

Mechanical forces and organoid biology: From mechanotransduction mechanisms to translational frontiers

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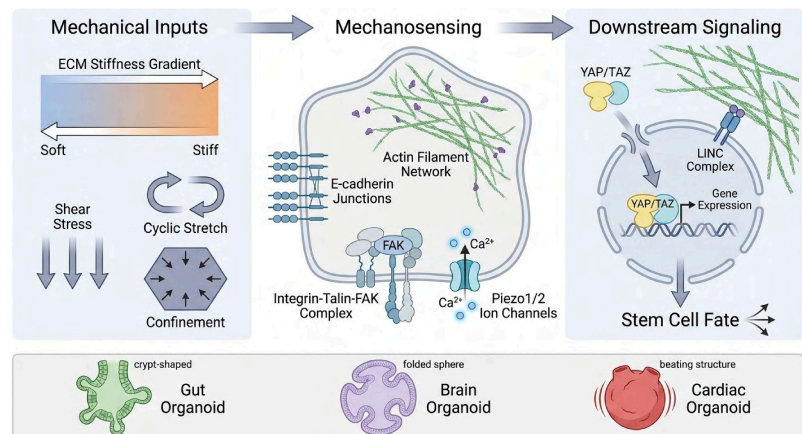
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In Brief

This review outlines core mechanotransduction machineries in organoids, including integrins, Piezo channels, and linker of nucleoskeleton and cytoskeleton (LINC) complexes. It illustrates how matrix mechanics and fluid forces regulate stem cell fate and morphogenesis of four major organoid types, and introduces bioengineered tools as well as translational advances in disease modeling and mechanopharmacology.

Graphical abstract



Highlights

- Mechanical forces coordinate with biochemical cues to govern organoid self-organization, stem cell fate and morphogenesis.
- Integrin–focal adhesion kinase (FAK) complexes, Piezo channels, and LINC complexes act as core mechanotransduction machineries in organoids.
- Tunable hydrogels, organ-on-chips and bioreactors enable precise recreation of physiological mechanical microenvironments.
- Organoid mechanobiology advances disease modeling, mechanopharmacology and clinical translational therapy development.

Mechanical forces and organoid biology: From mechanotransduction mechanisms to translational frontiers

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ABSTRACT

Organoids have revolutionized the field of biomedical research by allowing the recapitulation of organ architecture in three dimensions. Though biochemical factors have long played an established role in organoid culture, it is presently recognized that mechanical forces are equally indispensable in the self-organization of tissues and the determination of stem cell and disease phenotypes. Here, this review integrates the biophysics of cellular mechanotransduction with the biology of organoid systems, examining how forces encoded in extracellular matrix stiffness, viscoelasticity, fluid shear, cyclic stretch, and geometric confinement are sensed and transduced by a specialized molecular machinery—including integrin–focal adhesion kinase (FAK) complexes, mechanosensitive Piezo1/2 ion channels, and the linker of nucleoskeleton and cytoskeleton (LINC) complex—to ultimately regulate Yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ)-mediated transcriptional programs. How engineered hydrogels with tunable mechanical properties, microfluidic organ-on-chip platforms, and bioreactor systems have enabled in-depth exploration of these forces in gut, brain, cardiac, and kidney organoids will be well discussed. Emerging work highlights Piezo channels as critical gatekeepers of intestinal stem cell (ISC) fate, extracellular matrix (ECM) stiffness as a driver of aberrant gyrification in lissencephaly brain organoids, and viscoelastic stress relaxation as a key determinant of neural progenitor maturation. Organoid mechanobiology is set to revolutionize human disease modeling and regenerative medicine with its convergence with patient-derived models, computational mechanics, and Good Manufacturing Practice (GMP)-compatible bioengineering platforms.

KEYWORDS

mechanotransduction, organoids, YAP/TAZ, Piezo channels, hydrogel mechanics, organ-on-chip, morphogenesis, stem cell fate, tissue engineering

Introduction

Organoids have emerged in the last decade as one of the key technologies in biomedical research, with three-dimensional (3D) cultures of organ architecture and cell diversity significantly surpassing the reductionist simplicity of traditional two-dimensional (2D) cell culture systems^[1,2]. Organoids have successfully leveraged the inherent self-organizing potential of pluripotent or tissue-resident stem cells to create breakthrough technologies for studying human development, disease, and treatment in ways that more closely mimic *in vivo* physiology. Nevertheless, there remains a disconnect between organoid systems and tissue-like cultures that is no longer thought to be solely due to the lack of vasculature and immune cells but is instead related to the overall lack of consideration of the cell's microenvironment^[3,4].

