Acta Biomaterialia 134 (2021) 32–42

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actbio

Review article

Deciphering and engineering tissue folding: A mechanical perspective

Yanlun Zhu[a,b,1], Shuai Deng[a,b,1], Xiaoyu Zhao[a,b,c], Guanggai Xia[d], Ruike Zhao[e], Hon Fai Chan[a,b,c,f,*]

[a] Institute for Tissue Engineering and Regenerative Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China
[b] Key Laboratory for Regenerative Medicine of the Ministry of Education of China, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China
[c] Shun Hing Institute of Advanced Engineering, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China
[d] Department of General Surgery, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, 600 Yishan Rd, Shanghai 200233, China
[e] Department of Mechanical and Aerospace Engineering, The Ohio State University, Columbus, OH, 43210, USA
[f] Hong Kong Branch of CAS Center for Excellence in Animal Evolution and Genetics, Hong Kong SAR, China

ARTICLE INFO

Article history:
Received 16 February 2021
Revised 16 July 2021
Accepted 21 July 2021
Available online 26 July 2021

ABSTRACT

The folding of tissues/organs into complex shapes is a common phenomenon that occurs in organisms such as animals and plants, and is both structurally and functionally important. Deciphering the process of tissue folding and applying this knowledge to engineer folded systems would significantly advance the field of tissue engineering. Although early studies focused on investigating the biochemical signaling events that occur during the folding process, the physical or mechanical aspects of the process have received increasing attention in recent years. In this review, we will summarize recent findings on the mechanical aspects of folding and introduce strategies by which folding can be controlled *in vitro*. Emphasis will be placed on the folding events triggered by mechanical effects at the cellular and tissue levels and on the different cell- and biomaterial-based approaches used to recapitulate folding. Finally, we will provide a perspective on the development of engineering tissue folding toward preclinical and clinical translation.

Statement of significance

Tissue folding is a common phenomenon in a variety of organisms including human, and has been shown to serve important structural and functional roles. Understanding how folding forms and applying the concept in tissue engineering would represent an advance of the research field. Recently, the physical or mechanical aspect of tissue folding has gained increasing attention. In this review, we will cover recent findings of the mechanical aspect of folding mechanisms, and introduce strategies to control the folding process *in vitro*. We will also provide a perspective on the future development of the field towards preclinical and clinical translation of various bio fabrication technologies.

1. Introduction

Tissue engineering has many applications in regenerative medicine, drug testing, and basic biology [1]. One of the major challenges faced by tissue engineers is the construction of tissues *in vitro* that can recapitulate the key structural features of the corresponding tissues *in vivo*. During morphogenesis, cells self-assemble into complex tissues and organs with specialized forms and functions through a process that is regulated by cues such as morphogens [2]. During embryonic development, folding events such as invagination and evagination are important morphogenic processes that cause flat tissue to fold either inward or outward, respectively, to produce a three-dimensional (3D) structure [3]. In hollow vertebrate organs such as the stomach, intestine, and bladder, tissue folds such as rugae and villi form important structural features. These folds, which primarily occur in the epithelial cells of the mucosal layer, serve important functions such as increasing the surface area for absorption in the intestine and facilitating the storage/passage of luminal contents by allowing stomach expansion. Aside from vertebrates, folding also occurs in inverte-

* Corresponding author at: Institute for Tissue Engineering and Regenerative Medicine; School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, China.
E-mail address: honfaichan@cuhk.edu.hk (H.F. Chan).
[1] These authors contributed equally.

https://doi.org/10.1016/j.actbio.2021.07.044
1742-7061/

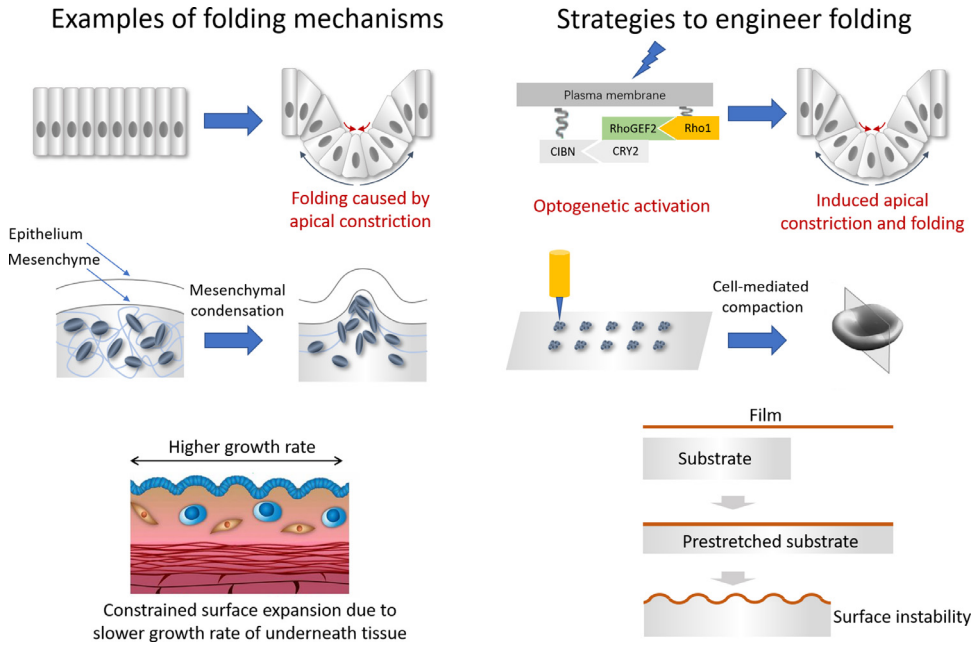

Fig. 1. Examples of tissue folding mechanisms and strategies to engineer folding. (Reproduced/adapted with permission from [11] and [9]. For [11], Copyright (2018) National Academy of Sciences).

brates and in plants. Some examples are the formation of the ventral furrow during *Drosophila* gastrulation and the opening/folding of conifer cones following hydration-induced shape-changes [4,5]. Hence, tissue folding not only serves important physiological functions but also represents a crucial phenomenon in morphogenesis and tissue movement.

Similar to origami structures that are made from flat sheets of paper, tissue folding begins with a flat epithelium that undergoes folding to generate complex 3D structures. Although early studies focused on investigating the biochemical signaling events that occur during folding [6–8], the physical and mechanical aspects have received increasing attention in recent years [9,10]. The general consensus is that folding can be driven by two types of mechanical effects: those at the cellular level and those at the tissue level [10]. Physical and mathematical models have since been developed to decipher the folding process and, more importantly, to guide the design or engineering of folding using various cell- and biomaterial-based strategies *in vitro* [9,11]. These strategies have opened up opportunities to direct or recapitulate tissue morphogenesis for tissue engineering applications. In view of emerging research on the engineering of tissue folding, we review the different mechanical effects that result in tissue folding. The model organisms included in this review are humans and other vertebrates such as mouse and chick that share similar folding morphologies, along with insects (*Drosophila*) and plants (pine) that adopt distinctive folding forms either during development or in response to environmental stimuli. This discussion will be followed by an overview of various cell- and biomaterial-based strategies used to engineer tissue folding. (Fig. 1).

2. General mechanisms of tissue folding

Tissue folding is a common morphological deformation process that occurs in a wide range of organisms. Both the local-scale effect that involves cells in and around the fold, and the more global effect that involves single or multiple tissue layers, have been shown to trigger fold formation. These two types of mechanism will be reviewed here.

2.1. Folding caused by cellular-level effects

During morphogenesis, epithelial cells, which are originally flat and typically polarized along their apical-basal axis in the form of a physically contiguous sheet, fold into complex structures. At the cellular level, folding can be triggered by events such as changes in cell shape, rearrangements of cells/contacts, and alterations in cell division [12]. Below, we will first discuss tissue folding as stimulated by changes in cell shape, including apical and basal constriction, that occur in various organisms. Next, we will review examples of rearrangements of cells/contacts and alterations in cell division, such as the shifting of cell junctions, intercalation of cells, and clustering/constriction of localized cells.

A classic example of tissue folding is ventral furrow formation during *Drosophila* gastrulation. Gastrulation is the first major morphogenetic event that occurs during *Drosophila* embryogenesis [13]. During ventral furrow formation, the furrow cells accumulate myosin on their apical surfaces to generate a gradient of contractility, leading to pulsatile contractions and apical constriction (**Fig. 2A**) [14–16]. This process depends on Rho guanine nucleotide exchange factor 2 (RhoGEF2), which accumulates apically through the action of Folded gastrulation (Fog) and T48 [17]. The expression of these factors is in turn regulated by the mechanosensitive transcription factors Twist and Snail [18]. Following cell shortening and basal expansion, the constricted cells form a tissue indentation along the ventral midline (ventral furrow), which later undergoes invagination to stimulate the development of mesodermal structures. Apical constriction also initiates bud formation during lung branching in embryonic chickens and neural tube formation in *Xenopus* [19,20]. However, apical constriction is not always coupled with invagination. For example, salivary gland invagination can be initiated even in the absence of apical constriction, by applying compressive forces through myosin [21]. The folding of the *Drosophila* leg epithelium also depends on cell apoptosis, which transiently pulls the apical surface inward [22]. This results in myosin accumulation and apical constriction, both of which drive fold formation. In some cases, as in mouse spinal neuroepithelium folding, basal expansion and not apical constriction is the more important mechanism [23]. Furthermore, basal constriction, rather

