cell-cell communication during development is called “morphogens”. Morphogens are diffusible molecules that disperse and form a concentration gradient in developing organs to control patterning and growth. For over 20 years, organ development of Drosophila melanogaster has served as a leading model to study the organ development through morphogens. Decapentaplegic (Dpp), a Bone morphogenetic protein (BMP) type ligand in flies, represents the first validated secreted morphogens to control patterning and growth of wing imaginal disc (wing precursor tissue). Previous studies have identified Dpp signaling components, downstream target genes, factors required for Dpp morphogen gradient formation. Recent studies combine mathematical approaches to model how these identified factors work together as a system to build organs. However, these bottom-up approaches are still far from understanding how morphogen acts. Therefore, in this proposal, I would like to take an alternative top-down approach to directly and acutely manipulate the endogenous Dpp morphogen gradient at the protein level. Keys to achieving this goal are protein binders such as nanobodies or DARPins (Designed Ankyrin Repeat Proteins) with strong binding affinity against their targets like antibodies. Unlike conventional antibodies, protein binders function as single domain proteins. Therefore, protein binders can be expressed and functionalized in the cells by fusing them with a functional domain of other proteins. Recently, I generated (1) a robust genome engineering platform to insert a tag or introduce mutations in the endogenous dpp gene, and (2) novel synthetic trap system consisting of protein binders (scFv, nanobodies, DARPins) fused to the transmembrane domain of CD8 to trap Dpp on the cell surface. By combining these novel tools, it is now possible to visualize and directly manipulate endogenous Dpp morphogen gradient at the protein level.Using these novel tools, I will ask the following specific questions:(1) What is the spatial and temporal requirement of Dpp dispersal for patterning and growth of wing disc?(2) What is the mechanism of Dpp gradient formation (exocytosis, dispersal, and endocytosis)(3) What is the mechanism of scaling of the Dpp morphogen gradient with tissue size?Direct manipulation of morphogen gradient using the synthetic receptors would allow me to distinguish between a variety of models proposed for how Dpp acts as a morphogen to control organ development. Furthermore, I am open to see unexpected results that require changing our current understanding of morphogen function. Since a variety of evolutionarily conserved signaling pathways have been repeatedly used as morphogens during development, my approach would give technological

and biological impact to study cell-cell communications in general. Given recent attempts reconstructing functional human organs in vitro, our approaches should also be applicable to investigate how human organs develop and how defects in cell-cell communications lead to malformations and diseases.

Keywords Morphogen; Dpp/BMP; patterning; growth; scFv; DARPins; Drosophila; nanobody
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