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Review

Tissue morphodynamics shaping the early mouse embryo

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ABSTRACT

Generation of the elongated vertebrate body plan from the initially radially symmetrical embryo requires comprehensive changes to tissue form. These shape changes are generated by specific underlying cell behaviors, coordinated in time and space. Major principles and also specifics are emerging, from studies in many model systems, of the cell and physical biology of how region-specific cell behaviors produce regional tissue morphogenesis, and how these, in turn, are integrated at the level of the embryo. New technical approaches have made it possible more recently, to examine the morphogenesis of the mouse embryo in depth, and to elucidate the underlying cellular mechanisms. This review focuses on recent advances in understanding the cellular basis for the early fundamental events that establish the basic form of the embryo.

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1. Introduction

Creating an elongated embryo with a distinct head and tail from a spherical ball of cells requires extensive tissue morphogenesis. The changes in tissue shape are driven by specific, coordinated behaviors of the cells that make them up, and these behaviors lead not only to changes in tissue shape, but also to specification and differentiation. Cell function in tissue shape change has been thought about for some time and in some depth. In seminal work, Gustafson and Wolpert [1,2] noted that, in theory, differential adhesions of lateral and basal surfaces of cells in sheets to one another or to surfaces of extracellular matrix could drive cell shape changes. In turn, these changes applied to a cuboidal cell, and integrated across cell sheets, could cause change in tissue shape. For example, cell thinning or flattening causes spreading of the sheet, cell columnarization or palisading causes shrinkage or contraction of the sheet, and cell wedging causes bending of the tissue. Others, such as Holtfreter [3–5], argued that internally driven, cell autonomous, changes in cell shape were also important in behavior of cell sheets, and locally autonomous, if not cell autonomous, changes in cell shape generate endogenous forces that reshape the neural plate [6,7]. Current work has built on these pioneering studies, providing evidence for actomyosin-based apical constriction driving bending of cell sheets (invaginations) [8–10], as well as apical-basal shortening with apical constriction [11]. Cell division, even without growth (increase in cell volume), as is the case in many yolky embryos, such as many amphibians [4], can contribute to tissue shape change by being oriented. Cell division with growth has long been thought to drive the folding movements of embryos [12–14], a particularly significant mechanism in embryos that show dramatic growth in early development, including birds and mammals [14,15]. Intercalation of cells along an axis within the plane of a multilayered tissue can produce a narrower, longer tissue (often called convergent extension, or CE), and cell intercalation normal to the plane of a multilayered tissue (radial intercalation) can thin the tissue [16,17]. Finally, movements and associations of cells may be regulated by cell-cell recognition and selective affinity [18], which is the notion that cells recognize one another on contact as similar or different, and that they can show either a positive or negative affinity, seen as a high or low probability of maintaining contact.

1.1. Passivity vs. activity

In all cases of tissue shape change, the question arises, is it endogenously driven and active, or is it a passive response to external forces? Many large morphogenic processes involve both active and passive phases, and it is only with detailed analysis of the relationship of cell behavioral changes and mechanical interactions of tissues can this be determined [19]. Only in a very few cases do we know where and how the forces are being generated, and this is particularly true in mammals. Recent advances in live imaging techniques [20–23] have made it possible to more fully analyze the morphogenesis of the mouse embryo and to elucidate the underlying cellular mechanisms. This review summarizes our current knowledge of the cell behaviors that generate the basic form of the mouse embryo, and identifies areas where further insight is needed.

2. Formation and migration of the distal visceral endoderm (DVE) to become anterior visceral endoderm (AVE).

One of the critical morphogenetic events that shapes the early mouse embryo is formation of the DVE at the distal tip of the embryo and its subsequent migration proximally to a position near the boundary with the extraembryonic tissues, to become the AVE ([24–26], reviewed [27]). How the AVE is formed is particularly important because it is a key signaling tissue that regulates establishment of the embryonic anterior/posterior (A/P) axis through inhibitory effects on Nodal signaling [28–30]. Cells of the AVE produce Cerberus-like 1 (*Cer1*) and Lefty 1 (*Lefty1*), inhibiting Nodal signaling anteriorly, inducing differentiation of ectoderm in the underlying epiblast, and restricting the position of the primitive streak to the posterior side ([29,30], reviewed [27,31]).

2.1. DVE formation: Potential uterine influence

A very novel cellular mechanism for the formation of the DVE has been proposed [32], that implicates mechanical constraint by the uterus as a morphogenic force. Circumferential restriction of the early embryo (E5.0) in in vitro culture, mimicking the compression forces of the decidua on the growing embryo in vivo, leads to preferential proximal-distal elongation of the embryo. The mechanical force imposed on the distal tip results in basement membrane breaches that allow extrusion of a small number of epiblast cells into the visceral endoderm (VE) layer, where they become the Cer1-positive cells that form the DVE. However, a recent report [33] calls this mechanism into question, demonstrating DVE formation and migration in embryos cultured in vitro without any physical restraint. Technical advances in in vitro culture of mouse embryos through the implantation stage should facilitate a more thorough analysis of this event to resolve these conflicting findings [34].

2.2. Migration and intercalation in the AVE

Once established, the DVE undergoes a very unusual migration [24,25,35], forming very long basal protrusions that extend in the direction of migration [25,36]. At the same time, DVE cells maintain their epithelial characteristics, and exchange neighbors along the migration pathway [35,37]. This behavior not only characterizes the leading DVE cells, but also surrounding cells that will contribute to the AVE [38], establishing this as a coordinated, or collective, cell migration. Genetic studies have identified roles for actin regulators Rac1 and the WAVE complex as well as PTEN in this migration [35,39,40], consistent with the active, directed protrusive behavior. The factors that regulate the directionality and extent of migration are currently unknown, but may emanate from the extraembryonic ectoderm (ExE). Regulation of DVE formation relies on repressive factors produced by the ExE [41], and the AVE cells shift from anteriorly- to laterally-directed migration when they reach the boundary with the DE overlying the ExE [25,35–37] suggesting a regulatory activity associated with this region. The AVE thus represents a very interesting model system for studying coordinated epithelial migration in an epithelium.

3. Gastrulation movements

3.1. Comparative overall cell movements

Formation of the AVE restricts Nodal signaling to the prospective posterior of the embryo, where it induces formation of the primitive streak and the onset of gastrulation [29], reviewed [27,42,43]. The primitive streak is a region of epithelial-mesenchymal transition (EMT) where epiblast cells ingress to generate a new population of mesenchymal cells that give rise to mesoderm and definitive endoderm (DE). The cellular mechanisms underlying this critical morphogenetic event have been most thoroughly studied in chick [44–47] and rabbit embryos [48–52], and much less is known about gastrulation in the mouse [21,53–57]. The chick and rabbit, which are relatively large, flat disc-shaped embryos at the time of gastrulation, exhibit large-scale movements of cells toward the midline. In the chick, epiblast cells located far laterally in the blastoderm