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Orchestrating size and shape during morphogenesis

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Living organisms exhibit tremendous diversity, evident in the large repertoire of forms and considerable size range. Scientists have discovered that conserved mechanisms control the development of all organisms. *Drosophila* has proved to be a particularly powerful model system with which to identify the signalling pathways that organize tissue patterns. More recently, much has been learned about the control of tissue growth, tissue shape and their coordination at the cellular and tissue levels. New models integrate how specific signals and mechanical forces shape tissues and may also control their size.

Questions such as how can groups of cells make up organized tissues, organs and bodies, how can development produce organisms with reproducible morphological patterns, and what mechanisms underlie the diversity of organ size and shape (Fig. 1) have haunted scientists for over a century. From the early observations of embryology to the quantitative models of systems biology, important discoveries marked the long history of morphogenesis.

Drosophila has proven to be a powerful system with which to elucidate the molecular mechanisms of morphogenesis, identifying the signals that pattern the body plan and characterizing cell mechanics and dynamics underling tissue remodelling. A principal challenge is to understand within a single mechanistic framework how these patterning signals and cellular responses—such as cell division and cell shape changes—are coordinated in tissue growth and tissue remodelling.

The size and shape of genetically marked clones of cells reflect in miniature the size and shape of the tissue they belong to. Cell division, cell death, cell shape changes and cell rearrangements are the building blocks on which tissues are shaped and organs are made (Fig. 2). The orchestration of these elementary processes depends on a constraining genetic programme operating on cell behaviour: for instance, a specific set of signalling molecules, growth factors, promote cell divisions and tissue size, whereas other proteins control the orientation of cell divisions, oriented cell rearrangements and so on, and hence tissue shape. A surveillance mechanism orchestrates proper tissue size and shape and involves reciprocal interactions between the cell and tissue scales. When a group of cells dies, compensatory mechanisms controlled at the tissue level ensure that the proper tissue size and shape are not compromised.

The aim of this review is to highlight recent important findings on the mechanisms of tissue growth and shape and to encapsulate them

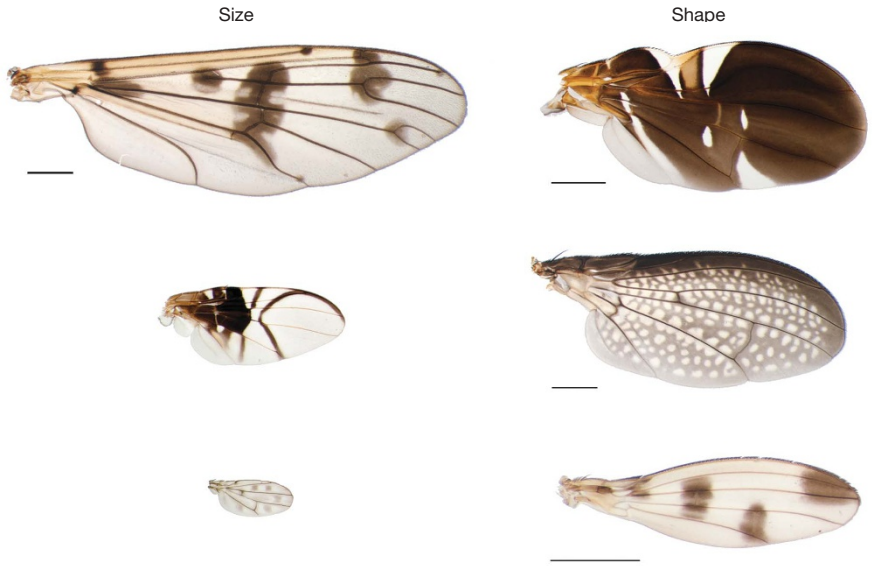

Figure 1 | Diversity of size and shape of organs during morphogenesis. Wings of dipterans illustrate marked differences in the size and shape of organs. Variations in wing length can almost reach tenfold (left). The width-to-length ratio can also vary significantly (right). Scale bar, 1 mm. (Images are courtesy of N. Gompel and B. Prud'homme.)

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in a single framework of morphogenesis. We first focus on how cell division and cell death control tissue growth. We then detail how the mechanics of cell shape and division underlie tissue shape. Finally, we discuss how feedback mechanisms may orchestrate tissue size and shape.

