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Review

Spindle orientation processes in epithelial growth and organisation

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ABSTRACT

This review focuses on the role of orientated cell division (OCD) in two aspects of epithelial growth, namely layer formation and growth in the epithelial plane. Epithelial stratification is invariably associated with fate asymmetric cell divisions. We discuss this through the example of epidermal stratification where cell division plane regulation facilitates concomitant thickening and cell differentiation. Embryonic neuroepithelia are considered as a special case of epithelial stratification. We highlight early ectodermal layer specification, which sets the epidermal versus neuronal fates, as well as later neurogenesis in vertebrates and mammals. We also discuss the heart epicardium as an example of coordinating OCDs with delamination and subsequent differentiation. Epithelial planar growth is examined both in the context of uniform growth, such as in Xenopus epiboly, the Drosophila wing disc and the mammalian intestinal crypt as well as in anisotropic growth, or elongation, such as Drosophila and vertebrate axial elongation and the mouse palate. Coupling between growth perpendicular to and within epithelial planes is recognised, but so are exceptions, as is the often passive role of spindle orientation sometimes hitherto considered to be an active driver of directional growth.

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1. Introduction

The question of how cell division orientation and tissue organisation are related is at the interface of cell biology with developmental biology. It is quite well established that spindle orientation is often non-random and there have been several excellent reviews examining spindle orientation regulation in a number of different developmental systems [1–5]. Rather than cover the same ground, this review will focus on the relationship between spindle orientation and tissue-level development, specifically tissue organisation and tissue growth (Fig. 1).

One aspect of tissue organisation assumed to be connected to cell division is growth. In fact, the relationship between cell division and tissue growth as such is complex. Even in a simple culture

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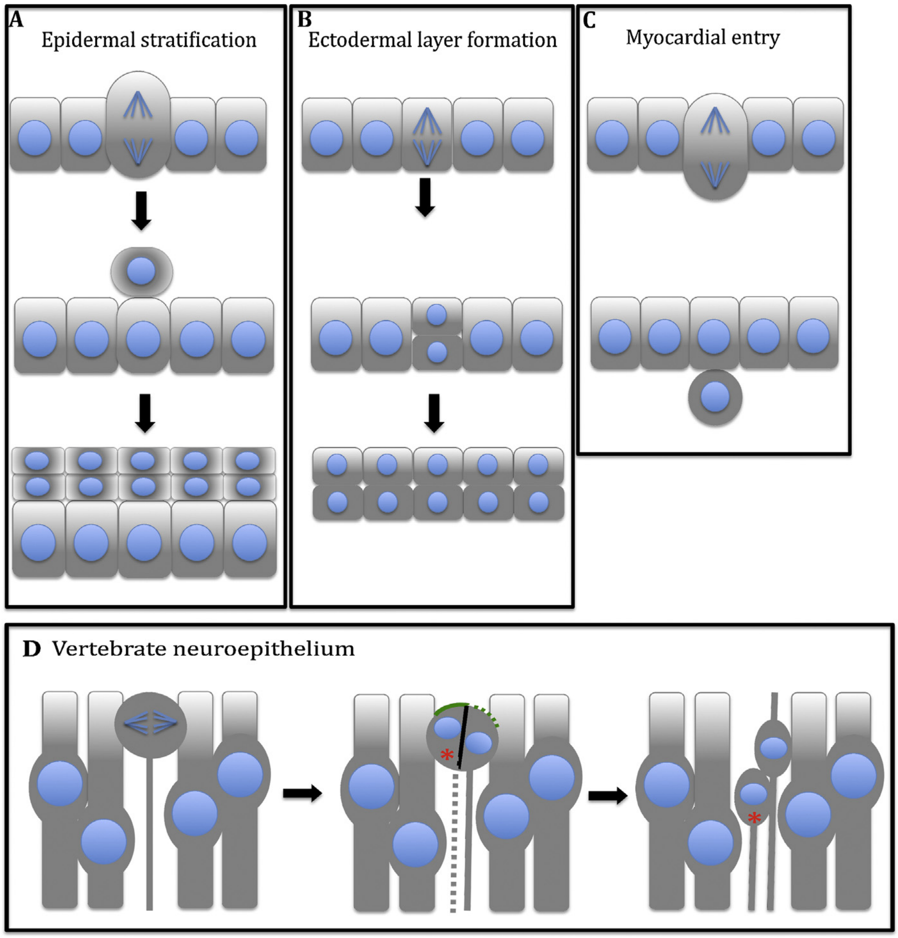

Fig. 1. Overview of cell division orientations in epithelial thickening. In all panels, apical is up and basal is down. (A) Apicobasal divisions in the epidermis contribute to stratification and facilitate tissue homeostasis. (B) Reduction divisions in the Xenopus ectoderm create two layers of distinct fate and later in development, positively correlate with specification of primary neurons. (C) In epicardial development, apicobasal divisions coincide with basal delamination of one daughter and myocardial entry. (D) In vertebrate neurogenesis, near-planar divisions result in fate asymmetry by regulation of inheritance of apical determinants and the basal process. In both cases, unexpectedly, daughters with more apical determinants (solid green line) are more likely to delaminate (marked by red asterisk) and those with a basal process and less apical determinant to remain as epithelial (apical) progenitors. This process is more deterministic in the zebrafish neural tube than in the mouse cortex, where apical determinants can be partially inherited by both daughter cells (dotted green versus solid green line) and it is the inheritance of the basal process (solid versus dotted grey line) that marks the daughter most likely to remain as a progenitor.

system there is a complex relationship between cell size and cell division [6] and it is clear that tissue growth must be related to cell division in an even more complex way. Cell division can, of course, be uncoupled from growth completely, for example in early insect and non-amniote vertebrate embryos (e.g. frogs, fish) in which the embryo remains at a constant volume while cleavages (reduction divisions) divide it into smaller and smaller cells.

Where tissue growth is associated with cell division, the idea that directional growth is therefore driven by directional cell division and orientated mitotic spindles is a powerful one: it seems almost self-evident that if the majority of daughter cells of cell divisions in a tissue are aligned in a particular direction, that growth in that direction will be greater than that in other directions. Whether this is indeed the case, or alternatively whether spindle orientation is sometimes not a driver but a follower of or even orthogonal to the direction of growth is addressed below.

In this review we will focus on cell division orientation in the context of two types of anisotropic epithelial development: stratification (with or without thickening) and elongation in the plane. Spindle orientation can play a role in both. We will focus here on physical organisation rather than cell fate, first in the context of stratification and then with respect to planar growth. Examples of each where spindle orientation and growth have been studied in any detail are in fact rather few. We present those where there is enough data to begin to get some insights into the critical processes.

1.1. Stratification

In simple growth of epithelial monolayers cell division planes are actively restricted to the plane parallel to the basal lamina [7,8]. However, epithelia also often need to thicken and form layers during development. The most well known example of this is in the epidermis, but this is not the only example. The linings of a number of ducts, such as the oesophagus and salivary ducts are examples of cuboidal stratified epithelia. Local stratification occurs, for example, during formation of both teeth and hairs [9]. The development of the central nervous system is not usually considered in the same way, but it also involves stratification of the neuroepithelium. Finally, the epicardium is an example of development by stratification [10]. A priori, stratification can happen in two different ways. Cells can simply delaminate from a monolayer, a process usually considered under the heading epithelial-to-mesenchymal transition. Alternatively, daughter cells can be separated from the monolayer by a horizontal or oblique “apicobasal” cell division. Clearly this latter process depends on regulation of spindle orientation. Here we will discuss three examples of epithelial stratification