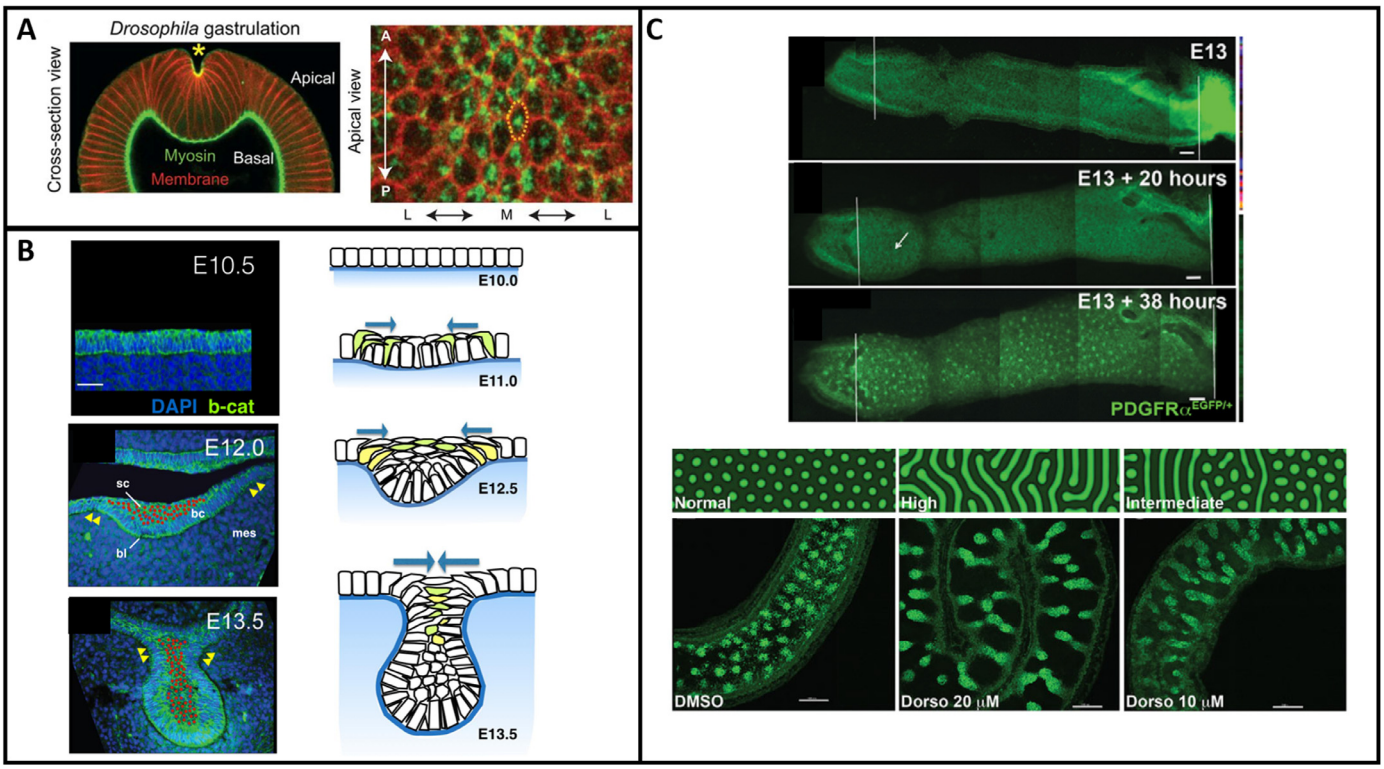

Fig. 2. Folding caused by effect at the cellular level. A. Apical constriction during *Drosophila* gastrulation. Cross-sections (left) and apical surface (right) views of *Drosophila* mesoderm cells during gastrulation. (Reproduced/adapted with permission from [16]) B. Contractile suprabasal tissue drives folding of the tooth placode. (Left) Images showing different stages of embryonic molar tooth development. (Right) Summary of the proposed model for ectodermal placode invagination based on contraction of superficial layer and bending of the noncontractile basal layer. (Reproduced/adapted with permission from [26]) C. Mouse villi emergence following cell cluster formation. (Top) Emergence of Pdgfrα+ cluster in mouse villi during development. (Bottom) Top panel: Images of Turing patterns predicted by simulation at different concentrations of activator. Bottom panel: Images of experimental results obtained under treatment conditions that matched the Turing simulations: control (DMSO); 20 μM dorsomorphin (BMP inhibitor); 10 μM dorsomorphin (BMP inhibitor). (Reproduced/adapted with permission from [28]).

than apical constriction, represents an essential step of basal epithelial folding during the formation of midbrain-hindbrain boundary in zebrafish [24]. Finally, the shifting of apical junctions in the basal direction can deform neighboring cells that are connected via adherens junctions [25]. This results in the collapse of the large apical domains of the initiating cells, in turn leading to cell shortening and the creation of an apical invagination.

A topologically similar process that does not involve actin and myosin has been observed in the early morphogenesis of ectodermal organs such as the teeth and mammary glands of mice **(Fig. 2B)** [26]. Following the emergence of a thickened epithelium known as the placode, the contractile tissue of the superficial layer undergoes horizontal contraction, bending the noncontractile basal layer into a curve. The contractile tissue then forms a canopy of elongated cells that intercalate when they converge at the center of the invagination.

Another well-documented localized effect that produces folds such as the intestinal villus and avian feather bud is localized cell clustering. In the mouse intestine, epithelial Hedgehog (Hh) induces the aggregation of sub-epithelial mesenchymal clusters in a uniformly distributed array, which determines the pattern of the villi [27]. Cells within these clusters express Patched1 and Gli1 in a concentrated manner, as well as platelet-derived growth factor receptor α (PDGFRα), a receptor known to participate in villus development. The spatial distribution of the clusters is modulated by bone morphogenetic protein (BMP) signaling. Consistent with the Turing reaction-diffusion model, this cluster cell pattern is affected by the availability of BMP inhibitors (activators) and ligands (inhibitors) and can be simulated by a mathematical model [28]. The emergence of feathers in chickens has also been shown to be mediated by another form of cellular self-organization [29]. In this case, dermal progenitors spontaneously aggregate due to contractility-driven cellular pulling, causing the surface of the epithelial layer to buckle. This aggregation activates β-catenin signaling to initiate follicle gene expression.

Finally, localized external constriction of the epithelium can also trigger folding. During mammalian lung development, the airway epithelium develops a complex branched structure through the sequential formation of new buds along the length of the epithelial tube. The tip of the elongated tube bifurcates to form daughter buds, similar to the creation of folds. This bifurcation is regulated by the localized differentiation of airway smooth muscle around the bud. As the airway epithelium grows, the smooth muscle constrains the epithelial tube to develop fold-like structures [30].

2.2. Folding caused by tissue-scale effect

Many vertebrate tissues/organs are characterized by extensive folding morphologies such as those in the brain, intestine, oviduct, and stomach. The brain contains widespread grooves (sulci) and ridges (gyri), whereas the stomach features rugae. A number of hypotheses have been proposed regarding the physiological mechanisms underlying the generation of such folds, one of which is differential growth between tissue layers [31 33]. In general, folding or buckling can result from residual strain between layers with distinct mechanical stiffnesses, (elastic moduli) which grow or expand at different rates [34]. In a mechanical system, the in-plane compression of layered structures generates surface buckling through a process known as mechanical or surface instability [35]. Unlike the

cellular effects described in the previous section, multilayer tissues induce various folding instabilities, and the folding pattern is determined by macroscale tissue properties such as tissue thickness and stiffness [36].

Let us consider the example of the brain. The convoluted structure of the human brain originates during gyrification, which itself begins after the mid-gestation period [37,38]. The outer layer (cortex) of the brain is made up of cell bodies and capillaries, and the inner core consists mostly of the white myelinated sheaths of neuronal axons. Brain folding, which occurs not only in humans but in a range of primates as well, allows the packing of a large cortex into a relatively small skull. Current hypotheses on the folding mechanisms include gyrogenetic theories, which postulate that the biochemical patterning of the cortex controls folding, the axonal tension hypothesis, which proposes that axons in the white matter beneath the cortex pull strongly interconnected regions together to drive folding, and differential expansion of the cortex [39–41]. Until now, no evidence of prepatterning has been found to support the gyrogenetic theories. In contrast to the case of apical constriction, despite the presence of axonal tension, this localized effect alone is not sufficient to drive folding [42]. The hypothesis of differential expansion of the cortex proposes that the outer layer of the brain grows at a faster rate than the inner layer, generating residual strains that drive instability and cortical folding **(Fig. 3A)** [43]. Computational modeling has been used to simulate the process and has successfully produced realistic folding patterns [44]. Moreover, biological data from the mouse cerebellum confirm that cells in the outer layer indeed grow faster than those in the center. The outer layer has also been shown to behave like a fluid, allowing cells to move and change positions freely [45].

The intestine is another organ that shows large-scale folding patterns. The previous section described how the aggregation of sub-epithelial mesenchymal clusters in a uniformly distributed array gives rise to villi in the mouse gut. In contrast, the formation of villi in the chick gut emerges from the differential growth of tissue layers **(Fig. 3B)** [31,46]. The sequential differentiation of the longitudinal and circular smooth muscle layers restricts the expansion of the growing endoderm and mesenchyme, leading to sequential folding along two directions. Consequently, villi form in a stepwise progression, wherein the mesenchyme and epithelium first develop a longitudinal fold, followed by a zigzag pattern, and finally forming individual villi. A quantitative computational model with specific biological parameters incorporated has been shown to recapitulate the folding patterns observed in native tissue. In addition to the villi pattern, the differential growth theory can explain the formation of vertebrate intestinal loops and the hindgut [47,48], which arise due to the different growth rates of the gut tube and the anchoring mesenteric sheet. The number, size, and shape of the loops can be predicted based on the measurable geometry, elasticity of the layer, and relative growth rates of the tissues.

In *Drosophila*, localized cell effects such as basal relaxation and lateral constriction contribute to the folding events in the wing disk. However, a recent study showed that differential growth between layers can initiate folding from the apical surface [49]. It has been possible to recapitulate the morphology of folding using a computational model. These simulations could predict fold perturbation in overgrowth and undergrowth mutants, which have been experimentally validated [49].

