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Model for the regulation of size in the wing imaginal disc of *Drosophila*

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Abstract

For animal development it is necessary that organs stop growing after they reach a certain size. However, it is still largely unknown how this termination of growth is regulated. The wing imaginal disc of *Drosophila* serves as a commonly used model system to study the regulation of growth. Paradoxically, it has been observed that growth occurs uniformly throughout the disc, even though Decapentaplegic (Dpp), a key inducer of growth, forms a gradient. Here, we present a model for the control of growth in the wing imaginal disc, which can account for the uniform occurrence and termination of growth. A central feature of the model is that net growth is not only regulated by growth factors, but by mechanical forces as well. According to the model, growth factors like Dpp induce growth in the center of the disc, which subsequently causes a tangential stretching of surrounding peripheral regions. Above a certain threshold, this stretching stimulates growth in these peripheral regions. Since the stretching is not completely compensated for by the induced growth, the peripheral regions will compress the center of the disc, leading to an inhibition of growth in the center. The larger the disc, the stronger this compression becomes and hence the stronger the inhibiting effect. Growth ceases when the growth factors can no longer overcome this inhibition. With numerical simulations we show that the model indeed yields uniform growth. Furthermore, the model can also account for other experimental data on growth in the wing disc.

Keywords: Organ size; Growth control; Wing disc; *Drosophila*; Dpp; Mechanical forces; Computer simulations

1. Introduction

During development it is crucial that growth ceases when tissues or organs have attained a certain form and size. However, the regulation of final tissue size is poorly understood. Because of its relatively simple structure and its accessibility for genetic manipulations, the wing imaginal disc of *Drosophila* has widely been used as a model system to study the regulation of growth. Genes that appear to be crucial for its regulation, have also been found to be expressed during development in other tissues in other organisms, raising the possibility that common mechanisms are employed in different species. Despite extensive experimental investigation of the imaginal discs, mechanisms underlying the determination of size remain elusive. Therefore, there is a need for models, which can explain the available data and possibly even inspire entirely novel experimental approaches.

Drosophila imaginal discs are epithelial structures that give rise to the adult body structures. The wing disc contains about 30 cells at the beginning of the first instar larva and reaches at metamorphosis, almost 4 days later, a number of about 50,000 cells (Milan et al., 1996b). The adult wing is produced by the eversion of the wing disc. Upon eversion, intervein regions divide once. Vein and intervein cells undergo two mitotic rounds, but only one full cell cycle (Milan et al., 1996a). Therefore, the size of the adult wing is largely predetermined by the final size of the wing

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disc (Day and Lawrence, 2000). Wing disc size seems to be mostly regulated disc autonomously, since transplantation of early discs into the abdomen of adult flies results in discs with normal size (Bryant and Levinson, 1985; Jursnich et al., 1990).

Decapentaplegic (Dpp) plays an important role in regulating growth in the wing disc. In *dpp* mutants the wings are reduced to small stumps whereas overexpression of *dpp* leads to larger wing discs (Burke and Basler, 1996; Capdevila and Guerrero, 1994; Lecuit et al., 1996; Posakony et al., 1990). *dpp* is expressed in a narrow stripe of anterior cells adjacent to the anteroposterior compartment boundary (Basler and Struhl, 1994; Posakony et al., 1990; Tabata and Kornberg, 1994) and forms a gradient in anterior and posterior directions (Entchev et al., 2000; Teleman and Cohen, 2000) (Fig. 1). Because of the growth promoting effect of Dpp, it may be expected that growth preferentially occurs where Dpp activity is highest. However, as judged by the occurrence of cell proliferation, this is not the case and growth occurs roughly uniformly throughout the disc (Milan et al., 1996b).

