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Biomechanics of epithelial fold pattern formation in the mouse female reproductive tract

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Tubular organs and tissues often show various morphological fold patterns in their luminal epithelia. Computational studies have revealed that these patterns could be explained by mechanical deformation of the epithelia. However, experimental validations of this are sparse, and the mechanisms linking genetic and cellular functions to fold mechanics are poorly understood. In the oviduct of the female reproductive tract, the epithelium forms multiple well-aligned straight folds. Disruption of *Celsr1*, a planar cell polarity-related gene, causes ectopically-branched folds in mice. Here we discuss the pattern formation of the folds with respect to the growth and mechanics of the epithelium, and the cellular and genetic functions, and compare these with other tubular organs such as the gut.

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Introduction

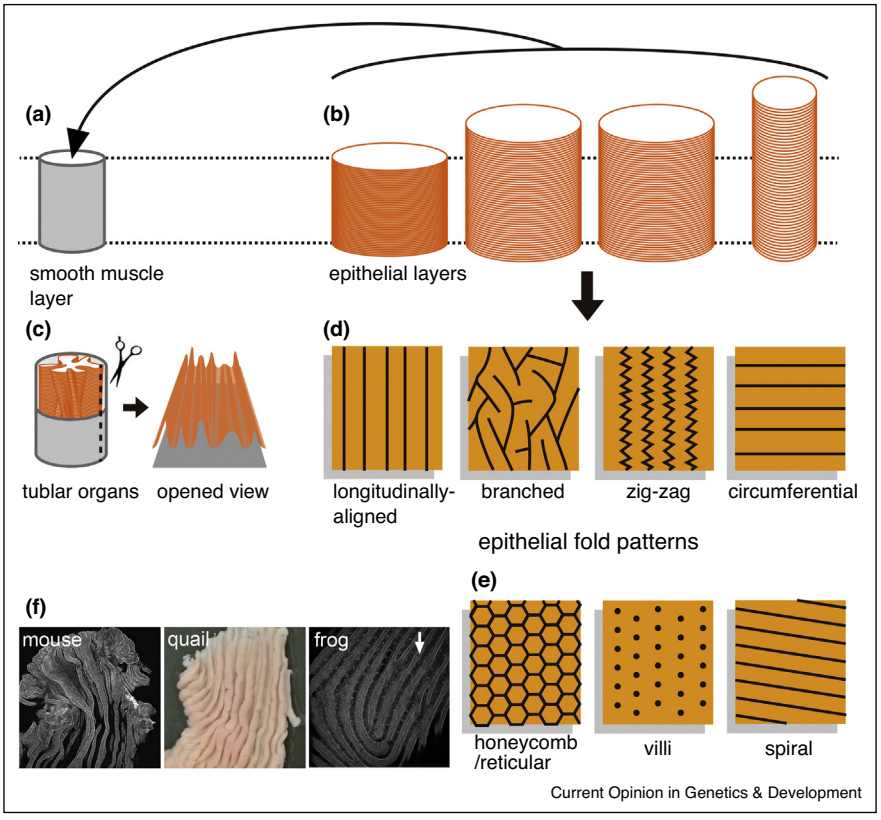
Organs and tissues in animals exhibit various three dimensional structures which provide the structural basis of their function. In developing embryos, tissues, and organs, epithelia often bend and form folds, resulting in the formation of complicated structures. Tubular tissues and organs also show epithelial folds. In the gut or the small intestine, villi and circumferentially-directed folds are generated (Figure 1) [1,2] (http://plaza.umin.ac.jp/~web-hist/secret.html). In the oviduct, or fallopian tube, multiple longitudinal well-aligned straight folds are generated, especially around the ampulla and the infundibulum, the most upstream region of the oviduct (Figure 1f) [3]. This fold pattern is conserved among various species such as mice, birds, reptiles, amphibians, and likely humans (Figure 1f) [4–8]. The oviduct's role is to transport eggs from the ovary to the uterus. The well-aligned folds would function with cilia on the luminal epithelia to increase the efficiency of the transportation [3]. Well-aligned folds are also observed during the development of the gut, which transform to zigzag folds and consequently to villi [1,9]. In cattle or sheep stomachs and snake small intestines, honeycomb or reticular folds are formed (Figure 1) [10–12]. In sharks, spiral folds are formed in their intestines (Figure 1) [13]. Folds are also observed in the airways, esophagi, and brains of mammals and in early embryos during gastrulation, neural tube formation, and head fold formation [14–20].