Another form of the tissue-scale effect has been observed in plants. Plants have evolved a multitude of 3D tissue shaping and folding mechanisms, such as differential cell growth, turgor pressure, cohesion forces, and osmotic swelling/shrinking [50]. Osmotic swelling/shrinking is implemented by a wide variety of plant species, a well-known example of which is the folding/opening of pine cones due to changes in air humidity. The cell walls of plants contain stiff cellulose fibrils surrounded by a pliant and flexible matrix. When the pine cone is subjected to drying, the upper side of the scales, which has the cell walls with cellulose fibrils oriented parallel to the cell axis, shrinks along a direction perpendicular to the cell axis. In contrast, the lower side of the scales, which contains fibrils arranged perpendicular to the cell axis, shrinks along the axial direction. These two effects together bend the scales and open the cone [51].

3. Strategies by which to engineer tissue folding *in vitro*

In vivo, tissue folding is a highly regulated and reproducible process that occurs across different organisms, as demonstrated by the examples above. Nevertheless, folding is difficult to recapitulate or control *in vitro* because it relies on simultaneous changes and rearrangements of cell shape, and interaction between multiple tissue layers. For example, although *in vitro* cultured brain organoids and stem cell-derived retinal epithelia can reproduce microscale epithelial folding [52,53], control over the size and shape of the folding is limited and the dimension of folding varies across organoids/cells. In theory, tissue engineers can use a variety of fabrication approaches such as conventional 3D printing and photolithography to generate different types of patterned structures [54,55]. However, these approaches can neither faithfully reproduce the morphological changes at the cellular level nor achieve the mismatch (compressive) stress that triggers folding; these events not only drive physical folding but also initiate many biochemical and mechanical signaling events important for development [56]. To engineer tissue folding via a biomimetic process, scientists have leveraged knowledge gained from the *in vivo* folding process. This has been achieved by controlling both localized and tissue-scale effects, such as by manipulating cells or designing biomaterial-based scaffolds. Here, we will review these two biofabrication strategies.

3.1. Engineering tissue folding by manipulating localized effects

During *Drosophila* gastrulation, apical constriction is typically initiated by the activation of Rho1 GTPase by RhoGEFs, which results in the activation of myosin and contraction of actin filaments [57]. To mimic this activation *in vitro* and precisely define the folding position, an optogenetic approach was proposed **(Fig. 4A)** [58]. Specifically, the cryptochrome 2/cryptochrome-interacting basic helix-loop-helix 1 (CRY2/CIB1) protein heterodimerization system was used to provide optogenetic control. A light-sensitive protein domain (RhoGEF2-CRY2) and N-terminal domain of the CRY2-binding partner CIB1 tagged with a plasma membrane anchor (CIBN::pmGFP) were engineered and expressed in *Drosophila*. In the dark, RhoGEF2-CRY2 is localized at the cytoplasm, separated from CIBN::pmGFP anchored at the plasma membrane. Under localized photo-activation, CRY2 binds to the CIBN::pmGFP at the plasma membrane to trigger the activation of Rho1 and its downstream effectors. With this approach, localized activation is sufficient to induce apical constriction and myosin accumulation. Pulsatile contractions result in tissue folding events that resemble the endogenous folding process. This study illustrated the utility of novel optogenetic approaches to guide tissue morphogenesis and folding.

Apart from inducing tissue bending or folding via genetic manipulation, it is also possible to engineer tissue folding by leveraging the natural behaviors of cells. For example, a 3D cell-patterning approach inspired by the phenomenon of cell-mediated contraction of the extracellular matrix (ECM) was reported to engineer folding **(Fig. 4B)** [9]. Adherent cells, such as fibroblasts, exert traction forces on the underlying environment, allowing them to migrate, differentiate, and maintain tissue integrity [59]. This creates

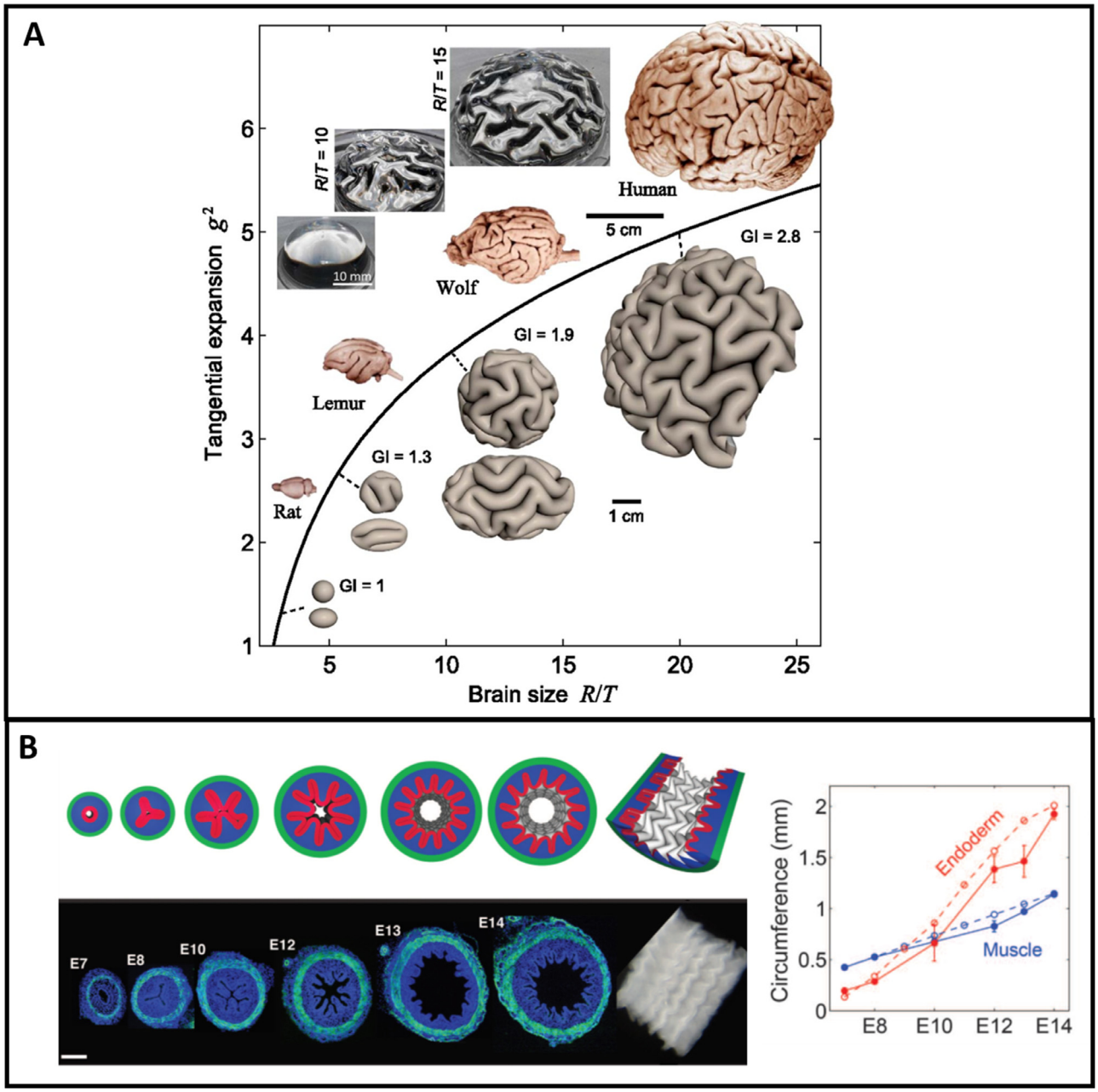

Fig. 3. Folding caused by effect between tissue layers. A. Differential growth between cortex and underlying white matter resulted in brain folding. Figure displayed various simulations, images of rat, lemur, wolf, and human brain, as well as physical model of brain folding of different brain size and tangential expansion. (Reproduced/adapted with permission from [44].
Copyright (2014) National Academy of Sciences). B. (Left) A simulation showing chick gut ridge-folds forming due to differential growth between endoderm and muscle layers, followed by buckling into a zigzag pattern. Sections of corresponding chick guts labeled with DAPI (blue) and smooth muscle actin (SMA) (green) are shown below. (Right) Circumference of the inner boundary of the muscle and endoderm. (Reproduced/adapted with permission from [31]).

strain and leads to the contraction of the matrices, as demonstrated by previous studies that reported the shrinkage of cell-laden collagen hydrogels over time. When cells are deposited onto a free-floating collagen hydrogel, they contract the surface by aligning the collagen fibers, creating compressive strain and producing bending [9]. Furthermore, when cells are laid in predetermined patterns on the top (apical) or bottom (basal) of a hydrogel, they drive folding along the programmed trajectories. These observations are supported by the prediction of folding shapes by finite element models, which offer guidance for the design of folded structures. As an example, a zigzag-shaped surface resembling the guts of embryonic day 13–16 chicks was created by depositing cells in a pattern analogous to the Miura origami fold. To constitute a functional tissue with multiple cell types, other cell types such as endothelial and epithelial cells were added without interfering with the folding trajectories, which was dominated by the major contracting cell type (*e.g.* fibroblast). Interestingly, cell migration was found to be biased along the incipient folds, suggesting that tissue folding feeds back onto the behavior of patterned cells. This technique was further developed to pattern cells onto hydrogels using a photolithographic approach, and was used to mimic the branch geometry of the kidney epithelial network by engineering folding of the hydrogel and promoting cell orientation [60].

