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Single cell pattern formation and transient cytoskeletal arrays

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A major goal of developmental biology is to explain the emergence of pattern in cell layers, tissues and organs. Developmental biologists now accept that reaction diffusion-based mechanisms are broadly employed in developing organisms to direct pattern formation. Here we briefly consider these mechanisms and then apply some of the concepts derived from them to several processes that occur in single cells: wound repair, yeast budding, and cytokinesis. Two conclusions emerge from this analysis: first, there is considerable overlap at the level of general mechanisms between developmental and single cell pattern formation; second, dynamic structures based on the actin cytoskeleton may be far more ordered than is generally recognized.

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Introduction

The enduring focus of developmental biology is the reproducible emergence of organized form out of an apparently formless substrate. By contrast, cell biology tends to consider cells as organized containers populated by persistent machines that accomplish, more or less at steady state, their appointed tasks. In fact, however, nearly all single cells repeatedly undergo transient departures from steady state in a predictable way, and cell biologists increasingly recognize that changes in cell state are often spatially, as well as temporally, patterned. The assembly of the cytokinetic apparatus from a stripe of Rho activity is a pattern formation event just as is the development of an insect segment from a stripe of *even-skipped* expression (Figure 1). Likewise, the formation of segregated cytoskeletal structures around single cell wounds or at the nascent bud of *Saccharomyces cerevisiae* represent pattern formation.

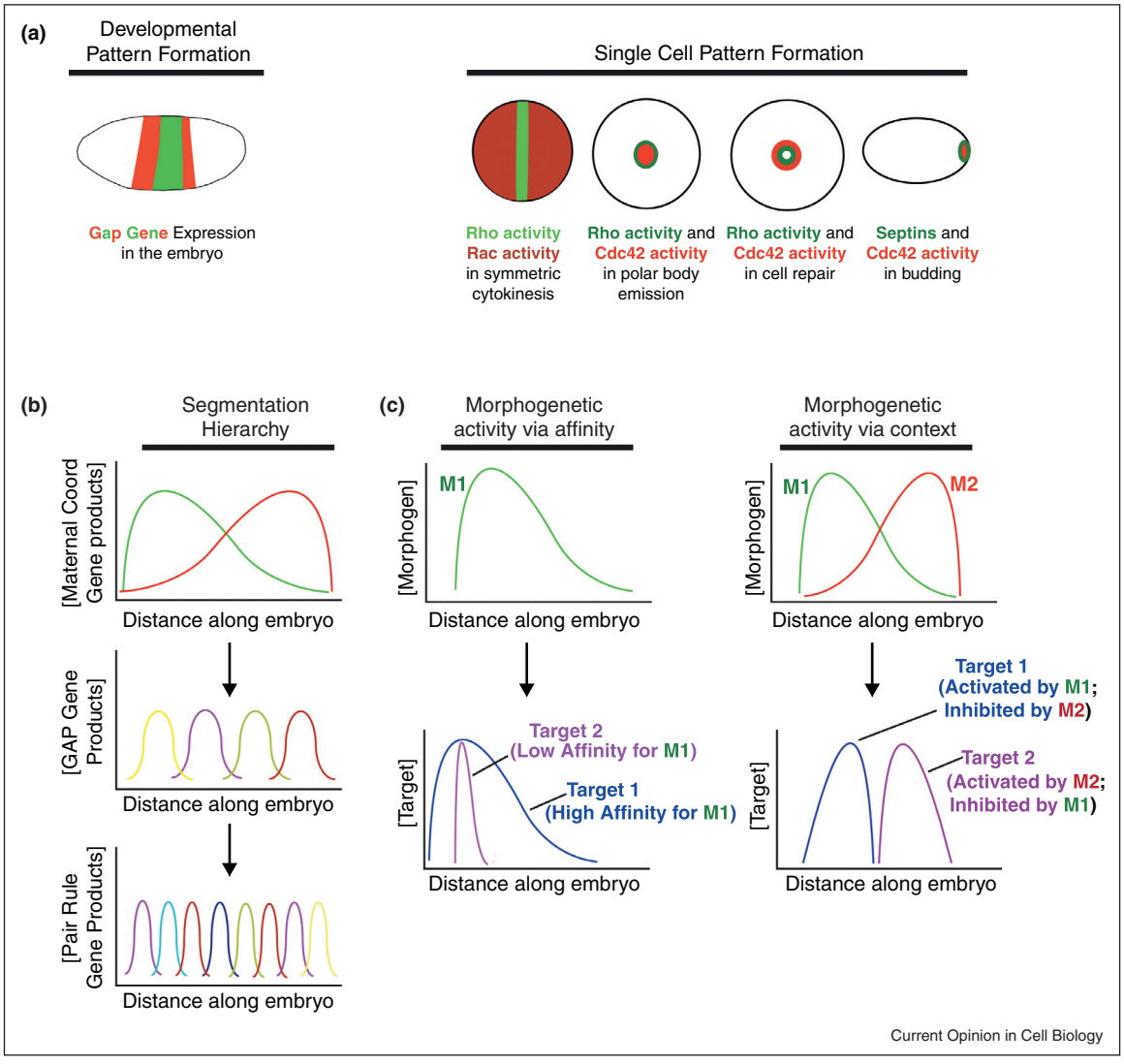
There are obvious differences between pattern formation in developing tissues and in single cells. Much developmental pattern formation is controlled by spatial differences in transcription compartmentalized within cell membranes, a strategy obviously impossible in a single cell. Intracellular signaling, meanwhile, often makes heavy use of cytoskeletally mediated advection or convection, which do not feature prominently in developing tissues. Developmental pattern formation is largely predetermined (in animals, at any rate), such that frogs keep developing from frog eggs and flies result from fly eggs, while intracellular structures such as the wound array can — and must be able to — form anywhere within the cell in response to unanticipated stimuli. And, of course, developmental pattern formation is typically far slower, requiring hours, days or more to unfold, rather than seconds or minutes. But these are differences of implementation, not design, and it seems likely that good, robust patterning mechanisms on both scales might have a lot in common. We therefore think it might be useful to view these intracellular processes in roughly the same way that developmental biologists investigate morphogenetic fields in embryos.