Tissue growth: to die, to survive, to divide

Tissue growth can be best studied in the *Drosophila* developing adult tissues called imaginal discs. Imaginal discs are epithelial layers growing from about 40 cells to 50,000 cells in 4 days of continued divisions. Although this massive increase in cell number and tissue mass is under organismal control as far as the provision of the necessary energy input is concerned, the control of tissue size is intrinsic to the disc. Proper tissue size is not reached by counting cells: changes in cell size often yield compensatory modifications in cell number, thereby maintaining tissue size[1,2]. This suggests that tissue dimensions (size or mass) may be measured.

Cell competition and apoptosis. Tissue-level control of tissue size is manifest in the process of cell competition discovered 30 yr ago[3,4], whereby faster growing cells can out-compete slow-growing cells (Fig. 2c). For example, wild-type clones can take over entire compartments initially occupied by slow-growing cells heterozygous for the *Minute* (*M*) mutations in genes encoding ribosomal proteins. Myc is another major regulator of cell competition, with as little as twofold changes in Myc expression being enough to trigger overgrowth of cells and competition with surrounding wild-type cells[5,6]. The cellular mechanisms underlying competition are only starting to be unravelled. To some extent, fast cells may compete with slow cells for limited amount of survival signals provided by the transforming growth factor (TGF)-β/BMP (bone morphogenetic protein) molecule Decapentaplegic (Dpp)[7]. There is no consensus, however, on the exact importance of Dpp in the competition process[5,6]. Competition also involves apoptotic elimination of the slow cells and their engulfment by the fast-growing cells[8]. The stress-response pathway mediated by Jun N-terminal kinase (JNK)[7] and the pro-apoptotic genes *hid* (also called *Wrinkled*) and *rpr*[5,6] were shown to be involved in the apoptosis of the out-competed cells. The link between cell competition and tissue size is manifest in the following set of experiments: uniform expression of *myc*, where no competition occurs, causes tissue overgrowth, whereas mosaic expression of *myc*, which triggers competition, leaves size unchanged, indicating that the out-competed cells buffer the overgrowth of *myc*-overexpressing cells. Consistent with this, mosaic expression of *myc* results in tissue overgrowth when cell competition is reduced by blocking apoptosis. Another notable observation indicates that cell competition in a wild-type tissue buffers variations in tissue size[5].

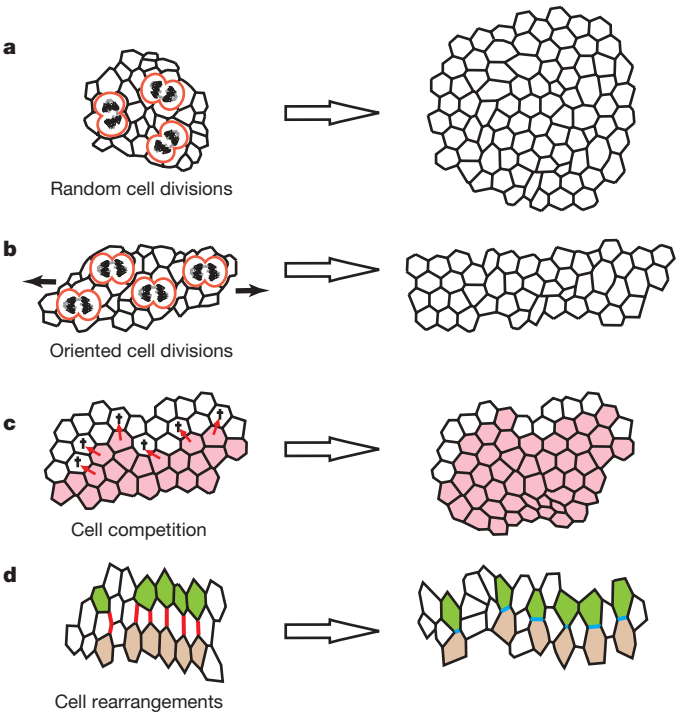

Figure 2 | Cellular mechanisms of tissue size and shape. a, Tissue proliferation and the increase in tissue mass are driven by continuous cell divisions (outlined in red). **b**, Oriented cell divisions, here along the horizontal axis, cause the elongated growth of the clone and of the organ. **c**, Cell competition is the process by which a fast-growing population (red) out-competes a slow-growing one (white). Out-competed cells die by apoptosis (cross symbol). This process is implicated in tissue size regulation. **d**, Cell rearrangements such as intercalation drive tissue elongation and affect tissue shape. Here the red interfaces shrink and new horizontal interfaces (blue) are formed, producing an exchange in cell neighbours.

