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A chemotaxis model of feather primordia pattern formation during avian development

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ABSTRACT

The orderly formation of the avian feather array is a classic example of periodic pattern formation during embryonic development. Various mathematical models have been developed to describe this process, including Turing/activator-inhibitor type reaction-diffusion systems and chemotaxis/mechanical-based models based on cell movement and tissue interactions. In this paper we formulate a mathematical model founded on experimental findings, a set of interactions between the key cellular (dermal and epidermal cell populations) and molecular (fibroblast growth factor, FGF, and bone morphogenetic protein, BMP) players and a medially progressing priming wave that acts as the trigger to initiate patterning. Linear stability analysis is used to show that FGF-mediated chemotaxis of dermal cells is the crucial driver of pattern formation, while perturbations in the form of ubiquitous high BMP expression suppress patterning, consistent with experiments. Numerical simulations demonstrate the capacity of the model to pattern the skin in a spatial-temporal manner analogous to avian feather development. Further, experimental perturbations in the form of bead-displacement experiments are recapitulated and predictions are proposed in the form of blocking mesenchymal cell proliferation.

1. Introduction

1.1. Theoretical background

The mechanisms that allow an embryo to self-pattern into a fully formed and functioning organism remain the subject of considerable speculation. Theoretical models for pattern formation have been developed from several viewpoints (for recent reviews, e.g. Baker et al., 2009; Hiscock and Megason, 2015; Othmer et al., 2009; Painter et al., 2012). Pre-pattern models, such as the "French-flag" model of positional information (Wolpert, 1969), suppose that structure arises iteratively through pattern building on pattern. On the other hand, self-organising models make no *a priori* assumption of previous pattern: structures can emerge from the inherent noise in an essentially homogeneous (uniform) tissue.

These self-organising or "symmetry-breaking" models can be further subdivided, for example into chemical- or cell-based. The well known Turing mechanism (Gierer and Meinhardt, 1972; Turing, 1952) is an example of the former, with its principal assumption being the existence of a network of reacting and diffusing chemical morphogens. In its simplest form it can be understood through the concept of short-range activation and long-range inhibition (Gierer and Meinhardt, 1972; Segel and Jackson, 1972), where one component plays the role of an "activator" that directly (or indirectly) upregulates its own activity (i.e. autocatalysis) while also promoting an "inhibitor" that acts to limit the activator's activity. If activation operates on a shorter spatial range, for example via lower molecular diffusion, these processes combine to generate a spatially periodic morphogen distribution that can provide a template for tissue patterning. Recent years have witnessed a growing number of systems where reaction-diffusion type principles are proposed to operate, including skin morphogenesis (Glover et al., 2017; Harris et al., 2005; Jung et al., 1998; Sick et al., 2006), tooth morphogenesis (Cho et al., 2011), tracheal patterning (Sala et al., 2011), generation of left-right asymmetry (Nakamura et al., 2006) and limb patterning (Raspopovic et al., 2014).

In cell movement and mechanical models it is the properties of cells and their mechanical interactions with the surrounding tissue that generate patterning. Classical chemotaxis models (Keller and Segel, 1970) describe the directed movement of cells in response to chemical attractants (or repellents) and predict the organisation of a population into clustered structures: self-organisation of dispersed *Dictyostelium discoideum* cells into

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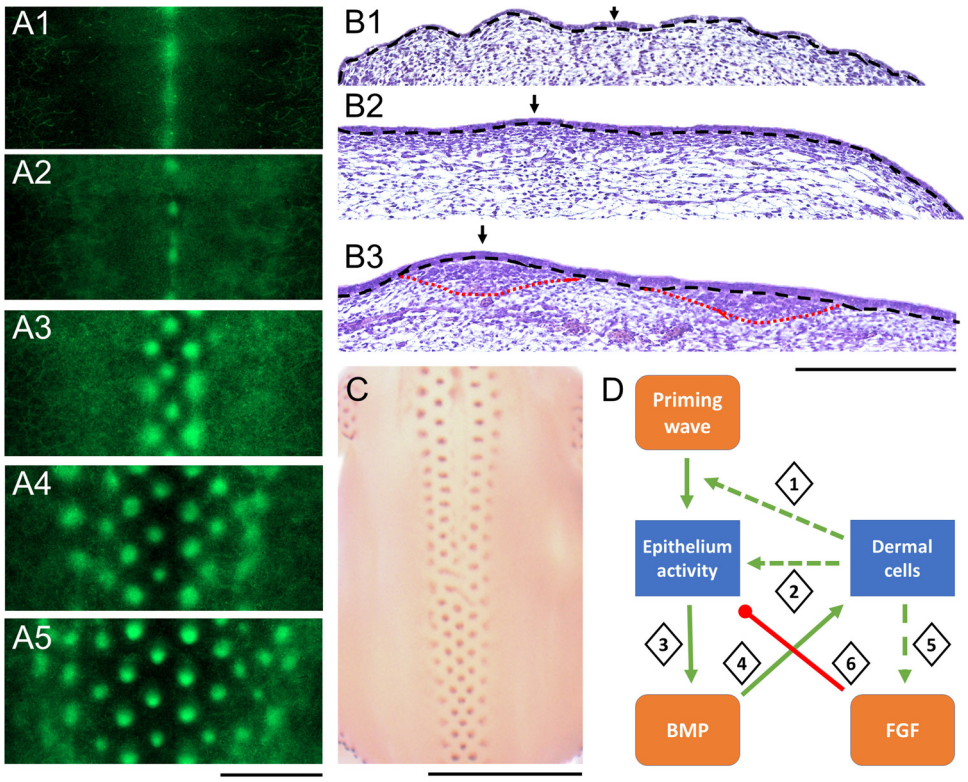

