CellPress

Review

Developmental Pattern Formation in Phases

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Cells in developing organs undergo a series of changes in their transcriptional state until a complete repertoire of cell types is specified. These changes in cell identity, together with the control of tissue growth, determine the pattern of gene expression in the tissue. Recent studies explore the dynamics of pattern formation during development and provide new insights into the control mechanisms. Changes in morphogen signalling and transcriptional networks control the specification of cell types. This is often followed by a distinct second phase, where pattern is elaborated by tissue growth. Here, we discuss the transitions between distinct phases in pattern formation. We consider the implications of the underlying mechanisms for understanding how reproducible patterns form during development.

Introduction

During embryonic development, pattern formation and tissue growth are inextricably linked. The coordination of pattern and growth is implicitly connected with the property of developing organs to form proportional, reproducible patterns of cell differentiation despite variations in size between individuals of the same species. However, the coordination mechanisms are still not fully understood. This is in part because pattern formation is a highly dynamic process. Gene expression patterns are established over time and often do not change in proportion with the growing tissue size [1–3] (Figure 1). For instance, during limb development, digits are specified one by one [4], yet the pattern and size of digits scale between different-sized adults. Likewise, the dorsoventral proportions of progenitor subtypes in the neural tube continuously change over time and are controlled by different mechanisms at different times of development [3]. This requires us to rethink how the changing proportions and transitions through different phases of pattern formation during development can be reconciled with the **scaling** (see Glossary) of pattern between individuals.

In many tissues, both pattern specification and growth are controlled by morphogens, which are signalling molecules that form concentration gradients in developing tissues [5]. Here, we review progress in understanding the relations between tissue growth and morphogen-mediated pattern formation. We describe the mechanisms underlying the temporal dynamics of morphogen-gradient interpretation and relate these to the control of developmental transitions. Finally, we discuss the implications for understanding how reproducible patterns form during development.

Distinct Phases of Pattern Specification and Growth

Many developing organs go through distinct developmental phases to establish the full repertoire and number of differentiated cell types. In the developing spinal cord, neural progenitors are initially exposed to antiparallel morphogen gradients of Sonic hedgehog (Shh) and Bone morphogenetic protein (BMP)/Wnt secreted from the ventral and dorsal poles, respectively. These morphogens control the formation of 14 transcriptionally distinct neural progenitor

Trends

Patterning proportions in the spinal cord change during development. This occurs in sequential phases, during which proportions are controlled by distinct mechanisms: specification in response to morphogen signalling followed by cell type-specific terminal differentiation.

Mechanisms controlling tissue growth have direct and indirect effects on the establishment and dynamics of pattern.

The dynamics of morphogen signalling are implicated in the transcriptional changes that accompany pattern specification and in the transitions between developmental phases.

Increasing quantitative knowledge of the gene regulatory network dynamics in developmental systems extends our understanding of how pattern scaling is established.

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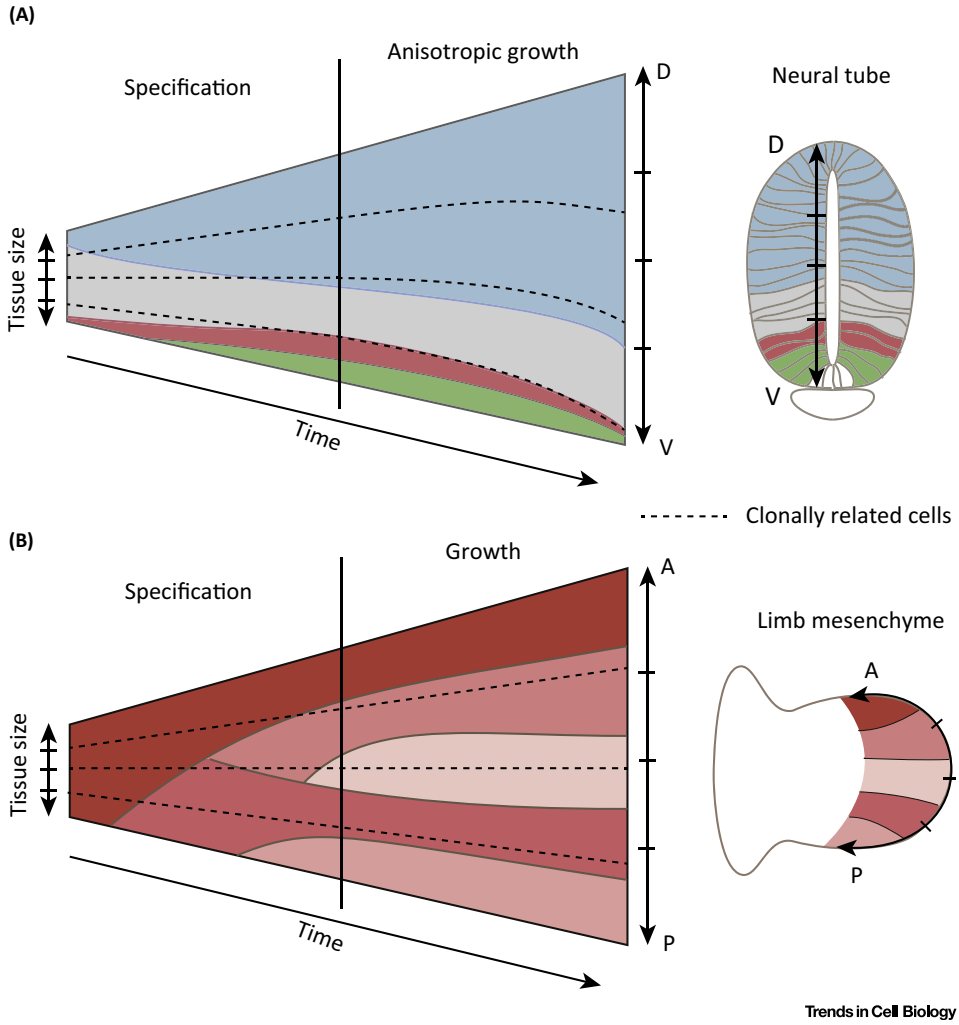