Cells are not merely inhabitants of their microenvironment; rather, they are actively engaged in sensing, processing, and

responding to mechanical cues, which are encoded in the stiffness of their surroundings, the geometry of their confinement, the pulsatile flow of their extracellular fluids, and the inherent contractility of their cytoskeletons. This complex process, termed mechanotransduction, translates mechanical inputs into biochemical signals, which regulate all aspects of cell biology, including cell division, differentiation, migration, polarity, and apoptosis^[5]. The significance of mechanotransduction in development and tissue homeostasis has been firmly established, including its role in mesenchymal stem cell differentiation in response to matrix stiffness^[6], endothelial cell specification in response to shear stress, and cardiac muscle cell differentiation in response to cyclic stretch^[7]. Similarly, its role in disease states, such as fibrosis, cancer progression, and cardiac hypertrophy, is equally potent.

In the organoid world, these discoveries necessitate a rethinking of the fundamental principles used in the development of model

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systems. For the majority of their history, organoids have been maintained on animal-derived extracellular matrix (ECM) extracts such as Matrigel, which, while providing biological support, are chemically undetermined, mechanistically variable, and utterly incapable of mimicking the complex mechanical environment experienced by cells *in vivo*^[6]. This is not simply an issue of technical capability, as it influences the development of stem cells, limits the maturation potential of organoids, and may impact their physiological relevance.

A new frontier for organoid research is therefore emerging at the crossroads of mechanobiology and bioengineering^[8,10]. Using chemically defined hydrogels with tailored elasticity and viscoelastic properties, microfluidic chips with precisely regulated fluid flows, and bioreactors with programmed mechanical loading, it is now possible to systematically investigate the role of forces on organoids at the molecular, cellular, and tissue levels. At the same time, landmark studies have identified mechanosensory molecules such as the Piezo1 and Piezo2 ion channels as critical regulators of stem cell behavior in the intestinal microenvironment^[11], and disease-causing mutations that alter the mechanical properties of brain organoids and mimic cortical folding disorders^[12].

This review aims to provide a comprehensive overview of the role of mechanical forces in organoid biology. First, we will outline the molecular basis of mechanotransduction, which includes integrin-based adhesion, ion channel mechanosensing, cytoskeletal mechanosensing, and nuclear mechanobiology. Next, we will discuss the role of matrix mechanics in organoid development and stem cell decision-making, particularly with regard to Yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ) signaling and Piezo channel biology. We will then discuss the role of forces in organoid morphogenesis, from symmetry breaking and lumenogenesis to cortical gyrification and cardiac maturation. Additionally, we will outline the increasing repertoire of tools for mechanically manipulating organoids and discuss the organ-specific mechanical environment in governing the biology of intestinal, brain, cardiac, and renal organoids. Finally, we will evaluate the potential for translating mechanobiology into disease models and therapeutic applications.

Cellular mechanotransduction: Molecular foundations

Integrin-mediated force sensing at the cell–matrix interface

The physical link between the cell and its ECM is dominated by integrins, which are heterodimeric cell surface receptors for fibronectin, laminins, and several types of collagen, while their intracellular domain interacts with the actin-based cell surface adhesomes^[13]. Upon ECM engagement, integrins cluster and nucleate focal adhesions, multi-molecular assemblies comprising scaffolding proteins (talin, vinculin, and paxillin), signaling kinases (focal adhesion kinase (FAK), Src), and cytoskeletal adaptors. Importantly, these focal adhesions are mechanosensitive, and it is believed that the applied stresses along the actin–integrin–ECM pathway unmask hidden binding sites and kinase activities, leading to signaling via various pathways, including MAPK, PI3K–Akt, and Rho GTPase pathways (Fig. 1)^[14].