Control of developmental pattern formation by morphogen gradients

Developing systems employ several general mechanisms for pattern formation, but conceptually the most important are 'reaction diffusion' mechanisms, in which spatial patterns are created by reactions amongst agents that vary in diffusivity. The credit for this idea goes to Turing who showed that complex patterns could spontaneously arise from simple chemical reactions among factors he referred to as 'morphogens' ([1]; Box 1). In Turing's formulation, a reaction produces an activator that stimulates its own production over a short length scale. The activator also stimulates the production of an inhibitor that counteracts the activator over a longer length scale. The difference in scales at which these two hypothetical factors work was assumed to result from differences in their diffusivity (Box 1). As anticipated by Turing, it is now clear that much of developmental pattern formation results from differential activation and inhibition of transcription and translation by diffusible factors that operate on various length scales. Although the details do not necessarily conform to the mechanisms proposed by Turing, this is hardly surprising, as his work preceded the discovery of transcription, transcription factors, and translation by many years.

The best understood system of reaction diffusion-based pattern formation is segmentation of the *Drosophila* embryo — ironically, a largely intracellular process — wherein a hierarchy of gradients progressively regionalize

Figure 1



Basic mechanisms underlying developmental and single cell pattern formation. **(a)** Left: schematic showing stripe-like expression of different GAP genes in a *Drosophila* embryo. Each stripe will give rise to subsidiary stripes of gene expression and will ultimately direct the formation of a particular segment of the animal. Right: schematic showing examples of single cell pattern formation. For cytokinesis and wound healing, Rho activity zones are shown in green and Rac or Cdc42 activity zones are shown in red; each zone will specify a different part of the F-actin and myosin-2 arrays that form during cytokinesis and wound repair. For budding septins are shown in green and the Cdc42 patch in red; each directs formation of a different region of the incipient bud. **(b)** Stylized representation of the gene expression hierarchy in *Drosophila* segmentation. Each line represents the gradient of distribution of a particular gene product along the anterior (left)-posterior (right) axis of the embryo. Thus, the maternal coordinate gene product represented by the green line is in a gradient with its peak concentration near the anterior pole of the embryo. The maternal effect gene products form long range gradients that control the expression of the GAP genes, which are expressed in shorter range gradients and which control the expression patterns of the pair rule genes. Ultimately, the hierarchy results in the formation of distinct segments along the anterior-posterior axis of the embryo. **(c)** Schematic representing two proposed mechanisms by which gradients of morphogens act in a qualitative manner. The red and green lines (M1 and M2) represent morphogen gradients; the blue and purple lines (target 1 and target 2) represent targets of the morphogen gradients. In morphogenetic activity via affinity, the low affinity target of M1 is only activated where the concentration of M1 is highest, while the high affinity target of M1 is activated proportionally along the entire M1 gradient. In morphogenetic activity via context, two overlapping morphogen gradients define the activity of targets. The activity of Target 1, which is activated by M1 and inhibited by M2 is confined to a narrow region within the M1 gradient while the activity of Target 2, which is activated by M2 and inhibited by M1 is confined to a narrow region within the M2 peak.

the anterior–posterior axis (Figure 1; [2]). At the top of the hierarchy are the products of the maternal coordinate genes *bicoid* and *nanos*, which are deposited at opposite poles as mRNA and whose protein products form shallow, opposite gradients, with Bicoid concentrated in the anterior and Nanos in the posterior. Bicoid activates transcription of several genes and represses translation of Caudal. *Caudal* is another maternal coordinate gene