Control of cell division. Control of tissue size also involves a regulation of cell division. Two remarkable properties of cell division in imaginal discs are that it is random but uniform across the discs and that it ceases uniformly when correct disc proportions are attained. Two models have been proposed to explain scale invariance in growing tissues. One model emphasizes the role of local communications between cells with different positional values to drive intercalary growth[9]. These communications could be mediated by the cell adhesion molecule Fat, an activator of the Hippo pathway that controls cell proliferation (reviewed in ref. 10). Alternatively, long-range signalling by extracellular morphogens is viewed as the principal determinant of growth[11]. Morphogens are molecules that form gradients of concentration from a source and activate different target genes at different concentration thresholds. The morphogen Dpp controls tissue pattern[12,13] and tissue growth[14,15]. Day and Lawrence[11] proposed that the slope of the gradient promotes cell division above a certain threshold. Provided that the addition of new cells decreases the slope of the gradient, growth would arrest when the gradient becomes too shallow (Fig. 2). Consistent with this, it was elegantly shown that cell division is transiently induced in regions where the slope of the Dpp gradient is experimentally modified[16]. Several observations, however, contradict a simple formulation of this model: (1) uniform Dpp expression causes overgrowth; (2) the assumption that the Dpp ligand gradient scales with the tissue is not experimentally supported[17,18]; (3) the model fails to account for uniform cell division in the tissue. Thus, additional mechanisms will be required to explain fully the control of tissue size. As detailed below, the mechanical constraints imposed by tissue growth on local cell division can also be considered in parallel with signalling.

Whereas an increase in cell number drives tissue growth, tissue shape involves changes in cell positions controlled by cell rearrangements and the orientation of cell division.

Tissue shape: orienting cell division and movements

Spatial control of cell divisions. A number of mechanisms have been proposed for tissue elongation. It was suggested a long time ago that polarized cell divisions might be important for morphogenesis in *Drosophila*[19] (Fig. 1a, b). However, the major role of polarized cell rearrangements during cell intercalation in vertebrates and invertebrates (see below) overshadowed this mechanism. As a result, experimental evidence that polarized cell division also has an essential role in plant and animal morphogenesis only accumulated recently[20–26], with striking examples in *Antirrhinum* petal morphogenesis[21] and zebrafish neurulation[24]. In *Drosophila* too, polarized cell divisions occur and participate in tissue morphogenesis. A detailed analysis of *Drosophila* imaginal discs showed, for example, that clones of cells grow anisotropically along the axis of tissue growth because cell divisions are biased along the proximal/distal axis[22]. Elongation of *Drosophila* embryonic epithelia is also controlled to some extent by oriented cell divisions[26].

What controls the orientation of cell division? Several components of the planar cell polarity pathway (PCP)—that orient other processes such as hairs and cilia—have been implicated. For instance, the cell adhesion molecules Dachsous and Fat, which orient PCP signalling, are required in the *Drosophila* wing[22]. However, core components of PCP signalling (for example, Dishevelled, Frizzled) have not been implicated in polarized cell division in the *Drosophila* wing. Note, however, that Frizzled controls orientation of the mitotic spindle during division of the sensory organ precursor in the *Drosophila* notum[27]. Moreover, PCP signalling controls polarized cell divisions in vertebrates. The search for signals controlling oriented cell divisions is thus still ongoing in *Drosophila* and other organisms.

Cell division and cell shape. Changes in cell shape have also been proposed to drive tissue extension. In an epithelial layer cells adopt characteristic polygonal shapes dictated largely by the interplay between adhesion and cortical tension[28]. Cell adhesion mediated by cadherins tends to increase cell contacts whereas cortical tension exerted by the actomyosin network reduces them. This is remarkably illustrated in post-mitotic tissues, such as the pupal *Drosophila* retina, where differential adhesion mediated by E- and N-cadherin controls the shape of cone cells[29]. In pupae, wing cells remodel their irregular contacts to produce a highly ordered hexagonal tiling by a mechanism implicating E-cadherin trafficking and PCP signalling[30]. In remodelling epithelia, cells may change shape markedly. Epithelial cell elongation accompanies several tissue extension processes such as *Drosophila* dorsal closure[31] and imaginal discs evagination[32]. The underlying mechanisms remain unclear.