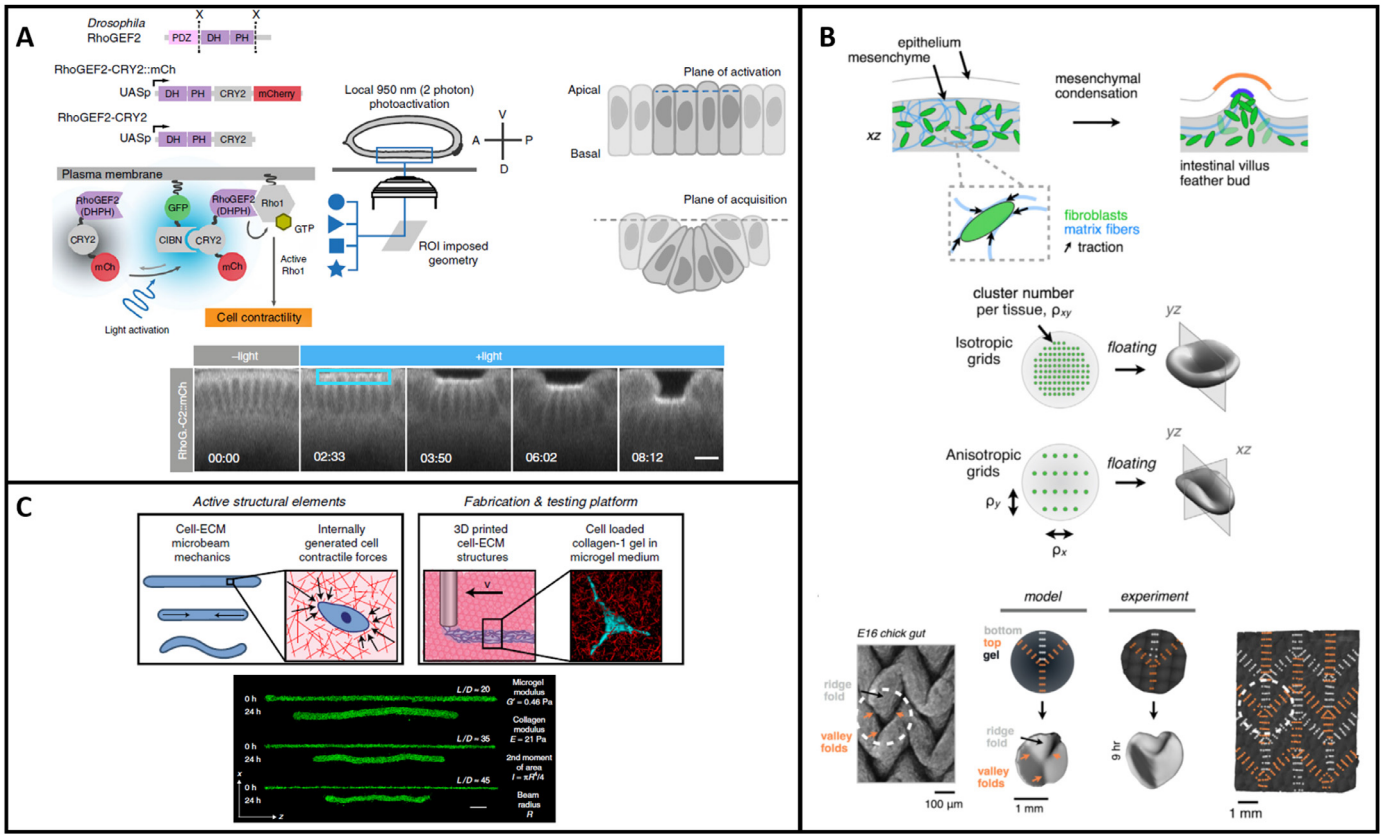

Fig. 4. Engineering folding via manipulating localized effect. A. (Top) Schematic illustration of the CRY2/CIBN optogenetic system used for controlling plasma membrane recruitment of the Rho1 activator RhoGEF2 during early *Drosophila* embryogenesis and the experimental setup. (Bottom) Time-lapse recording of embryos showing light-induced tissue folding. (Reproduced/adapted with permission from [58]) B. (Top) Traction force generated by mesenchymal cells on extracellular matrix could account for strains that drive folding and schematic depicting how various types of folding could be generated in floating gels containing either isotropic or anisotropic cell cluster grids. (Bottom) Top view and cross-sections showing that mesenchymal condensates drive folding of hydrogel resembling that of chick gut. Colored regions indicate location of deposited cell clusters. (Reproduced/adapted with permission from [9]) C. (Top) Schematic showing how 3D printed cell-laden microbeam hydrogel generated contractile forces to drive folding in packed microgels. (Bottom) 3D printed microbeam developed folding over time. (Reproduced/adapted with permission from [61]).

Based on a similar strategy, a 3D bioprinting method has also been proposed to engineer folding [61]. Microbeams made from cells and collagen I hydrogel were 3D printed within a growth medium comprising packed polyacrylamide microgels (**Fig. 4C**). The soft microgels provide mechanical support to the microbeams while simultaneously facilitating deformations driven by cell contraction. Within the growth medium containing packed microgels, the microbeams contract due to cell-collagen interactions. By varying the cell density, collagen concentration, microbeam diameter, and the material properties of the surrounding medium, the microbeam can be controlled to exhibit one of the following behaviors: folding, breakup, or axial contraction. Using the Euler-Bernoulli theory, the wavelength of and critical stress for folding can be predicted. Similar to depositing cells on a free-floating hydrogel, this approach allowed the design and fabrication of structures comprising cells and ECM that could produce folding under cell-generated forces. The results also suggest that both the intrinsic and extrinsic environments of the printed structure influence folding behaviors.

3.2. Engineering tissue folding by recapitulating tissue-scale effects

As introduced earlier, tissue folding can be initiated by tissue-scale effects that involve either single or multiple layers of tissue. For example, local swelling behavior can induce morphological changes in plants. Inspired by this, folding has been fabricated by four-dimensional (4D) printing [62]. It is a process by which a 3D printed object is transformed into another structure under specific conditions [63,64]. For example, composite hectorite clay hydrogel was encoded with localized, anisotropic swelling behavior [63], which was in turn controlled by the shear-induced alignment of cellulose fibrils during 3D printing such that the swelling behaviors along the longitudinal and transverse directions differed. When immersed in water, the printed object exhibited plant-inspired shape changes, yielding complex 3D morphologies such as bending and twisting. Another reported 4D printing approach utilized digital light to encode a temperature-responsive hydrogel with spatially controlled growth (expansion and contraction) behaviors, which transformed the hydrogel into the prescribed folding structures [65]. Self-folding can also be induced by generating a crosslinking gradient within the printed polymer (**Fig. 5A**) [64,66]. For example, a self-curved collagen hydrogel was achieved by introducing a cell adhesive peptide into certain regions of a hydrogel to program the trajectories of stromal cell contraction, leading to the formation of cornea-shaped curved stromal tissue (**Fig. 5B**) [67]. It was recently demonstrated that programmed ferromagnetic domains can be 3D printed in an elastomer composite containing ferromagnetic microparticles aligned along the external magnetic field applied during printing [68]. The resulting 3D printed structure exhibits rapid shape transformation in the presence of a magnetic field. This strategy could potentially be leveraged to engineer tissue folding and attain eventual shape transformations *in vivo*.

Differential growth between tissue layers can also cause strain and subsequent surface folding [69]. Typically, these tissues are composed of a thin surface layer (film) overlaying thick tissue

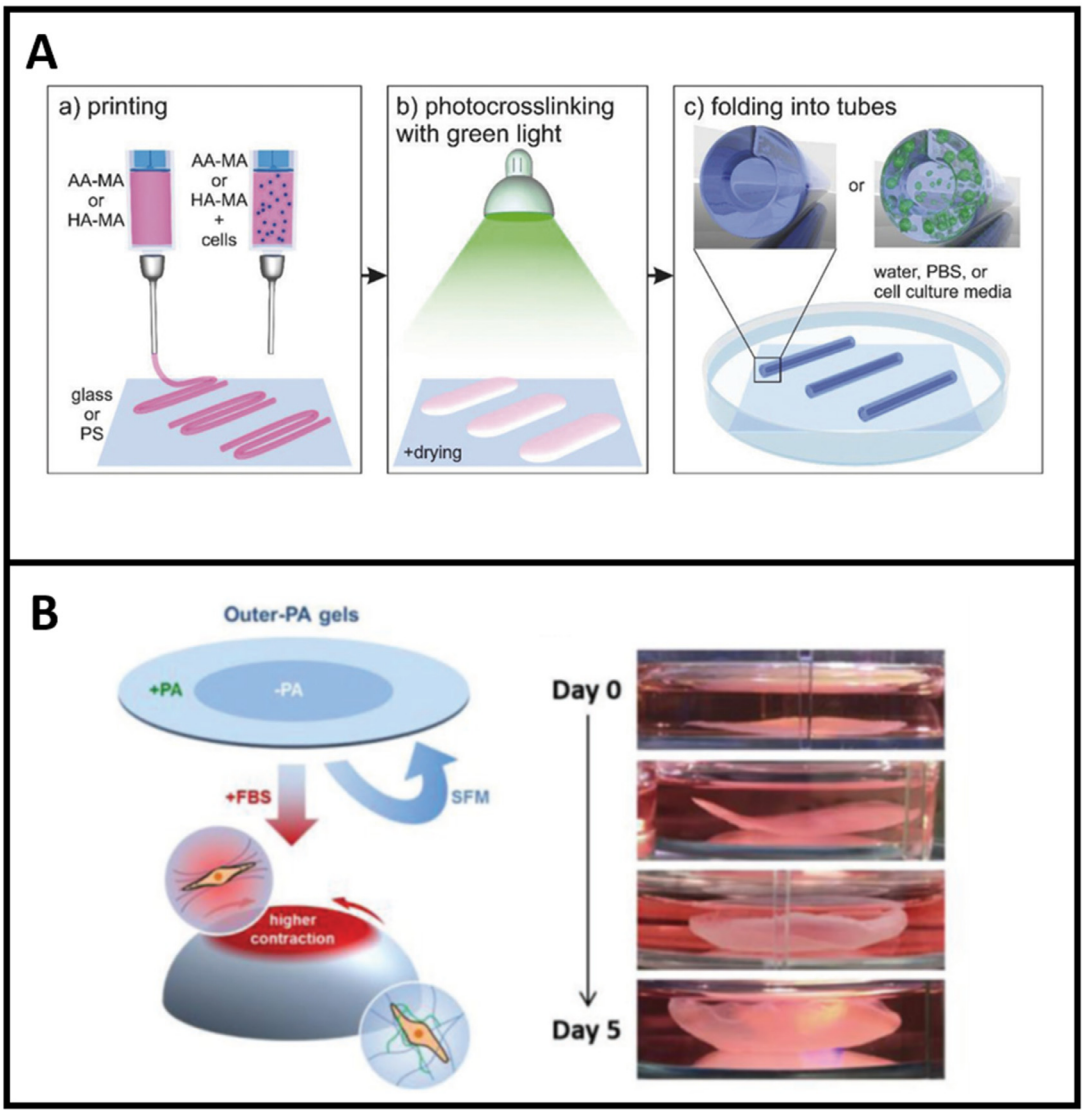

Fig. 5. Engineering folding via self-folding effect. A. Schematic of the 4D printing of self-folding hydrogel (AA-MA or HA-MA polymer with or without living cells). Instant folding of printed film into tubes upon immersion of the crosslinked films in water, possibly due to the presence of a crosslinking gradient in the film. (Reproduced/adapted with permission from [64]) B. Self-folding of collagen hydrogel achieved by introducing a cell adhesive C16G3RGDS peptide amphiphile (PA) in certain regions of the hydrogel to program the trajectories of stromal cell contraction. (Reproduced/adapted with permission from [67]).