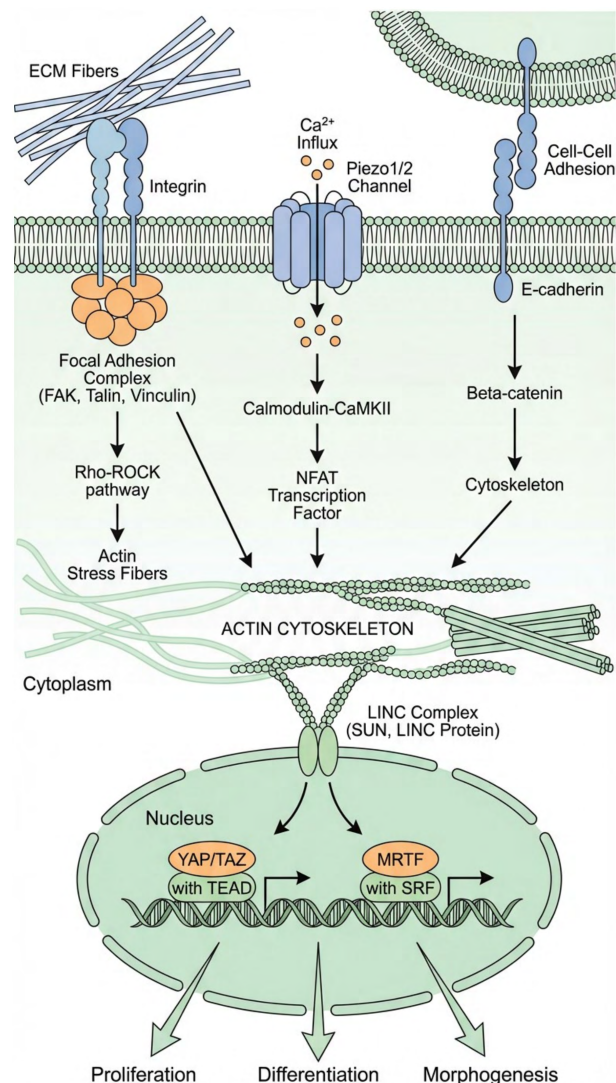


Figure 1. Mechanotransduction signaling pathways in organoid-forming cells.

Three principal mechanical signal transduction axes converge to regulate gene expression and cell fate. (Left) The integrin–FAK–Rho/ROCK axis links ECM stiffness to actin cytoskeletal tension and downstream MAPK and YAP/TAZ activation. (Center) Piezo1/2 mechanosensitive channels mediate calcium influx in response to membrane tension, triggering calmodulin–CaMKII signaling and modulating the NOTCH and Wnt pathways. (Right) Cadherin-mediated junction forces engage β -catenin and cytoskeletal coupling. All three axes converge on the nucleus through the LINC Complex and YAP/TAZ–TEAD transcriptional complexes. Key downstream outputs include proliferation, lineage commitment, and morphogenetic remodeling.

The substrate stiffness is transduced through this integrin-based machinery in proportion to the resistance to traction force generation. When cultured on soft substrates, cells are able to generate traction forces, but the matrix is easily deformed, resulting in reduced cytoskeletal stress fibers and focal adhesion formation. When cultured on stiff substrates, cells experience high resistance to traction force generation, resulting in increased thickness of actin bundles and proportionate increases in focal adhesion area and signaling intensity. Such mechanical transduction is sufficient to direct cellular lineage specification, as seminal work by Engler et al. demonstrated that human mesenchymal stem cells differentiated into neurogenic, myogenic, or osteogenic phenotypes when cultured on substrates matching

the stiffness of brain (~0.1–1 kPa), muscle (~8–17 kPa), or bone (~25–40 kPa) tissue, respectively, in the complete absence of lineage-inductive soluble factors^[6].

Piezo ion channels: Calcium gateways for mechanosensing

Although this signaling pathway takes minutes to hours to complete, mechanosensitive ion channels respond in a matter of milliseconds to mechanical input. Of these, Piezo1 and Piezo2 have emerged as paradigm-defining mechanosensors. Piezo channels are large, trimeric transmembrane proteins that create a propeller-like structure that is capable of deforming in response to membrane tension, bilayer curvature, or cytoskeletal forces to create a non-selective cation channel that is permeable to calcium^[9].