Fig. 1. (A) Feather primordia form across the skin in a coordinated spatiotemporal manner, visualised by the sequential formation of discrete dermal cell condensates (localised regions of intense green) in bi-lateral tracts that extend laterally from the dorsal midline. Skin explants prepared from the dorsal tracts of E6.5 GFP chicken embryos, with stills in (A1–A5) taken at 8 hourly intervals from 0 to 32 h (Scale bar = 1 mm). In each frame, anterior to posterior runs from top to bottom, lateral to medial to lateral from left to right. (B) Histological cross-sections showing skin development at: (B1) E5.5, showing a sparsely populated underlying dermis; (B2) E6.5, displaying a medial to lateral decreasing gradient of dermal cell density; and (B3) E8.5 days, showing individual primordia visualised as discrete dermal cell aggregates (enclosed by red dotted lines). Black dashed lines indicate the epidermal-dermal boundary, black arrows the dorsal midline and scale bar = 200 μm. (C) Expression of *FGF20* along dorsal embryo (scale bar = 2.5 mm). Wholemount in situ detection of *FGF20* RNA transcripts in E7.5 chicken embryos. The darker spots showing gene expression lie within developing feather primordia. Expression of *BMP* shows similar localisation (data not shown). Anterior to posterior runs from top to bottom, lateral to medial to lateral from left to right. (D) A "signalling network" summarising the key interactions incorporated into the mathematical model: (1,2) Dermal cells stimulate epithelium activation, where a priming wave lowers the critical dermal density at which this occurs; (3) Activated epithelium secretes FGF protein; (4) FGF induces positive chemotaxis of dermal cells; (5) Clustered dermal cells secrete BMP protein; (6) BMP inactivates epithelium. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

aggregation mounds is founded on a chemotactic response to self-secreted cAMP (Bonner, 2009). Chemotaxis has been implicated in various developmental process, including chick gastrulation (Yang et al., 2002), neural crest migration (Shellard and Mayor, 2016) and, of particular relevance here, feather development (Lin et al., 2009).

Avian feather formation offers a classic example of embryonic patterning. During skin development these structures emerge via molecular signalling and tissue crosstalk leading to localised cell condensates that subsequently bud into feathers. Pattern formation occurs at numerous levels and stages, from the spatiotemporal process that lays out a pattern of "primordia" across the skin's surface (Fig. 1A) to the within-bud patterning that leads to an intricate and pigmented feather. The skin's accessibility coupled to the diversity of feather patterns across the natural world offers an elegant model system for understanding how pattern can arise and evolve (Painter et al., 2012).

Earlier theoretical works pre-dated molecular-level understanding: models typically relied on a central self-organising mechanism, such as mechano-chemical interactions (e.g. Murray et al., 1983), reaction-diffusion (e.g. Nagorcka, 1986) or a combination of the two (e.g. Cruywagen et al., 1992; Nagorcka et al., 1987; Shaw and Murray, 1990). Activator-inhibitor (AI) principles proved particularly influential when it came to resolving the core molecular components controlling patterning (Jiang et al., 1999; Jung et al., 1998; Patel et al., 1999), and recent studies have formally linked experiment and theory such that model variables describe specific molecular components/cell populations and simulations can be tested against experimental observations (Harris et al., 2005; Lin et al., 2009; Michon et al., 2008; Mou et al., 2011; Prum and Williamson, 2002).

1.2. Biological background

The skin serves as a barrier and carries various appendages, including feathers, hairs, nails, scales and glands, which begin their development during embryonic growth. The most numerous appendages, such as hairs, feathers and scales, are rapidly laid out in a periodic pattern that, for many organisms, covers the vast majority of the skin surface. The process of defining the locations of these appendages involves communication between the two tissue layers of the skin, see Fig. 1B; the ectoderm-derived epidermis is an epithelial sheet laden with cell-cell physical contacts that restrict movement, while the mesoderm or neural crest-derived mesenchyme called dermis features unconnected cells loosely embedded in a matrix of their own production, thus capable of relatively unrestricted movement.

Definition of the feather pattern begins in chicken embryos around embryonic day 7 (E7.0) and, by hatch at 21 days post egg laying, culminates in a downy plumage. Each presumptive feather is first indicated by a tighter packing of ectodermal cells