such as muscle (substrate). These film-substrate composite structures abound not only in biological but also engineering systems such as flexible electronics, wearable devices, and superhydrophobic surfaces. Mismatch strains due to the expansion of the film or shrinkage of the substrate can trigger various surface instabilities such as wrinkling, creasing, and ridging [36,70,71]. Over the past few decades, these instabilities have been studied systemically and categorized using phase diagrams. The modes of instabilities have largely been determined using properties such as stiffness of the materials, adhesion energy between the film and substrate, and the mismatch strain or compressive strain exerted on these structures [36].

To recapitulate the mismatch strain required to initiate instability, a number of engineering strategies have been proposed. First, differential swelling of a gel can generate mismatch strain. For example, bilayer elastomer gels (*e.g.* polydimethylsiloxane [PDMS]) with different stiffnesses can be fabricated to mimic the white matter and cortical gray matter layers of the brain [40]. When immersed in solvents (*e.g.* hexane), the composite gel would first swell at the surface, causing the relative expansion to compress the outer layer. This will lead to the progressive formation of cusped sulci and smooth gyri in the bilayer construct, mimicking the morphology of the real brain. This method has been reported in a number of studies due to its ease of fabrication and control of material properties in a facile manner **(Fig. 6A)** [44,72–74]. Similarly, a bilayer poly(ethylene glycol) (PEG) scaffold can exhibit self-folding due to the differential swelling of two PEG layers of different molecular weights in an aqueous solvent [75].

Aside from solvents, other stimuli that can trigger swelling/deswelling in gels have been described. Poly(N-isopropylacrylamide) (PNIPAM), a temperature-responsive hydrogel, coated on a rigid surface undergoes creasing in response to changes in temperature [76]. By incorporating light-absorbing iron oxide particles in the PNIPAM hydrogel, creasing can also be generated by illumination-induced heating [77]. A two-dimensional (2D) hydrogel of PEG-based film containing *ortho*-nitrobenzyl (o-NB) moieties has been shown to transform into folded 3D structures after exposure to ultraviolet (UV) light, which induces a cross-link density gradient in the gel [78]. A multi-stimuli responsive bilayer structure consisting of PDMS coated with anthracene-containing

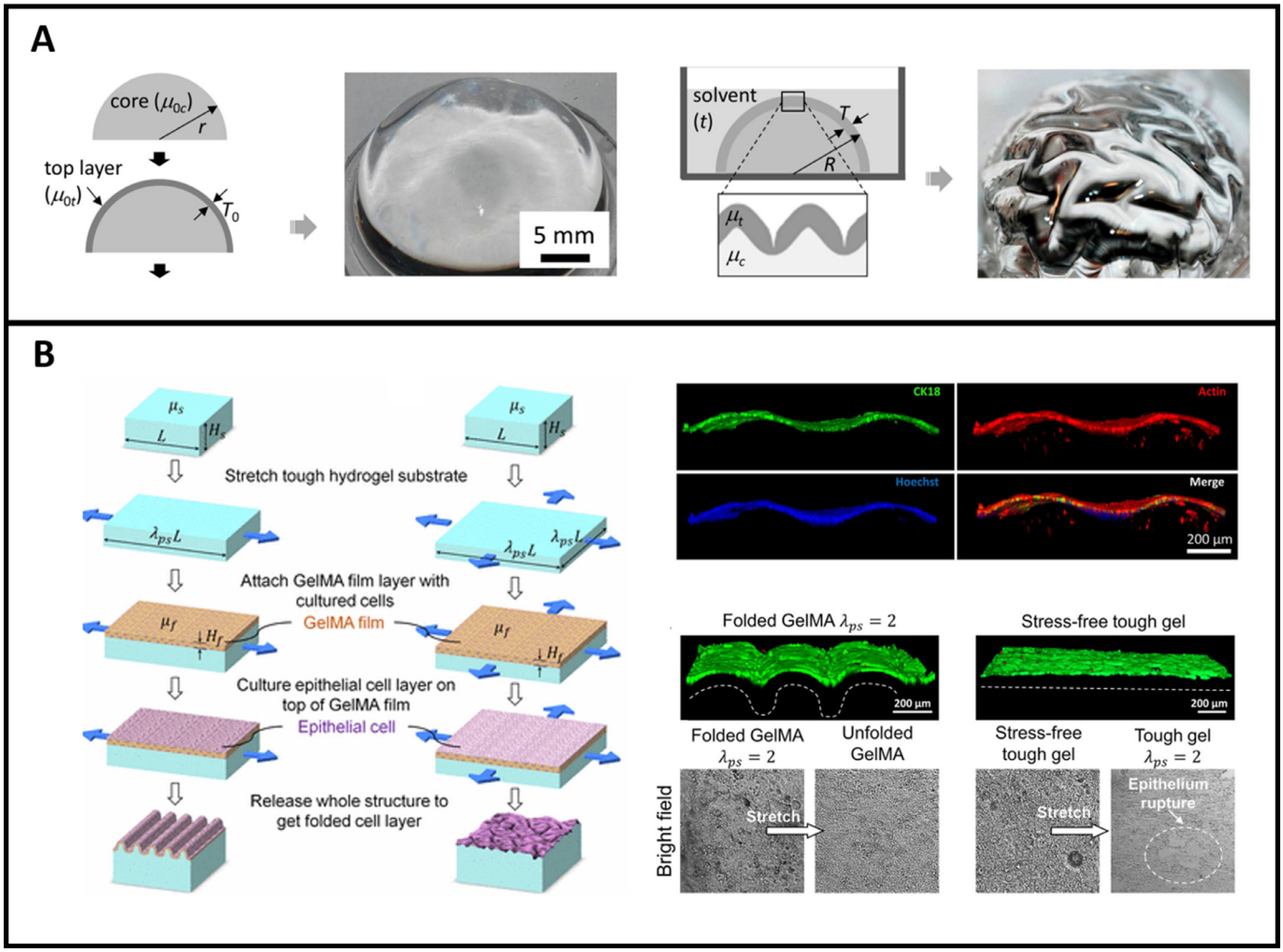

Fig. 6. Engineering folding via induced surface instability. A. Brainlike instability recapitulated using a hemispherical elastomer coated with a top elastomer layer that swelled by absorbing solvent over time. (Reproduced/adapted with permission from [44] Copyright (2014) National Academy of Sciences) B. (Left) Schematic showing how the tough PAAm-alginate hydrogel substrate was prestretched either uniaxially or biaxially before a cell-laden gelatin methacrylate hydrogel film was attached on top to induce folding after tension was released. (Right) Confocal microscope images showing the cell-laden hydrogel recapitulated epithelial and stromal cells in the mucosa layer and the folded tissue protected the epithelium from damage during the folding-unfolding process. (Reproduced/adapted with permission from [11] Copyright (2018) National Academy of Sciences).

polymer and disulfide-based diacrylate monomer also develops wrinkled patterns upon combined stimulation with heat and UV [79]. UV irradiation induces the formation of a double interpenetrating network as the film. After heating at 80 °C to promote thermal dilation of the structure, compressive stress can be generated by cooling the system to room temperature, which induces wrinkle formation. Electric fields can also be used to trigger creasing in conductive polymers such as PNIPAM-based polyanionic hydrogels that undergo electrically triggered changes in volume [80]. Creases can be reversibly formed and eliminated on the time-scale of a few seconds by switching on and off the electric field.

Although stimulus-responsive mechanisms can effectively induce folding and other instability patterns on demand, the administration of stimuli such as heat and electric fields can be unfavorable to living cells incorporated in the engineered tissue. Therefore, a purely mechanical approach based on an elastic substrate that generates compressive strain has been developed. Briefly, an elastic substrate such as PDMS is prestretched either uniaxially or biaxially before a film is coated on top of it through either spin coating, dip coating, or chemical vapor deposition [81,82]. The substrate is later relaxed to induce compressive strain on the film, which experiences surface instability and evolves morphological patterns. A phase diagram can be constructed with input parameters such as applied compressive strain, film substrate stiffness ratio, and adhesion energy between film and substrate to predict the instability patterns in both theoretical studies and numerical simulations [36]. A critical requirement for such fabrication is an elastic substrate that can provide the compressive strain, which is usually fulfilled by adopting elastomers such as PDMS. However, these elastomers typically do not have sufficient water permeability and degradability for engineering living tissue. Although hydrogels are popular biomaterials that can circumvent these issues, they are usually mechanically weak and have low stretchability. Our group recently engineered a tough and exceptionally stretchable hydrogel containing polyacrylamide (PAAm) and alginate, making it a good candidate for the substrate [11]. We attached a cell-laden gelatin methacrylate hydrogel film containing epithelial and stromal cells to recapitulate the mucosa layer to a prestretched PAAm-alginate hydrogel substrate. (**Fig. 6B**). Relaxation of the prestretched substrate led to fold formation, which could be predicted by finite element modeling. In addition, the folded tissue could protect the epithelium from damage during the folding-unfolding process, as during stomach expansion and deflation. A more recent study re-

ported that chemically crosslinked chitosan can serve as an elastic substrate. After prestretching, the surface can be further physically crosslinked to produce a film, which produces wrinkles after the tension is released [83]. Finally, wrinkling can also be induced in a single-layer hydrogel using the prestretching strategy [84]. When a hydrogel consisting of both chemical (PAAm) and physical networks (polyvinyl alcohol [PVA]) is stretched, the networks deform to the same extent, but recover differently after the stress is removed. The contraction force generated from the elastic deformation of PAAm induces mass redistribution of the PVA, leading to the formation of wrinkled hydrogels.