A landmark study in 2024 by Baghdadi et al. has shown that, far from being just mechanosensors, Piezo1 and Piezo2 play critical roles in the regulation of intestinal stem cell (ISC) fate^[11]. This study, which utilized conditional double knockout mouse models, three-dimensional organoid culture systems, crypt-targeted stretching technology, and bioengineered substrates with specific stiffness, has shown that the PIEZO mechanosensors detect the stiffness of the crypt environment and the mechanical stretch induced by the stretching of neighboring cells. Activation of the Piezo channels results in calcium signaling, which downregulates NOTCH and induces secretory cell differentiation. Conversely, knockout of both Piezo1 and Piezo2 resulted in the catastrophic failure of ISC homeostasis and the rapid lethality of the knockout mice. A related study by Fang et al. showed that Piezo1 also regulates colonic stem cell proliferation via a SCD1-Wnt- β -catenin metabolic pathway, thus placing Piezo channels at the crossroads of mechanical and metabolic sensing in intestinal homeostasis^[14].

Nuclear mechanotransduction via the LINC complex

The mechanical forces detected at the cell surface do not only trigger the initiation of cytoplasmic signaling cascades; rather, these forces are transmitted to the nucleus via the linker of nucleoskeleton and cytoskeleton (LINC) complex, which is a molecular bridge between the nucleoskeleton and the cytoskeleton, consisting of SUN domain proteins in the inner membrane of the nuclear envelope and KASH domain nesprins in the outer membrane of the nuclear envelope^[15,16]. This complex links the cytoskeleton (actin, microtubules, and intermediate filaments) to the lamins and ultimately to chromatin itself. Mechanical forces are transmitted to the nucleus via this pathway, leading to the alteration of the shape of the nucleus, the organization of the lamins, and chromatin, thereby regulating the transcriptional program of the cell via biophysical mechanisms, independent of classical signal transduction pathways^[16].

The nucleus is therefore seen to function as an intrinsic mechanosensory organelle: its stiffness, controlled by lamin A/C expression levels, is adjusted to match tissue-level mechanical properties (stiff nuclei in stiff tissues and compliant nuclei in soft brain tissue), and alterations in this stiffness through mutations in the nuclear envelope (as in laminopathies) impact mechanosensing and disease pathology. In organoid systems, this pathway links matrix mechanics to epigenetics and cell fate in a way that provides a physical basis for the transmission of environmental mechanical information over long distances.

YAP and TAZ: Mechanotransductive transcriptional co-activators

Key effectors of transcriptional responses to mechanical stimuli include Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ), two paralogous transcriptional co-activators that cycle between cytoplasmic and nuclear compartments in response to cytoskeletal tension, substrate stiffness, and tissue geometry^[17]. On stiff substrates or under conditions of high cytoskeletal tension, dephosphorylation of YAP/TAZ leads to nuclear translocation and binding of YAP/TAZ with TEAD family transcription factors to induce transcription of cell proliferation and stemness gene expression programs. On soft substrates or in confined geometries, activation of the Hippo kinase cascade leads to cytoplasmic retention of YAP/TAZ via phosphorylation and induction of differentiation gene expression.

This mechanical control of YAP/TAZ is closely linked to organoid biology. For example, YAP nuclear localization is necessary and sufficient for stem cell expansion and regenerative activation in intestinal organoids^[18]. In liver organoids, progressive matrix stiffening, as observed in fibrosis, maintains YAP nuclear localization and upregulation of TGF- β target genes and transcriptional programs^[19]. Importantly, this interaction between YAP/TAZ and organoids is context-dependent in 3D systems. As has been shown in an extensive review of 3D mechanotransduction pathways by Saraswathibhatla et al.^[9], while there is an almost universal correlation between matrix stiffness and YAP nuclear localization in 2D systems, this interaction is significantly more complex in 3D systems, where matrix degradability and stress relaxation can independently influence YAP/TAZ activity.

Matrix mechanics and organoid development

The primacy of stiffness: From linear elasticity to tissue-specific optima

The extracellular matrix is the physical structure in which organoids form, and it is known to significantly affect the developmental pathways that are possible for stem and progenitor cells embedded in it. The most commonly investigated property is the elastic modulus, or “stiffness”, which varies over several orders of magnitude in human tissues. Brain parenchyma is among the softest tissues, at around 0.1–1 kPa, whereas intestinal tissue is intermediate in stiffness at around 0.5–2 kPa, and bone tissue is much stiffer, at around GPa. Matching organoid culture matrices to these tissue-specific mechanical environments is a critical aspect of their design^[8].