What is the effect of cell division on cell shape? During division epithelial cells exhibit a rounder (less polygonal) morphology, but live imaging has shown that cell contacts are not remodelled and daughter cells remain in contact[33]. This explains the old observation that clones remain compact in imaginal discs. Defects in the even distribution of E-cadherin after cell division lead to a disruption of cell contacts and to cell scattering[34]. Remarkably few constraints on the process of cell division (such as the production of two new vertices at each round of mitosis) conspire to produce a single topological equilibrium with a majority of hexagons[33,35], without assumptions on the mechanics of cell shape[28]. Heterogeneities in the rate of cell division locally affect the distribution of cell shape.

Thus, the shape of cells in a growing tissue is influenced by cell surface mechanics and by local cell division rates.

Cell rearrangements and intercalation. Another major mechanism driving tissue extension is cell intercalation, whereby cells change position by remodelling their adhesive contacts. The evagination of pupal imaginal wing and leg discs, for instance, was proposed early on to stem from changes in the organization of cell contacts[32]. Intercalation has been carefully studied during elongation of the embryo, called germband elongation[36,37] (Fig. 2d). In this system, contacts between anteroposterior neighbours shrink (Fig. 2d, red) and new contacts are formed at a perpendicular axis (Fig. 2d, blue). This process does not depend on external forces exerted at tissue boundaries, but on the local increase in cortical tension imposed by the enrichment of Myosin-II at shrinking junctions[36]. Adhesion is also probably downregulated, as Bazooka (also called Par-3)[38]—a determinant of E-cadherin stabilization[39,40]—and E-cadherin[37] are downregulated in shrinking junctions. Planar junction remodelling and intercalation are controlled by embryonic polarity[36,38,41]. Surprisingly, the non-canonical Wnt PCP pathway is not required for cell intercalation during germband extension. The signals orienting cell rearrangements remain elusive.

The proper shaping of a growing organ thus requires that, as new cells are formed, their relative positions be controlled. This is achieved by regulation of the cell division orientation and of cell rearrangements. Cell division itself and cell mechanics thus underlie important aspects of tissue shaping. A complete understanding of the coordination of tissue size and shape must integrate the regulation of tissue growth by signalling pathways with the mechanics and dynamics of morphogenesis at the cellular level.

Feedback mechanisms coordinating size and shape

Cell division and cell growth drive tissue expansion. Yet, attaining the proper tissue size and shape does not simply rely on cell counting. Thus, a tissue-intrinsic property informs, in return, dividing cells about their division rate, growth or eventual death. Such a feedback mechanism is required to understand growth arrest and tissue shape. Stochastic fluctuations or persistent variations in growth rate could produce changes of an internal variable (for example, pressure or Dpp activity) that would, in return, affect growth rate. An inhibitory negative feedback signal can have a stabilizing effect, smoothening fluctuations and providing the system with a dynamic control to ensure homogeneous growth.

What mechanisms could generate a feedback? Two plausible alternatives have been proposed. Local regulation of the morphogen-ligand or activity gradient might be a way. Regions of enhanced growth could locally reduce the slope of the Dpp gradient, and hence feed back on growth (Fig. 3a). Quantitative analysis of the