It is important to note that many examples of fabricated folded structures are planar, but the folded tissues in biological systems are usually curved, such as in the form of a tube. Although it is possible to roll the planar structure into a tube after the folds are produced, folded structures can be directly engineered on both the interior and exterior surfaces of a silicon rubber tube by depositing Parylene N film on a stretched tube via chemical vapor deposition prior to releasing the tension [85]. Similarly, a bilayer hydrogel (PNIPAM/clay/MXene)-elastomer (TPE) tube can be made to mimic the wrinkled morphology of the inner wall of a blood vessel through temperature-induced swelling and shrinkage of the hydrogel layer [86]. Such a stimulus-responsive folding design enables flow regulation in a manner similar to physiological autoregulation. A number of other examples show that folded film can be fabricated on spherical materials using a similar strategy [87–89]. Nevertheless, these deposition methods are applicable only to certain materials and are often incompatible with living cells. Therefore, further development in this direction is required. In addition, simulation studies have shown that, aside from mismatch strains and stiffness ratio, the curvature of the substrate also influences the types and properties of the instability patterns formed [90].

4. Conclusion and future perspective

Tissue engineering can contribute to significant advances in tissue replacement, disease modeling, and drug development. Given that many tissues fold into complex shapes during morphogenesis and that the folds often assume important functions, it is crucial to decipher and control the folding process *in vitro*. A number of diseases such as stomach cancer and inflammatory bowel disease often necessitate the surgical removal of parts of the stomach and intestine with folded features, and therefore, the implantation of engineered tissue that recapitulates the folded features of the native tissues/organs offers a potential therapeutic approach. Over the past few years, the mechanisms that drive folding, particularly the physical and mechanical aspects, have been gradually unveiled. This knowledge has effectively guided the development of strategies to engineer tissue folding *in vitro*. In this review, we summarized the mechanisms of tissue folding and strategies used to engineer them. At the cellular level, it has been shown that constriction of the cell membrane drives fold formation in *Drosophila*. Using an optogenetic approach, the localized activation of Rho1 GTPase can be used to trigger apical constriction and folding. Localized cell clustering in the form of Turing patterns or that induced by contractility-driven cellular pulling can also precede the biochemical signaling that initiates folding. Inspired by this, a 3D cell-patterning approach was developed to recapitulate contractility-driven folding via the contraction of deposited cells on a hydrogel. At the tissue level, instabilities induced by mismatch strain between different tissue layers have been widely reported to drive folding. Various bilayer biomaterial systems can be engineered to recapitulate this phenomenon. Finally, the 3D shape-changes that occur in plants can be reproduced using strategies such as 4D printing and cell-driven curving of scaffold materials.

These diverse bio fabrication approaches can contribute to tissue engineering in the following aspects:

1 First, the engineered tissue/organ containing folded structures can be used for tissue and organ repair and regeneration. In the case of esophagus, for example, the folded structure helps to close the lumen, attenuating reflux processes and allowing the expansion of esophageal tissue to accommodate a large food bolus. Previous studies have reported that a decellularized esophagus scaffold, with the folded structure preserved using a controlled perfusion process, has the potential to act as a human tissue substitute [91]. The construction of folded tissue using engineering principles offers an alternative to the use of decellularized tissues and organs. In addition, self-folding hydrogels made through 4D printing and cell-driven contraction can be used to engineer blood vessels or other curved or tubular tissues/organs for use in regenerative medicine [64,66,67,92].
2 Second, the technology can be adopted to develop tissue/organ models to study human diseases and perform drug screening. Conventional *in vitro* 2D models such as epithelial cell monolayer cultures do not effectively reproduce human physiological functions. For example, the monolayer culture of Caco-2 cells, which is a human colon epithelial cell line, cannot accurately mimic the physiological functions of cell differentiation, mucus production, and drug absorption as it lacks the unique 3D villi present in the intestine [93]. Therefore, a 3D tissue model with folded structures, similar to those reported previously [93–95], can be fabricated by 3D cell-patterning or by inducing surface instabilities to overcome the limitations of 2D models, and more accurately represent human physiology.
3 Finally, scaffolds with parallel folded structures can induce cellular alignments for tissue engineering. Several tissue types such as muscle and neural tissue are characterized by a high degree of cellular alignment, which enables the efficient transmission of force and electrical signals. As micro- or nanofabricated surfaces containing wrinkled patterns or gratings can promote cellular alignment during *in vitro* culture [81,96], the adoption of engineering strategies to create parallel folded or wrinkled structures can guide such alignments to mimic native tissue architecture.

Despite the promising advances in the engineering of tissue folding guided by theories, several key issues need to be overcome before these technologies can be translated to preclinical or clinical applications. Some of the approaches require materials (*e.g.* PDMS) or stimuli (*e.g.* heat) that are incompatible with living, implantable tissue. These techniques should be replaced with more cell-friendly approaches. Moreover, only very few studies have reported the *in vivo* performance of folded tissue. One study described the formation of a micro-scaled hollow tubule through a self-forming approach and demonstrated its ability to promote microcirculation *in vivo* [66]. It remains to be seen whether the folded tissue generated by other approaches can maintain their shape after implantation and whether the materials used will induce any adverse immune reactions *in vivo*. Given that multiple folding mechanisms could come into play simultaneously [97], a multifaceted approach that integrates both cellular-level and tissue-level effects would be preferable. From a clinical perspective, there is currently no tissue engineered product that can replace folded tissues/organs such as stomach and intestine. The above-described strategies for engineering folding may prove useful for the fabrication of functional tissue for regenerative medicine in the future.

Taken together, a collaboration between developmental biologists, biomechanical researchers, and tissue engineers could uncover more detailed mechanisms of folding and help develop strategies to apply this knowledge to the engineering of folded systems. Advances in the development of biomaterials and fabri-

cation technologies will enable the use of engineered folded tissue for biomedical applications to soon become a reality.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the National Key Research and Development Program of China (2019YFA0111300); Research Grants Council of Hong Kong (ECS (24204819), NSFC/RGC (N_CUHK432/20); Shun Hing Institute of Advanced Engineering (#BME–p5–19), VC discretionary Fund (8601014), and Direct Grant of The Chinese University of Hong Kong.