For instance, in intestinal organoids, Gjorevski and colleagues showed that a biphasic mechanical approach involving initial culture in soft and permissive matrices of ~100–300 Pa to support ISC survival and expansion, followed by differentiation in stiffer matrices of ~1.3 kPa, significantly increases organoid formation efficiency compared to uniform stiffness matrices. This biphasic approach mirrors the soft crypt and stiffer villus environments *in vivo*^[8]. More recent work surveyed by Lai et al. has confirmed tissue-type optimal stiffness for hepatic (~0.5–2 kPa for hepatocyte function), renal (~1–5 kPa for tubular epithelium), and neural (~0.1–1 kPa for neuronal differentiation) organoids and defined the corresponding states of YAP/TAZ, Notch, and integrin

signaling pathways associated with these stiffness-mediated phenotypes^[10].

Viscoelasticity: Beyond the elastic modulus

In addition, biological tissues are not purely elastic materials but rather viscoelastic materials with time-dependent responses to applied forces that cannot be characterized by a modulus value. ECM viscoelasticity, defined by its ability to relax stress over time—a measure of its ability to decrease its resistance to deformation over time—has been established as an important mechanobiological parameter that is often decoupled from its elastic modulus^[20,21].

Hydrogels with controlled rates of stress relaxation can be used to investigate cell behavior under various viscoelastic conditions. Faster rates of relaxation create dynamic environments that promote cell spreading, proliferation, and matrix deposition, while slower rates create constricting and elastically solid-like environments that limit cell cytoskeleton dynamics. In terms of neural organoids, Roth et al. showed that viscoelastic stress relaxation rate, with a constant elastic modulus, is a major and largely unrecognized factor in determining human induced pluripotent stem cell (iPSC)-derived neural progenitor cell maturation *in vitro*^[22]. Specifically, faster rates of relaxation were associated with longer and more complex networks of neurites and higher levels of maturation markers *in vitro*. These data have broad implications for current Matrigel-based cultures that may not accurately mimic key viscoelastic signatures of brain and gut tissue development *in vivo* and where synthetic matrices offer a major opportunity to advance organoid maturation^[23].

Degradability, reciprocity, and the living matrix

This is not to say that organoids are passive recipients of matrix properties; instead, they actively remodel their mechanical microenvironment through the secretion of matrix metalloproteinases (MMPs) and the deposition of newly synthesized ECM constituents. This interplay is dynamic and constantly changing and is known to impact organoid development in a feedback manner. Synthetic hydrogels with degradable crosslinks enable organoids to create channels in the matrix, allowing for lumen expansion, crypt formation, and branching morphogenesis^[24]. On the other hand, non-degradable hydrogels tend to arrest organoid development in cyst-like structures because of their inability to physically permit the morphogenetic remodelling that is required for organoid development. The recognition of the dynamic and constantly changing nature of organoid mechanics is driving the creation of “living” matrices that mimic dynamic and constantly changing mechanical properties of tissues^[25].

Mechanical forces in stem cell fate determination

ECM stiffness as a lineage selector

This ability of matrix mechanics to define stem cell lineage is arguably one of the most revolutionary discoveries in mechanobiology, and it has profound implications for organoid technology. The importance of matrix mechanics in defining tissue context has been demonstrated in pioneering work by Engler et al.^[6], which has since been validated in numerous cell types and tissue types, showing that the elastic modulus of the

physical microenvironment is a biophysical selector that influences stem cells to develop along tissue types corresponding to their physical context. For example, in epithelial tissue, ISCs grown in soft matrices of similar stiffness maintain their proliferative and Lgr5+ stem cell phenotype, whereas increased matrix stiffness induces differentiation into cell types corresponding to differentiated cells in intestinal crypts and villi^[6]. Neural progenitor cells grown in soft hydrogels with stiffness <0.5 kPa have a strong bias toward neuron differentiation, whereas cells grown in stiffer hydrogels (>1 kPa) have a bias toward glial cell differentiation^[25]. These findings suggest that the mechanical microenvironment functions as a biophysical switchboard that, in concert with morphogen gradients and cell–cell signals, narrows the field of accessible developmental outcomes.