Several models have been formulated for the regulation of size (Day and Lawrence, 2000; Garcia-Bellido and Garcia-Bellido, 1998; Nijhout, 2003). To our knowledge, the gradient model of Lawrence and Day is the only model that explicitly takes into account a role for a centrally produced growth factor gradient in the wing disc (Day and Lawrence, 2000). In its simplest form, the model proposes that the high Dpp level in the center and the low Dpp levels at the ends of the disc are fixed. Growth anywhere in the disc extends the gradient and thus reduces its rake. Cells

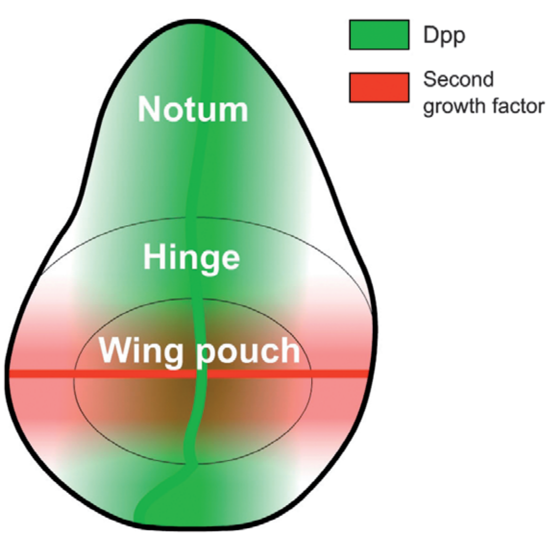

Fig. 1. Different regions of the wing imaginal disc. Dpp is produced in a stripe adjacent to the anteroposterior boundary and forms a gradient. According to the model, a second growth factor gradient is formed perpendicular to the Dpp gradient and the presence of both growth factors is required to induce growth. Then, the distribution of net growth factor activity resembles a tent, with highest activity in the center of the disc and lowest activity at the edges. Our model does not include growth in the notum.

only grow when the local Dpp gradient is sufficiently steep and therefore cell proliferation ceases when the local steepness falls below a threshold (Day and Lawrence, 2000). This model predicts that growth does not occur in a disc with homogeneous Dpp signaling, since the Dpp slope is near zero in such discs. However, considerable growth has been observed in wing discs with homogeneous Dpp signaling (Martin-Castellanos and Edgar, 2002; Nellen et al., 1996), thus contradicting the gradient model in the case of the wing disc. There are several other models available to account for uniform growth in the presence of a Dpp gradient (Gibson et al., 2002; Rogulja and Irvine, 2005; Serrano and O'Farrell, 1997; Shraiman, 2005), but none of them explicitly considers final disc size as well.

Here, we formulate a new model for the regulation of size in the wing imaginal disc, which can simultaneously account for the observed homogeneous growth in the presence of a Dpp gradient as well as alterations of growth caused by experimental interventions.

2. Results and discussion

2.1. The model

There are a number of biological assumptions underlying the model. First and most fundamentally, it is assumed that net growth is not solely regulated by growth factors, such as Dpp, but by mechanical forces as well. In particular, it is posited that compression within the plane of the wing disc inhibits net growth and that stretching stimulates it. Note that the term net growth here denotes increase in epithelial surface area, and does not distinguish between changes in average cell size and changes in cell number. A second important assumption constitutes the presence of another growth factor, which forms an activity gradient perpendicular to that of Dpp, i.e. its activity is highest at the dorsoventral boundary (Fig. 1). Growth is induced if both Dpp and the second growth factor are present. This implies that the net growth factor activity is highest in the center of the wing disc and lowest in the peripheral regions. Third, it is assumed that the Dpp activity gradient and that of the other growth factor are scaled, i.e. that they adjust to changes in wing disc size during growth. Fourth, the model assumes that there is no growth when growth factor levels as well as stretching are too low. Lastly, stretching is assumed to only induce growth above a certain threshold. For the model as presented below, this is equivalent to a stimulation of growth above a certain cell elongation threshold.

Qualitatively, the model can be described as follows: at a very early stage of wing disc development, Dpp and the second growth factor are present, but mechanical stress has not yet evolved. In the center, growth will be induced by the combined high activity of Dpp and the second growth factor. In contrast, growth will not be induced in the more peripheral regions, because of lack of stimulation by either growth factors or mechanical forces (Fig. 2a and b).