References

[1] P. Bajaj, R.M. Schweller, A. Khademhosseini, J.L. West, R. Bashir, 3D biofabrication strategies for tissue engineering and regenerative medicine, Annu. Rev. Biomed. Eng., 16 (2014) 247–276.
[2] D. Gilmour, M. Rembold, M. Leptin, From morphogen to morphogenesis and back, Nature 541 (7637) (2017) 311–320.
[3] E.J. Pearl, J. Li, J.B. Green, Cellular systems for epithelial invagination, Philos. Trans. R Soc. Lond. B Biol. Sci., 372 (1720) (2017).
[4] D. Sweeton, S. Parks, M. Costa, E. Wieschaus, Gastrulation in Drosophila: the formation of the ventral furrow and posterior midgut invaginations, Development 112 (3) (1991) 775–789.
[5] E. Reyssat, L. Mahadevan, Hygromorphs: from pine cones to biomimetic bilayers, J R Soc. Interface 6 (39) (2009) 951–957.
[6] C.M. Nelson, Geometric control of tissue morphogenesis, Biochim. Biophys. Acta., 1793 (5) (2009) 903–910.
[7] T.C. Seher, M. Narasimha, E. Vogelsang, M. Leptin, Analysis and reconstitution of the genetic cascade controlling early mesoderm morphogenesis in the Drosophila embryo, Mech. Dev., 124 (3) (2007) 167–179.
[8] V. Kolsch, T. Seher, G.J. Fernandez-Ballester, L. Serrano, M. Leptin, Control of Drosophila gastrulation by apical localization of adherens junctions and RhoGEF2, Science 315 (5810) (2007) 384–386.
[9] A.J. Hughes, H. Miyazaki, M.C. Coyle, J. Zhang, M.T. Laurie, D. Chu, Z. Vavrusova, R.A. Schneider, O.D. Klein, Z.J. Gartner, Engineered tissue folding by mechanical compaction of the Mesenchyme, Dev. Cell 44 (2) (2018) 165–178 e6.
[10] M. Tozluoglu, Y. Mao, On folding morphogenesis, a mechanical problem, Philos. Trans. R Soc. Lond. B Biol. Sci., 375 (1809) (2020) 20190564.
[11] H.F. Chan, R. Zhao, G.A. Parada, H. Meng, K.W. Leong, L.G. Griffith, X. Zhao, Folding artificial mucosa with cell-laden hydrogels guided by mechanics models, Proc. Natl. Acad. Sci. U S A 115 (29) (2018) 7503–7508.
[12] C.A. Ettensohn, Mechanisms of epithelial invagination, Q Rev. Biol., 60 (3) (1985) 289–307.
[13] D. St Johnston, B. Sanson, Epithelial polarity and morphogenesis, Curr. Opin. Cell Biol., 23 (5) (2011) 540–546.
[14] P. Spahn, R. Reuter, A vertex model of Drosophila ventral furrow formation, PLoS ONE 8 (9) (2013) e75051.
[15] V. Conte, F. Ulrich, B. Baum, J. Munoz, J. Veldhuis, W. Brodland, M. Miodownik, A biomechanical analysis of ventral furrow formation in the Drosophila melanogaster embryo, PLoS ONE 7 (4) (2012) e34473.
[16] A.C. Martin, B. Goldstein, Apical constriction: themes and variations on a cellular mechanism driving morphogenesis, Development 141 (10) (2014) 1987–1998.
[17] R.E. Dawes-Hoang, K.M. Parmar, A.E. Christiansen, C.B. Phelps, A.H. Brand, E.F. Wieschaus, Folded gastrulation, cell shape change and the control of myosin localization, Development 132 (18) (2005) 4165–4178.
[18] E. Farge, Mechanical induction of twist in the Drosophila foregut/stomodeal primordium, Curr. Biol., 13 (16) (2003) 1365–1377.
[19] H.Y. Kim, V.D. Varner, C.M. Nelson, Apical constriction initiates new bud formation during monopodial branching of the embryonic chicken lung, Development 140 (15) (2013) 3146–3155.
[20] Y. Inoue, M. Suzuki, T. Watanabe, N. Yasue, I. Tateo, T. Adachi, N. Ueno, Mechanical roles of apical constriction, cell elongation, and cell migration during neural tube formation in Xenopus, Biomech. Model Mechanobiol., 15 (6) (2016) 1733–1746.
[21] S. Chung, S. Kim, D.J. Andrew, Uncoupling apical constriction from tissue invagination, Elife 6 (2017).
[22] B. Monier, M. Gettings, G. Gay, T. Mangeat, S. Schott, A. Guarner, M. Suzanne, Apico-basal forces exerted by apoptotic cells drive epithelium folding, Nature 518 (7538) (2015) 245–248.
[23] P. Ybot-Gonzalez, A.J. Copp, Bending of the neural plate during mouse spinal neurulation is independent of actin microfilaments, Dev. Dyn., 215 (3) (1999) 273–283.
[24] J.H. Gutzman, E.G. Graeden, L.A. Lowery, H.S. Holley, H. Sive, Formation of the zebrafish midbrain-hindbrain boundary constriction requires laminin-dependent basal constriction, Mech. Dev., 125 (11–12) (2008) 974–983.
[25] Y.C. Wang, Z. Khan, M. Kaschube, E.F. Wieschaus, Differential positioning of adherens junctions is associated with initiation of epithelial folding, Nature 484 (7394) (2012) 390–393.
[26] E. Panousopoulou, J.B. Green, Invagination of ectodermal placodes is driven by cell intercalation-mediated contraction of the suprabasal tissue canopy, PLoS Biol., 14 (3) (2016) e1002405.
[27] K.D. Walton, A. Kolterud, M.J. Czerwinski, M.J. Bell, A. Prakash, J. Kushwaha, A.S. Grosse, S. Schnell, D.L. Gumucio, Hedgehog-responsive mesenchymal clusters direct patterning and emergence of intestinal villi, Proc. Natl. Acad. Sci. U S A 109 (39) (2012) 15817–15822.
[28] K.D. Walton, M. Whidden, A. Kolterud, S.K. Shoffner, M.J. Czerwinski, J. Kushwaha, N. Parmar, D. Chandhrasekhar, A.M. Freddo, S. Schnell, D.L. Gumucio, Villification in the mouse: bmp signals control intestinal villus patterning, Development 143 (3) (2016) 427–436.
[29] A.E. Shyer, A.R. Rodrigues, G.G. Schroeder, E. Kassianidou, S. Kumar, R.M. Harland, Emergent cellular self-organization and mechanosensation initiate follicle pattern in the avian skin, Science 357 (6353) (2017) 811–815.
[30] H.Y. Kim, M.F. Pang, V.D. Varner, L. Kojima, E. Miller, D.C. Radisky, C.M. Nelson, Localized smooth muscle differentiation is essential for epithelial bifurcation during branching morphogenesis of the mammalian lung, Dev. Cell 34 (6) (2015) 719–726.
[31] A.E. Shyer, T. Tallinen, N.L. Nerurkar, Z. Wei, E.S. Gil, D.L. Kaplan, C.J. Tabin, L. Mahadevan, Villification: how the gut gets its villi, Science 342 (6155) (2013) 212–218.
[32] H. Koyama, D. Shi, M. Suzuki, N. Ueno, T. Uemura, T. Fujimori, Mechanical regulation of three-dimensional epithelial fold pattern formation in the mouse oviduct, Biophys. J. 111 (3) (2016) 650–665.
[33] M.Ben Amar, F. Jia, Anisotropic growth shapes intestinal tissues during embryogenesis, Proc. Natl. Acad. Sci. U S A 110 (26) (2013) 10525–10530.
[34] C.M. Nelson, On buckling morphogenesis, J Biomech. Eng., 138 (2) (2016) 021005.
[35] E. Cerda, L. Mahadevan, Geometry and physics of wrinkling, Phys. Rev. Lett., 90 (7) (2003) 074302.
[36] Q. Wang, X. Zhao, A three-dimensional phase diagram of growth-induced surface instabilities, Sci. Rep., 5 (2015) 8887.
[37] K.E. Garcia, E.C. Robinson, D. Alexopoulos, D.L. Dierker, M.F. Glasser, T.S. Coalson, C.M. Ortinau, D. Rueckert, L.A. Taber, D.C. Van Essen, C.E. Rogers, C.D. Smyser, P.V. Bayly, Dynamic patterns of cortical expansion during folding of the preterm human brain, Proc. Natl. Acad. Sci. USA 115 (12) (2018) 3156–3161.
[38] K.R. Long, B. Newland, M. Florio, N. Kalebic, B. Langen, A. Kolterer, P. Wimberger, W.B. Huttner, Extracellular matrix components HAPLN1, lumican, and collagen I cause hyaluronic acid-depend ent folding of the developing human neocortex, Neuron 99 (4) (2018) 702–719 e6.
[39] K.E. Garcia, C.D. Kroenke, P.V. Bayly, Mechanics of cortical folding: stress, growth and stability, Philos. Trans. R Soc. Lond. B Biol. Sci., 373 (1759) (2018).
[40] T. Tallinen, J.Y. Chung, F. Rousseau, N. Girard, J. Lefevre, A. Mahadevan, On the growth and form of cortical convolutions, Nat. Phys., 12 (2016) 588–593.
[41] D.C. Van Essen, A tension-based theory of morphogenesis and compact wiring in the central nervous system, Nature 385 (6614) (1997) 313–318.
[42] G. Xu, A.K. Knutsen, K. Dikranian, C.D. Kroenke, P.V. Bayly, L.A. Taber, Axons pull on the brain, but tension does not drive cortical folding, J Biomech. Eng., 132 (7) (2010) 071013.
[43] M.J. Razavi, T. Zhang, T. Liu, X. Wang, Cortical folding pattern and its consistency induced by biological growth, Sci. Rep., 5 (2015) 14477.
[44] T. Tallinen, J.Y. Chung, J.S. Biggins, L. Mahadevan, Gyrification from constrained cortical expansion, Proc. Natl. Acad. Sci. USA 111 (35) (2014) 12667–12672.
[45] A.K. Lawton, T. Engstrom, D. Rohrbach, M. Omura, D.H. Turnbull, J. Mamou, T. Zhang, J.M. Schwarz, A.L. Joyner, Cerebellar folding is initiated by mechanical constraints on a fluid-like layer without a cellular pre-pattern, Elife 8 (2019).
[46] A.E. Shyer, T.R. Huycke, C. Lee, L. Mahadevan, C.J. Tabin, Bending gradients: how the intestinal stem cell gets its home, Cell 161 (3) (2015) 569–580.
[47] T. Savin, N.A. Kurpios, A.E. Shyer, P. Florescu, H. Liang, L. Mahadevan, C.J. Tabin, On the growth and form of the gut, Nature 476 (7358) (2011) 57–62.
[48] N.L. Nerurkar, C. Lee, L. Mahadevan, C.J. Tabin, Molecular control of macroscopic forces drives formation of the vertebrate hindgut, Nature 565 (7740) (2019) 480–484.
[49] M. Tozluoglu, M. Duda, N.J. Kirkland, R. Barrientos, J.J. Burden, J.J. Munoz, Y. Mao, Planar differential growth rates initiate precise fold positions in complex epithelia, Dev. Cell 51 (3) (2019) 299–312 e4.
[50] I. Burgert, P. Fratzl, Actuation systems in plants as prototypes for bioinspired devices, Philos. T R Soc. A 367 (1893) (2009) 1541–1557.
[51] J. Dawson, J.F.V. Vincent, A.M. Rocca, How pine cones open, Nature 390 (6661) (1997) 668 -668.
[52] Y. Li, J. Muffat, A. Omer, I. Bosch, M.A. Lancaster, M. Sur, L. Gehrke, J.A. Knoblich, R. Jaenisch, Induction of expansion and folding in human cerebral organoids, Cell Stem Cell 20 (3) (2017) 385–396 e3.
[53] M. Eiraku, N. Takata, H. Ishibashi, M. Kawada, E. Sakakura, S. Okuda, K. Sekiguchi, T. Adachi, Y. Sasai, Self-organizing optic-cup morphogenesis in three-dimensional culture, Nature 472 (7341) (2011) 51–56.
[54] A.D. Graham, S.N. Olof, M.J. Burke, J.P.K. Armstrong, E.A. Mikhailova, J.G. Nicholson, S.J. Box, F.G. Szele, A.W. Perriman, H. Bayley, High-resolution