Figure 1. Specification and Growth Phases in Pattern Formation. (A) Dorsoventral (DV) pattern of expression of four neural progenitor marker genes (different colours) in the neural tube over time. The contoured lines represent 'clonal boundaries', that is, positions of clonally related cells. During the specification phase, the uniform proliferation results in scaling the clonal boundaries to tissue size. Given that progenitors can change their gene expression, the boundaries of the gene expression domains can cross the clonal boundaries. During the growth phase, progenitor types do not change and clonal and domain boundaries coincide. In the spinal cord, the rate of terminal neuronal differentiation differs between cell types, which causes unequal growth of the domains. As a consequence, the clonal boundaries do not scale with tissue size. (B) Model of the anteroposterior (AP) digit pattern of the mouse limb-bud mesenchyme. Each colour represents one digit and adjacent interdigit territory, where digits can be distinguished by SRY (Sex-determining region Y) box 9 (Sox9) expression. The clonal boundaries are represented as scaling with tissue size; however, this does not correspond to the measured growth in the limb bud and a more detailed description of the growth anisotropies can be found in [93,108].

domains along the dorsoventral axis, which later give rise to different subtypes of neurons and glia [6,7]. The identity of each progenitor domain is defined by the combination of transcription factors ('identity TFs') that it expresses [6]. During initial stages of neural development, morphogen signalling from the poles directs progressive changes in the combination of identity TFs expressed by a given progenitor. As a consequence, switches in progenitor identity in response to morphogen signalling are frequent at early stages and some progenitor domains expand at the expense of others (Figure 1A) [3]. At later stages, cell identities stabilize; consequently, the net rate at which progenitors switch between identities is reduced. Nevertheless, alterations in progenitor domain proportions continue because the rate at which progenitors differentiate into neurons markedly increases and different subtypes of progenitor undergo cell cycle exit and

Glossary

Hysteresis: derived from the Greek ὑστέρησις, 'lagging behind'. Hysteresis is observed in systems that are multistable and indicates that the state adopted by a system depends on the history of its past inputs. It arises when the state of the system does not depend purely on its current input, but also on other factors, which change in response to the input. In developmental transcriptional networks, signalling effectors regulate target gene expression in combination with other factors, which themselves depend on morphogen signalling. Initial exposure to signalling creates dynamic changes in the levels of many of the regulatory factors. These will affect how the target gene expression will change upon removal or interruption of the signal and can create a situation in which target gene expression is maintained despite a decrease in signal.

Multistability: a property of complex dynamical systems indicating the existence of more than one stable equilibrium state (often referred to as an attractor) for a given set of system parameters. Such systems are sensitive to initial conditions and noise, and the stability of each state depends on how quickly the system can return to that state following a perturbation. In the context of gene regulatory networks, this means that fluctuations in initial conditions or parameters can lead to qualitatively different gene expression profiles.

Nonautonomous dynamical systems: dynamical systems modelling is a mathematical formalism for describing the behaviour over time of complex systems of interacting components. Typically, the state of the system is described as a function of its variables, i.e. quantities that change over time. Parameters help to define the relations between variables and, in autonomous systems, these are constants. Nonautonomous dynamical systems are systems in which some or all of the parameters depend on time. Gene regulatory models typically use autonomous descriptions for simplicity. Nevertheless, many biological processes have time-dependent parameters.

Scaling: a geometric linear transformation of an object.