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Review

Role of physical forces in embryonic development

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ABSTRACT

Physical forces play essential roles in animal development. Given that embryonic development takes place under spatial constraints, cells experience forces from neighboring cells and/or remote tissues and can transduce such forces into biochemical signals. Cells can also generate forces through active migration, movement, or deformation and thereby influence the behavior of their neighbors. Although the contribution of mechanical forces to development has been well established in general, here I will focus on recent findings that address the involvement of physical forces in body axis determination, gastrulation and cardiovascular development.

Contents

1. Introduction

Mechanical forces have profound effects on physiology including animal development [1–3]. For example, mechanical stimuli may result in conformational changes of cytoskeletal actin or may affect interaction between cell adhesion molecules and their accessory proteins [4]. Physical forces can be also converted into biochemical signals by various mechanisms. One such mechanism is through a change in the conformation of a mechanosensitive protein with stretch-sensitive ion channels; MscL in *Escherichia coli* [5] provides the best examples of such proteins. Force-induced signals can also be transmitted to the nucleus and result in a change in gene expression. For example, mechanical tension may lead to the translocation of a transcription factor from the cytoplasm to the nucleus, where it can then access to its target genes [6,7].

Mechanical forces play key roles in embryogenesis. The deformations caused by germ band extension in *Drosophila* triggers nuclear translocation of Armadillo, which in turn induces *Twist* expression for subsequent midgut formation [7]. External tension applied by stretching of frog embryo explants was found to affect the differentiation of embryonic tissues [8]. Moreover, the relaxation of circumferential tension by the introduction of slits into frog embryos was shown to impair morphogenetic cell movements such as those associated with gastrulation [9]. Such classical experiments have been followed by many studies that have provided evidence for the contribution of mechanical forces to embryogenesis. In this review, I will address four aspects of mouse embryonic development that have recently been shown to involve physical forces.

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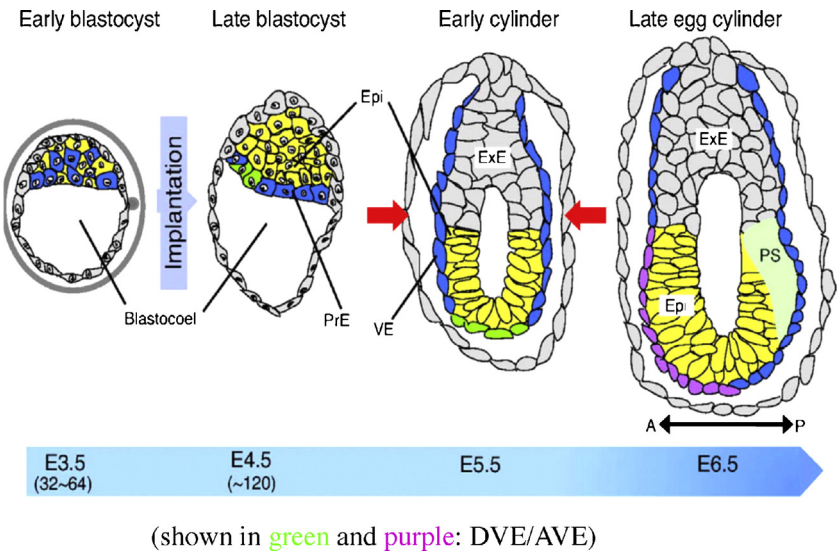

Fig. 1. Mouse embryo development from blastocyst to gastrulation. Cell types are color-coded. In particular DVE/AVE is shown in green and purple. Physical forces from the uterus that constrain the embryo are shown by red arrows. *Source*: Modified from Takaoka and Hamada [12].

