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Review

Sizing it up: The mechanical feedback hypothesis of organ growth regulation

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ABSTRACT

The question of how the physical dimensions of animal organs are specified has long fascinated both experimentalists and computational scientists working in the field of developmental biology. Research over the last few decades has identified many of the genes and signaling pathways involved in organizing the emergent multi-scale features of growth and homeostasis. However, an integrated model of organ growth regulation is still unrealized due to the numerous feedback control loops found within and between intercellular signaling pathways as well as a lack of understanding of the exact role of mechanotransduction. Here, we review several computational and experimental studies that have investigated the mechanical feedback hypothesis of organ growth control, which postulates that mechanical forces are important for regulating the termination of growth and hence the final physical dimensions of organs. In particular, we highlight selected computational studies that have focused on the regulation of growth of the *Drosophila* wing imaginal disc. In many ways, these computational and theoretical approaches continue to guide experimental inquiry. We demonstrate using several examples how future progress in dissecting the crosstalk between the genetic and biophysical mechanisms controlling organ growth might depend on the close coupling between computational and experimental approaches, as well as comparison of growth control mechanisms in other systems.

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1. Introduction

1.1. The questions of organ size control

Size control at the level of both organs and organisms has long fascinated biologists due to the large variation of sizes in the animal kingdom and the medical importance of growth control in many diseases such as cancer and genetic birth defects. Early work exemplified by D'Arcy Thompson's treatise "On growth and form" focused on biophysical principles of morphogenesis [1]. The last few decades have witnessed significant advances in identifying biochemical signaling pathways involved in growth control regulation, but an integrated, holistic view of how information on the physical dimensions of tissues is transduced by biochemical signaling pathways to regulate cell growth and homeostasis is still lacking [2]. The question of size control has been approached from multiple angles: physiology, genetics, developmental biology, biophysics, and mathematical and computational modeling [3–13]. Computational studies play a role not only in better understanding mechanisms of development but also in integrating information between different biochemical and biophysical phenomena into an unified, predictive model [14,15].

Computational modeling has played a significant role in experimental inquiry through the development, refinement and testing of the mechanical feedback hypothesis, which postulates that mechanical forces play an important role in coordinating growth between cells within tissues and as well as modulating instructive inputs from growth factors and morphogens. This hypothesis views mechanical forces not merely as physical constraints, but also as information-providing regulatory inputs into the calculations performed by cells during development. Despite the appreciation of mechanical stress as an integral factor controlling tissue size and an expanding understanding of the gene regulatory networks that control growth [16–21], decisive experimental tests are still needed to elucidate how the signaling mechanisms integrate mechanical constraints with biochemical signals in specific organs. Here, we focus on a select set of computational and experimental studies that have helped shape the mechanical feedback hypothesis of organ growth. Our discussion centers on the particular context of *Drosophila* wing disc development, which has served as a paradigm for growth control research.

1.2. Wing discs as a model organ for growth control

Our understanding of size control at the level of individual organs or the whole body is most highly advanced in the "golden insect" *Drosophila melanogaster* [22]. While the developmental specifics for a particular organ are unique, there is an overarching conservation of signaling pathways and regulatory mechanisms that are informative toward human development and disease ontogenesis [23–26].

The adult wings of *Drosophila* are derived from imaginal discs that are specified during embryogenesis and proliferate throughout larval development (also called the imago stage) to expand from approximately 50 to 50,000 cells, a thousand-fold increase, over the course of five days (Fig. 1A and B). This developmental period covers three sequential instars or moltings that occur during larval development [27–29]. The wing imaginal disc consists of an epithelial monolayer sac with a lumen. As development proceeds, multiple folds form within the monolayer (Fig. 1B–B″). The wing blade is derived from the central oval shaped "pouch" of the wing disc, with the cells in the center of the pouch forming a pseudostratified epithelium of highly packed cells. Above the pouch is a squamous epithelium called the peripodial membrane. Historically, the majority of studies in wing disc growth have focused on the size and shape of the pouch region of the wing disc due to the accessibility of imaging a relatively flat portion of the tissue. The pouch also contains the morphogenetic center of the wing disc.

Organ size regulation depends on both intrinsic and extrinsic factors [9]. Intrinsic growth control is the inherent ability of organs within the body to regulate final size based on its genetic program, which each individual cell within the organ contains. In general, it is understood that morphogen signaling pathways are "master architects" coordinating patterning and growth in developing organs [30]. Extrinsic growth control is the influence of systemic signals – hormones and nutrients – on organ development. For example, Insulin Receptor (InR) signaling and the target of rapamycin (TOR) pathways are essential regulators of growth rate and duration. These pathways communicate the nutrient status of the animal and couple nutrition to growth [7,31–33]. Additionally, extrinsic mechanical forces from neighboring tissues can also potentially provide input into the growth potential of the organ. Outstanding questions in the growth control field include the mechanism of size regulation by each modality (intrinsic and extrinsic). Interorgan communication can play an important role in the size control of wing discs [5,34–36]. However, potential crosstalk between intrinsic and extrinsic growth control modalities has not been approached to any significant degree using computational approaches to date [9].

2. Overview of chemical factors regulating growth

Several intercellular signaling pathways impact growth in the *Drosophila* wing disc, including Decapentaplegic (DPP, a TGFβ family member), Wingless (WG)/WNT, Notch, EGFR and Fat-Dachsous (which provides input into the Hippo pathway) [10,37–46]. In particular, DPP and WG belong to a class of molecules called morphogens that are locally secreted and transported across the tissue to regulate growth and the spatial pattern of transcriptional activity and cellular differentiation. These two morphogens define a coordinate axis for the wing with DPP patterning the anterior–posterior (AP) and WG patterning the dorsal–ventral axis (DV) and jointly provide input into the Dachsous/Fat/Hippo signaling pathway (Fig. 1B) [43,47]. Studies in the wing disc have played an important role in establishing the role of morphogen protein gradients in regulating pattern formation and organ size [30,48], which is covered in greater detail by several recent reviews [10,30,37,49]. How cells convert morphogen concentration gradients into the observed spatially uniform pattern of proliferation remains unclear and several competing models have been proposed.

Secreted morphogens have been implicated genetically in growth control, including Wingless (WG), Decapentaplegic (DPP) and Hedgehog (HH). For example, the morphogen DPP is crucial in the size regulation of a developing wing imaginal disc of *Drosophila* along the AP axis. Experiments have shown that insufficient DPP hinders growth, while over expression increases the size significantly [50–54]. The distribution of DPP is inhomogeneous throughout the wing disc, yet cell proliferation is uniform throughout the organ during later stages of growth [55,56]. An important criteria for a successful model of growth regulation must explain how non-uniform signaling by an inductive signaling gradient results in the observed uniform growth across the tissue [57]. Whether, and how, morphogen gradients are required in growth regulation, however, has become less clear with the finding that intercellular transport of Wingless is not absolutely required [58]. Other intercellular pathways such as Notch (N), Epidermal Growth Factor (EGFR), and Fat-Dachsous/Hippo signaling are also implicated in the regulation of organ growth [42,45,47,59–63]. The complexity of the signaling network therefore demands continually refined computational approaches to capture emergent properties of the regulatory system. Notably, however, recent quantification

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