patterned cellular constructs by droplet-based 3D printing, Sci. Rep., 7 (1) (2017) 7004.
[55] J.M. Karp, Y. Yeo, W. Geng, C. Cannizarro, K. Yan, D.S. Kohane, G. Vunjak-Novakovic, R.S. Langer, M. Radisic, A photolithographic method to create cellular micropatterns, Biomaterials 27 (27) (2006) 4755–4764.
[56] P.A. Janmey, R.T. Miller, Mechanisms of mechanical signaling in development and disease, J Cell Sci., 124 (Pt 1) (2011) 9–18.
[57] K. Barrett, M. Leptin, J. Settleman, The Rho GTPase and a putative RhoGEF mediate a signaling pathway for the cell shape changes in Drosophila gastrulation, Cell 91 (7) (1997) 905–915.
[58] E. Izquierdo, T. Quinkler, S. De Renzis, Guided morphogenesis through optogenetic activation of Rho signalling during early Drosophila embryogenesis, Nat. Commun., 9 (1) (2018) 2366.
[59] S.A. Hilton, L.C. Dewberry, M.M. Hodges, J. Hu, J. Xu, K.W. Liechty, C. Zgheib, Mesenchymal stromal cells contract collagen more efficiently than dermal fibroblasts: implications for cytotherapy, PLoS ONE 14 (7) (2019) e0218536.
[60] J.M. Viola, C.M. Porter, A. Gupta, M. Alibekova, L.S. Prahl, A.J. Hughes, Guiding cell network assembly using shape-morphing hydrogels, Adv. Mater., 32 (31) (2020) e2002195.
[61] C.D. Morley, S.T. Ellison, T. Bhattacharjee, C.S. O'Bryan, Y. Zhang, K.F. Smith, C.P. Kabb, M. Sebastian, G.L. Moore, K.D. Schulze, S. Niemi, W.G. Sawyer, D.D. Tran, D.A. Mitchell, B.S. Sumerlin, C.T. Flores, T.E. Angelini, Quantitative characterization of 3D bioprinted structural elements under cell generated forces, Nat. Commun., 10 (1) (2019) 3029.
[62] H. Chu, W. Yang, L. Sun, S. Cai, R. Yang, W. Liang, H. Yu, L. Liu, 4D Printing: a review on recent progresses, Micromachines (Basel) 11 (9) (2020).
[63] A.S. Gladman, E.A. Matsumoto, R.G. Nuzzo, L. Mahadevan, J.A. Lewis, Biomimetic 4D printing, Nat. Mater., 15 (4) (2016) 413–418.
[64] A. Kirillova, R. Maxson, G. Stoychev, C.T. Gomillion, L. Ionov, 4D Biofabrication using shape-morphing hydrogels, Adv. Mater., 29 (46) (2017) 1703443.
[65] A. Nojoomi, H. Arslan, K. Lee, K. Yum, Bioinspired 3D structures with programmable morphologies and motions, Nat. Commun., 9 (1) (2018) 3705.
[66] L. Zhang, Y. Xiang, H. Zhang, L. Cheng, X. Mao, N. An, L. Zhang, J. Zhou, L. Deng, Y. Zhang, X. Sun, H.A. Santos, W. Cui, A biomimetic 3D-self-forming approach for microvascular scaffolds, Adv. Sci. (Weinh) 7 (9) (2020) 1903553.
[67] M. Miotto, R.M. Gouveia, A.M. Ionescu, F. Figueiredo, I.W. Hamley, C.J. Connon, 4D Corneal tissue engineering: achieving time-dependent tissue self-curvature through localized control of cell actuators, Adv. Mater., 29 (2019) 1807334.
[68] Y. Kim, H. Yuk, R. Zhao, S.A. Chester, X. Zhao, Printing ferromagnetic domains for untethered fast-transforming soft materials, Nature 558 (7709) (2018) 274–279.
[69] M.R. Nelson, J.R. King, O.E. Jensen, Buckling of a growing tissue and the emergence of two-dimensional patterns, Math. Biosci., 246 (2) (2013) 229–241.
[70] R. Al-Rashed, F.Lopez Jimenez, J. Marthelot, P.M. Reis, Buckling patterns in biaxially pre-stretched bilayer shells: wrinkles, creases, folds and fracture-like ridges, Soft. Matter., 13 (43) (2017) 7969–7978.
[71] T. Ouchi, J. Yang, Z. Suo, R.C. Hayward, Effects of stiff film pattern geometry on surface buckling instabilities of elastic bilayers, ACS Appl. Mater. Interfaces 10 (27) (2018) 23406–23413.
[72] P. Nardinocchi, E. Puntel, Swelling-induced wrinkling in layered gel beams, Proc. Math. Phys. Eng. Sci., 473 (2207) (2017) 20170454.
[73] F. Weiss, S. Cai, Y. Hu, M.K. Kang, R. Huang, Z. Suo, Creases and wrinkles on the surface of a swollen gel, J Appl. Phys., 114 (2013).
[74] N. Gao, X. Zhang, S. Liao, H. Jia, Y. Wang, Polymer swelling induced conductive wrinkles for an ultrasensitive pressure sensor, ACS Macro Lett., 5 (7) (2016) 823–827.
[75] M. Jamal, S.S. Kadam, R. Xiao, F. Jivan, T.M. Onn, R. Fernandes, T.D. Nguyen, D.H. Gracias, Bio-origami hydrogel scaffolds composed of photocrosslinked PEG bilayers, Adv. Healthc. Mater., 2 (8) (2013) 1142–1150.
[76] J. Yoon, J. Kim, R.C. Hayward, Nucleation, growth, and hysteresis of surface creases, Soft Matter 6 (2010) 5807–5816.
[77] J. Yoon, P. Bian, J. Kim, T.J. McCarthy, R.C. Hayward, Local switching of chemical patterns through light-triggered unfolding of creased hydrogel surfaces, Angew Chem. Int. Ed. Engl., 51 (29) (2012) 7146–7149.
[78] E. Kapyla, S.M. Delgado, A.M. Kasko, Shape-changing photodegradable hydrogels for dynamic 3d cell culture, ACS Appl. Mater. Interfaces 8 (28) (2016) 17885–17893.
[79] L. Zhou, T. Ma, T. Li, X. Ma, J. Yin, X. Jiang, Dynamic interpenetrating polymer network (ipn) strategy for multiresponsive hierarchical pattern of reversible wrinkle, ACS Appl. Mater. Interfaces 11 (17) (2019) 15977–15985.
[80] B. Xu, R.C. Hayward, Low-voltage switching of crease patterns on hydrogel surfaces, Adv. Mater., 25 (39) (2013) 5555–5559.
[81] C. Cao, H.F. Chan, J. Zang, K.W. Leong, X. Zhao, Harnessing localized ridges for high-aspect-ratio hierarchical patterns with dynamic tunability and multifunctionality, Adv. Mater., 26 (11) (2014) 1763–1770.
[82] J. Zou, S. Wu, J. Chen, X. Lei, Q. Li, H. Yu, S. Tang, D. Ye, Highly efficient and environmentally friendly fabrication of robust, programmable, and biocompatible anisotropic, all-cellulose, wrinkle-patterned hydrogels for cell alignment, Adv. Mater., 31 (46) (2019) e1904762.
[83] X. Lei, D. Ye, J. Chen, S. Tang, P. Sun, L. Chen, A. Lu, Y. Du, L. Zhang, Customizable multidimensional self-wrinkling structure constructed via modulus gradient in chitosan hydrogels, Chem. Mater. 31 (2019) 10032–10039.
[84] C. Wang, S. Yang, Q. Guo, L. Xu, Y. Xu, D. Qiu, Wrinkled double network hydrogel via simple stretch-recovery, Chem. Commun. (Camb) 56 (88) (2020) 13587–13590.
[85] A. Takei, L. Jin, H. Fujita, A. Takei, H. Fujita, L. Jin, High-aspect-ratio ridge structures induced by plastic deformation as a novel microfabrication technique, ACS Appl. Mater. Interfaces 8 (36) (2016) 24230–24237.
[86] X. Wen, S. Sun, P. Wu, Dynamic wrinkling of hydrogel-elastomer hybrid microtube enables blood vessel-like hydraulic pressure sensing and flow regulation, Mater. Horiz., 7 (2020) 2150–2157.
[87] J. Song, Y. Tan, Z. Chu, M. Xiao, G. Li, Z. Jiang, J. Wang, T. Hu, Hierarchical reduced graphene oxide ridges for stretchable, wearable, and washable strain sensors, ACS Appl. Mater. Interfaces 11 (1) (2019) 1283–1293.
[88] Q. Li, X. Han, J. Hou, J. Yin, S. Jiang, C. Lu, Patterning poly(dimethylsiloxane) microspheres via combination of oxygen plasma exposure and solvent treatment, J Phys. Chem. B 119 (42) (2015) 13450–13461.
[89] J. Yin, X. Han, Y. Cao, C. Lu, Surface wrinkling on polydimethylsiloxane microspheres via wet surface chemical oxidation, Sci. Rep., 4 (2014) 5710.
[90] R. Zhao, X. Zhao, Multimodal surface instabilities in curved film–substrate structures, J. Appl. Mech., 84 (8) (2017).
[91] S. Sitthisang, M.F. Leong, K.S. Chian, Perfusion decellularization of porcine esophagus: study of two processing factors affecting the folded mucosal structure of the esophageal scaffold, J. Biomed. Mater. Res. A 109 (5) (2021) 745–753.
[92] K. Kuribayashi-Shigetomi, H. Onoe, S. Takeuchi, Cell origami: self-folding of three-dimensional cell-laden microstructures driven by cell traction force, PLoS ONE 7 (12) (2012) e51085.
[93] S.H. Kim, M. Chi, B. Yi, S.H. Kim, S. Oh, Y. Kim, S. Park, J.H. Sung, Three-dimensional intestinal villi epithelium enhances protection of human intestinal cells from bacterial infection by inducing mucin expression, Integr. Biol-Uk 6 (12) (2014) 1122–1131.
[94] W. Kim, G. Kim, Intestinal villi model with blood capillaries fabricated using collagen-based bioink and dual-cell-printing process, Acs. Appl. Mater. Inter., 10 (48) (2018) 41185–41196.
[95] C.M. Costello, R.M. Sorna, Y.L. Goh, I. Cengic, N.K. Jain, J.C. March, 3-D intestinal scaffolds for evaluating the therapeutic potential of probiotics, Mol. Pharmaceut., 11 (7) (2014) 2030–2039.
[96] E.K. Yim, S.W. Pang, K.W. Leong, Synthetic nanostructures inducing differentiation of human mesenchymal stem cells into neuronal lineage, Exp. Cell Res., 313 (9) (2007) 1820–1829.
[97] H. Koyama, T. Fujimori, Biomechanics of epithelial fold pattern formation in the mouse female reproductive tract, Curr. Opin. Genet. Dev., 51 (2018) 59–66.