2. Force from the uterus for establishment of the anteroposterior axis

The anterior–posterior (future cranial–caudal) axis in the mouse is established by a group of cells known as the distal visceral endoderm (DVE) or the anterior visceral endoderm (AVE) [10,11]. DVE and AVE have different origins and are not the same [12], but I will refer to both as DVE for simplicity. DVE cells express specific genes, such as *Cerl1* and *Lefty1*, and are located at the distal end of the mouse embryo at embryonic day 5.5 (E5.5), and migrate soon thereafter toward the proximal side to form the future anterior side of the embryo (Fig. 1). A recent study [13] showed that mechanical force exerted by maternal uterine tissue is required for formation of DVE at E5.5.

Mammalian embryos undergo implantation into the uterus. Given that implanted embryos are spatially restricted by the surrounding uterine tissue, they are under mechanical constraints. Hiramatsu and colleagues developed a unique in vitro culture system in which mouse embryos dissected (free of uterine tissue) slightly before E5.5 are cultured in a microcavity with or without the imposition of artificial mechanical force. While embryos cultured without mechanical force failed to form DVE (*Cerl1*-expressing cells), the application of physical force to embryos supported DVE formation [13].

These results thus suggest that mechanical force resulting from embryo-uterus interaction is essential for DVE formation, but there are other studies that do not support this notion. Mouse preimplantation embryos can be cultured from the blastocyst stage to the egg cylinder stage [14,15]. Development during such in vitro culture apparently resembles that of in situ. Importantly, DVE (*Cerl1*-expressing cells) is formed in the correct region and undergoes migration in such cultured embryos [14,15]. Given that these embryos are not under physical constraint, these observations suggest that mechanical force imposed by the uterus is not essential for DVE formation and migration. In addition, *Lefty1*-expressing cells were generated when preimplantation mouse embryos were cultured in a hanging drop in vitro [16], although it is not known whether such cells would later become DVE.

3. Physical force for convergent extension

Formation of the notochord is characterized by convergence of notochord cells at the midline and elongation of the resulting structure along the anterior–posterior axis of the embryo. This type of morphogenetic cell behavior is generally referred to as convergent extension (CE) (Fig. 2). In the mouse embryo, the notochord elongates between E7.5 and E8.25, during which time the amniotic cavity (AC) also expands substantially (Fig. 2). Piercing of the AC with a glass capillary at E7.5 was found not only to prevent AC expansion but also to impair CE of the notochord, which remained wider than normal and with its cells randomly oriented [17]. Given that AC expansion acts upstream of planar cell polarity signaling, physical force exerted by the expanding AC may be a driving force for CE during notochord formation.

However, a similar mechanism involving global tension may not be operative for notochord elongation in the frog embryo, given that dorsal tissue explants of *Xenopus laevis* embryos, apparently unconstrained by tension, are able to undergo CE [18]. Instead, forces generated by cell migration are implicated in notochord elongation

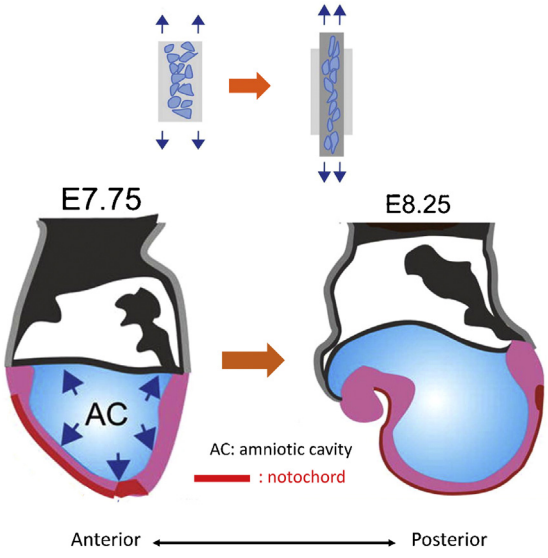

Fig. 2. Role of amniotic cavity expansion in notochord formation. The amniotic cavity (AC) expands between E7.75 and E8.25, while the notochord (red) expands along the anterior–posterior axis. Physical forces exerted by the AC expansion are shown by blue arrows. Morphogenetic changes of cells during mouse convergent extension are shown at the top. See the text for detail. *Source*: Modified from Imuta et al. [17].