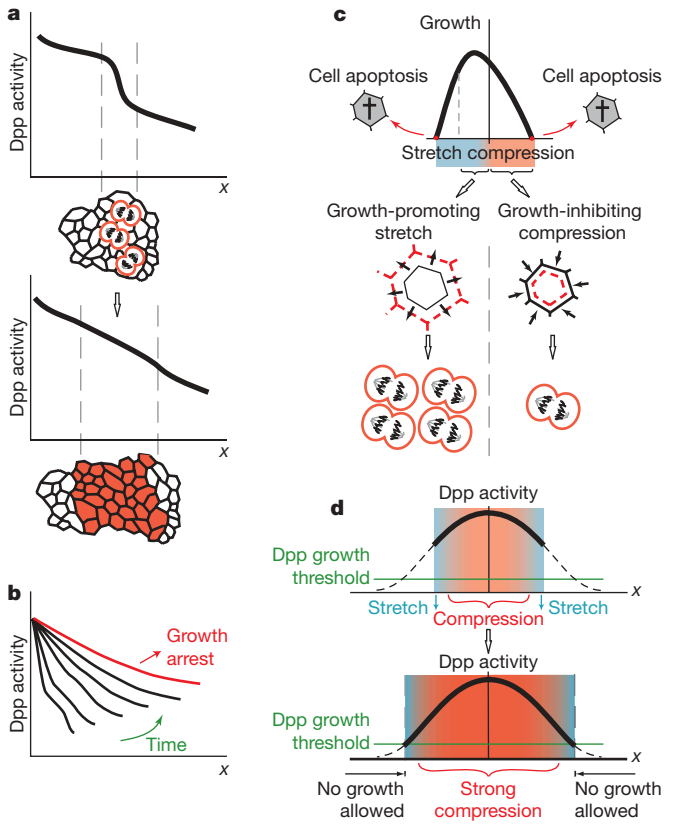

Figure 3 | Models of size control by feedback. **a**, **b**, Gradient model. **a**, A spatial gradient in Dpp signalling controls growth by promoting cell divisions. A local increase in the slope of the gradient (between dashed lines) would locally stimulate increased proliferation (outlined in red in the schematic diagram of epithelium), resulting (below) in the insertion of new cells and tissue expansion. The model proposes that growth changes the local slope of the gradient and thereby feeds back on the activity profile of the morphogen gradient. **b**, Evolution of the morphogen activity (not necessarily the ligand) gradient profile: as the tissue grows, the Dpp activity gradient scales with the tissue. Growth arrest is triggered when the gradient becomes too flat. **c**, **d**, Mechanical feedback model. **c**, Growth is proposed to be influenced by mechanical forces, with compression (in red) inhibiting cell division and mild stretch (blue) promoting it. Above extreme stretch or compression, cells die by apoptosis. This mechanical feedback explains uniform cell divisions in a growing tissue. **d**, The combination of this mechanical feedback and the graded growth-promoting function of the Dpp gradient above a threshold value (green) explains uniform growth and homogeneous growth arrest. Cells at the periphery stop dividing when, as a result of growth, they fall below this threshold Dpp activity. Simultaneously, cells in the centre no longer divide because of the increased compression (dark red) imposed onto them by cell division arrest at the periphery. *x* indicates spatial coordinates.

establishment of the Dpp ligand gradient[18,42,43] showed that it forms on short timescales (minutes) not commensurate with the long timescales (hours) of tissue growth, consistent with the fact that the ligand gradient does not scale with the tissue[17]. However, the activity gradient (monitored by phosphorylated Mad or expression of target genes) is clearly influenced by the local tissue growth[43]. Further tests of this model will thus require a better characterization of the temporal lag between ligand and activity gradients and of the effect of growth on the latter.

The interplay between cell mechanics and the cell cycle[44,45] is another potential way to provide dynamic regulation of tissue growth, as recently suggested in the *Drosophila* ovary[46]. Indeed, an inhibition of growth by mechanical compression (and stimulation by stretch, Fig. 3c) would provide a negative feedback to reprehend heterogeneities of growth. Using quantitative modelling, Shraiman proposed that mechanical feedback could account for the uniformity of cell division[47]. Moreover, combining mechanical feedback with the growth-promoting function of a non-scaling Dpp gradient predicts growth arrest and scale invariance[17,48] (Fig. 3d).

This opens up new perspectives and prompts a better integration of the cellular and signalling aspects of morphogenesis in fly and other organisms. A better understanding of the causal relationships between growth and activity gradient dynamics will be important to probe further how morphogens orchestrate size and shape. Whether morphogens also control cell division orientation and cell rearrangements remains an open and major question to investigate. It will also be important to test the mechanical feedback model: do stretch and compression influence cell division and survival? Do fields of forces constrain tissue growth in parallel with growth factors? This mechanical feedback could have other implications on organ shape. It could orient cell division—as was suggested in plants[49]—or cell rearrangements. These important discoveries in *Drosophila* should prompt further studies testing how they apply to size and shape control in mammals.

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