Piezo channels as context-specific fate determinants

The recent discovery that Piezo1 and Piezo2 play an essential role in the fate decisions of the ISC population also provides an additional dimension of mechanobiological control that is based on calcium rather than cytoskeletal tension. Piezo channels are opened in response to the physical forces that ISCs experience within the crypt environment. This includes the stiffness of the Paneth cell niche, the compression between adjacent cells resulting from the division of neighboring cells, and the stretch caused by the expansion of the crypt. The calcium responses that follow Piezo activation inhibit NOTCH receptor cleavage and the subsequent expression of HES1. This reduces the NOTCH signaling that is responsible for maintaining stem cell fate. Thus, the activation of Piezo channels provides the trigger for differentiation that directly converts physical cues into cell fate decisions^[11]. Notably, Piezo1 is also associated with the Wnt signaling pathway because a pharmacological approach using GsMTx4 in colonic organoid culture led to an increase in β -catenin expression and stem cell numbers^[14], suggesting that Piezo channels have a role in suppressing Wnt-dependent stemness. These studies highlight the dynamic relationship between the regulation of stem cell fate through mechanobiology because the stiffness of the matrix and Piezo channels are not merely permissive or inhibitory of differentiation processes.

Force-mediated niche architecture

Cellular fate is not determined by individual stem cells but by the stem cell niche ecosystem—a well-defined physical and chemical environment in which stem cells and their supportive cells live. Mechanical influences on stem cell niches are multifaceted. For instance, Paneth cells in the intestinal crypt environment secrete ECM to create stiffness gradients that place stem cells in a soft environment. Peristaltic deformations of microfluidic chips containing gut organoids are used to pattern stem cell turnover in a mechanical manner. Similarly, cell traction forces orchestrate collective cell dynamics to maintain crypt geometry^[26]. Tissue tension in neural organoids dictates progenitor domain boundaries to control the spatial arrangement of neural progenitor zones similar to those seen in the ventricular and subventricular zones of the human cortex^[27]. Therefore, to fully grasp organoid stem cell biology, one must shift from cell-autonomous signaling to how mechanical forces shape and orchestrate stem cell niches in which stem cell decisions are made.

Mechanical forces in organoid morphogenesis

Symmetry breaking, confinement, and lumenogenesis

The development of multicellular organization from an ensemble of identical cells in a spheroid form depends on spontaneous symmetry breaking, in which random physical or chemical fluctuations are amplified into persistent and spatially distinct patterns. Mechanical confinement has an instructive function in promoting symmetry breaking, and micropatterned substrates and microwells have boundary effects that can bias the positions of morphogenetic processes. In human embryonic stem cell colonies with defined geometry, circular confinement reliably generates patterns of germ layers similar to those in embryos, mediated by BMP gradients that are confined at colony edges due to mechanical boundary effects^[28]. Likewise, microfabricated confinement of intestinal organoid cultures controls the formation of the crypt-villus axis and polarizes lumenogenesis. This shows that geometric boundaries are capable of providing positional information for the self-organization of organoids^[29].

The process of lumen formation is also a mechanically regulated event. In cerebral organoids, hydrostatic pressure, a result of ion transport across the neuroepithelium, is responsible for the formation and expansion of fluid-containing ventricular-like structures. Interference with hydrostatic pressure blunts lumen formation and neurogenesis in these structures^[30]. On the other hand, actomyosin contractility is also a crucial event in lumen formation. In brain organoids, apical constriction, mediated by Rho-associated kinase (ROCK)-dependent myosin activation, is required for generating the forces necessary for the shape of neural tube-like folded structures. Interference with this event blunts lumen formation in various types of organoids, demonstrating the importance of physical force generation in these structures, a process just as crucial as chemical events in these structures.