Mechanical buckling is often discussed as the underlying mechanism for folding (Figure 2a). When an elastic sheet, such as an epithelial sheet, is pushed inward from the boundaries, it becomes buckled and folds. Alternatively, when an epithelial sheet gradually grows by cellular proliferation under spatial constraints, folds are also generated. Many computational studies have revealed that various folds including well-aligned folds, circumferential folds, labyrinths, and villi, can be formed through buckling [16–18,21–25]. Another possibility is that the complicated patterns of folds are determined by reaction-diffusion systems based on chemical signaling [26••]. For both hypotheses, sound experimental validations have not been performed.

To investigate the mechanisms of folding, histological observations, measurements of mechanical properties, analyses of cell shapes and dynamics, and analyses of gene functions would all provide basic information (Figure 3). For example, the growth of epithelial sheets, which is a key parameter of buckling, can be calculated by histological observations. The growth of epithelial sheets is dependent on cell proliferation or deformation. It is also important to understand whether the gene products related to folding are growth factors and cell shape regulators, or secretory and diffusion proteins. However, our current understanding of these topics is quite poor, because few of the genes involved have been identified.

In the oviduct, our group found that the *Celsr1* gene, a planar cell polarity (PCP)-related gene, is critical for fold pattern formation as folds have ectopic branches in the mutant (Figure 1) [3]. Moreover, *Celsr1* mutant mice are

Figure 1



Relationship between epithelial fold pattern and length of epithelial layer. **(a)** A smooth muscle layer of tubular organs. **(b)** Various lengths of epithelial layers. The first layer corresponds to the wild-type oviduct; the longitudinal or the circumferential length is the same as or increased compared with that of the smooth muscle layer **(a)**, respectively. The second layer corresponds to the *Celsr1* mutant oviducts. In the second and third layer, the longitudinal lengths are increased compared with the first layer. In the fourth layer, the longitudinal or the circumferential length is increased compared with, or is the same as that of, the smooth muscle layer **(a)**, respectively. **(c)** A tubular organ with a smooth muscle layer and an epithelial layer. An opened view of the tube is also shown to present epithelial folds. **(d)** Various epithelial fold patterns in opened views. These are produced when various lengths of epithelial layers **(b)** are embedded into a smooth muscle layer **(a)**. Black lines represent the ridges of the folds. The epithelial layers with the same length can generate different patterns (second and third panels). **(e)** Other epithelial fold patterns in opened views. These are observed in some living organisms. **(f)** Epithelial folds of the oviducts in various species. These images were experimentally captured in opened views. The first panel, mouse; the second panel, quail; the third panel, frog (*Xenopus laevis*). The first, stained by phalloidin, is adapted from Shi *et al.* [3]. The second was captured by a digital camera. The third, stained by phalloidin, was captured by confocal microscopy, and then, a maximum intensity projection image was obtained. The folds sometimes exhibit a *U*-shaped topology. Arrow, a longitudinal fold.

infertile. In general, the PCP factors are localized at specific epithelial cell boundaries (Figure 3a) and regulate the polarity of tissues and cytoskeletal proteins [27–29]. We previously reported that the fold patterns are mechanically regulated in the oviducts [21].

In this review, we mainly focus on the pattern formation of folds in the oviduct and discuss it from protein, cellular, and tissue-level perspectives, along with theoretical aspects.

Histological observation and growth of tissues

Histological observations provide most of the fundamental information such as the composition of organs, their size, their growth, and the morphologies of folds. In typical tubular organs, a luminal epithelial layer is surrounded by a stiff smooth muscle layer (Figure 1). Between these two layers, mesenchymal cells form a layer with variable thickness: the layer is thinner than the epithelial layer in the oviduct (Figure 3b and c) [3], and it is extremely thick in the gut [1]. In mature oviducts, the epithelium is single-layered while it is pseudostratified in premature oviducts [8]. The difference in thickness should affect the mechanical properties and the morphologies of the folds [16,30].

The number of folds is gradually increased as the tube develops in the oviducts and the gut. In the mouse oviducts, longitudinally well-aligned folds are formed and the number of folds is approximately 20 in a