Tissue folding, gyrification, and branching morphogenesis

One of the most striking visual representations of the principles of mechanobiology in organoids is tissue folding. The human brain has a feature in the cerebral cortex that is defined by an extremely folded and convoluted gyrencephalic surface, which has an expansive impact on cortical surface area and neural potential in comparison to lissencephalic species. This has been shown to occur due to mechanical instability, where the outer cortical plate grows at a rate that exceeds that of the inner subventricular zone, leading to compressive forces that exceed the buckling threshold, thus creating cortical folds and sulci^[31]. In human brain organoids, this has been shown to occur, where, upon attaining a critical size in microfluidic confinement, wrinkles on the surface are induced, with the spacing and amplitude of these wrinkles predicted by classical shell buckling mechanics, with strain in the nuclei within the outer zone being the driving force^[31].

Disease states have a profound effect on such mechanics. Karlinski Zur et al. showed that brain organoids generated from patient iPSCs derived from individuals with a mutation in LIS1 causing Lissencephaly had significantly stiffer tissue mechanics compared to isogenic controls by atomic force microscopy^[12]. The tissue mechanics are caused by changes in ECM composition and organization due to the mutation in LIS1 that caused

Lissencephaly. The tissue mechanics disrupted the differential growth instability that is necessary for brain folding, which is a cause of lissencephaly. The tissue mechanics can be pharmacologically treated by making it normal by MMP9 treatment^[12].

Apart from folding, lung and kidney organoids display branching morphogenesis processes that are determined by the balance between cell-generated traction forces and ECM resistance. For branching morphogenesis to occur, compliant matrices must be present to allow epithelial protrusions and invasion to take place, thereby facilitating iterative bifurcation processes to yield arborescent branch structures. On the contrary, stiffer matrices inhibit branching morphogenesis processes^[29]. Computational modeling has been used to explain branching morphogenesis processes, including those related to mechanical feedback between tissue growth and ECM deformation, to explain how branch spacing, branch orientation, and branch number are determined by the mechanical properties of organoids and ECM systems^[32]. These processes are related to how mechanical strains generated during branching morphogenesis affect the distribution of secreted morphogens such as Wnt, BMP, and FGF, which in turn determine the mechanical properties of cells.

Collective epithelial dynamics and emergent organoid architecture

Collectively, organoid morphogenesis is a result of individual cell processes such as division, migration, polarity establishment, and apical constriction being coordinated across tens to thousands of cells through mechanical coupling at cell-cell junctions and through the ECM. Cadherin-based adherens junctions are responsible for transmitting and buffering tension across epithelial sheets over supercellular lengths^[33]. ROCK-mediated actomyosin contractility within the crypt base drives collective cell flow in intestinal organoids to shape villus-like structures^[24], and its perturbation affects organoid crypt geometry in ways that cannot be accounted for by changes in gene expression. Similarly, anisotropic tension fields drive cell division and migration in brain organoids to establish cortical plate-like stratification^[27]. These architectural organoid properties are arguably some of the most compelling demonstrations to date that organoid self-organization is as much a function of physical laws as biochemical laws.

Engineering mechanical microenvironments for organoid research

Engineered hydrogels: Synthetic matrices with defined mechanics

The substitution of undefined animal-derived matrices with synthetic hydrogels with well-defined mechanical properties has revolutionized organoid mechanobiology research^[24,34]. For example, hydrogels made from polyethylene glycol (PEG), gelatin methacryloyl (GelMA), and protein-engineered hydrogels can be simultaneously tailored to achieve desired ranges of elastic modulus (within the physiological range of 0.1–40 kPa), viscoelasticity (relaxation times from seconds to hours), degradability (cleavage by MMPs or light), and bioactivity (functionalization with RGD, IKVAV, or laminin peptides)^[30,23].

Using PEG hydrogels functionalized with RGD and laminin-111 epitopes, Cruz-Acuña et al.^[24] showed that robust organoid

formation from human ISCs and colon cancer cells is supported. This work demonstrated that synthetic hydrogels can be used to replace Matrigel while providing independent control over hydrogel mechanical parameters. In situ matrix softening techniques involve altering hydrogel stiffness after initial organoid formation (from 500–100 Pa using photodegradable crosslinks), which has been shown to greatly improve organoid budding efficiency^[8]. Most recently, hydrogels with well-controlled stiffness and viscoelasticity profiles revealed that neural progenitor cell fate is independent from stiffness sensing if viscoelasticity is appropriately fine-tuned^[22], illustrating the importance of multidimensional mechanical design in organoid matrices.

Microfluidics and organ-on-a-chip platforms

Microfluidic devices—most compellingly realized as organ-on-a-chip (OOC)—allow for the precise application of fluid shear stress, concentration gradients, and fluctuating mechanical stress to organoids in ways that are beyond the spatial and temporal resolution of standard dishes or wells^[35,36]. The combination of organoids and organ-on-a-chip technology has been recognized as one of the main areas of convergence for the field^[37,38]; organoids offer the cellular heterogeneity and three-dimensional tissue structure that cell monolayers simply cannot, while microfluidic technology offers the fluid flow and mechanical stress that static cultures simply cannot.

In the context of the gastrointestinal system, gut-on-a-chip systems with primary human cells lining the organoids and subjected to peristalsis-like cyclic mechanical strains (~10% at 0.15 Hz) and luminal flow (~0.5–2 dyn/cm² shear) showed villus-like architecture, stronger tight junction integrity, increased mucus secretion, and faster microbial colonization compared to static organoids^[26,36]. Perhaps one of the most impressive demonstrations of the utility of these systems was described by Ballerini et al.^[39], who used living human faecal microbiome samples to populate a gut-on-a-chip system subjected to peristalsis-mimetic cyclic mechanical strains. These authors showed that such systems could be used to predict patient responses to immune checkpoint inhibitor therapies in melanoma patients, with functional accuracy being dependent on mechanical actuation to ensure microbiome viability and epithelial integrity.

Perfusion of kidney organoids through microfabricated chips significantly accelerates vascularization and tubule maturation, which enhances gene expression profiles that are more similar to adult kidney tissue and allows for the application of physiological tubule shear stresses that regulate endocytic transporters and polarized ion channels^[40,41]. Cerebral organoids grown using spinning bioreactor systems have better oxygen and nutrient delivery, which enhances cortical layer thickness^[42].

Bioreactors and dynamic mechanical conditioning

In tissues that are significantly deformed during their life *in vivo*, such as those of the heart, lung, and musculoskeletal system, bioreactor systems that allow for mechanical stimulation such as cyclic stretch, compression, or perfusion are necessary for organoid phenotype development that is close to physiological. Cardiac organoids that are exposed to gradually increasing levels of cyclic electromechanical stimulation during 4–8 weeks of culture, from 1% to 5% strain, show remarkable organoid maturation. The length of their sarcomeres increases from 1.6 to 2.2 μm , which is close to adult values. The twitch forces are

increased by a factor of 10, and their electrophysiological properties are close to those of adult cardiomyocytes^[7]. These changes cannot be achieved by supplementation of organoids with growth factors; thus, cyclic mechanical stimulation is an indispensable tool for organoid maturation. The mechanistic basis for organoid maturation is mechanosensing by sarcomeres through their length-sensing protein titin and by calcium handling through Piezo1 that fine-tunes excitation–contraction coupling^[9].

Organ-specific mechanobiology in organoid systems

Intestinal organoids: The crypt as a mechanosensory niche

The intestinal epithelium is considered one of the most mechanically active tissues in the body, with a range of mechanical inputs, including peristalsis, villus deformation during luminal passage, and crypt anchoring forces. The crypt base, where ISCs are located, has a unique mechanical microenvironment. Paneth cells secrete laminin and collagen IV, producing a basement membrane with a specific mechanical stiffness, ranging from 150 to 400 Pa, which is significantly softer than the villus tissue, ranging from 1.5 to 2 kPa^[8]. This mechanical gradient is not only permissive for stem cell maintenance but also instructive, with positional information provided by differential integrin engagement and YAP/TAZ localization^[18].

A discovery made in 2024 that both Piezo1 and Piezo2 are essential for ISC fate decisions has rewritten our understanding of this information in fundamental ways^[11]. The Piezo channels are stimulated by a mechanical input from niche stiffness, intercellular compression, and tissue tension. These mechanical stimuli are then transduced into a calcium signal that directly influences the major molecular switch for cell fate decisions in the ISC/TAC/DCC lineage: NOTCH signaling (Fig. 2). The beautiful implication is that the intestinal crypt harbors a mechanical developmental program in which stem cells sense their position within the stiffness gradient through piezo channels and that this sensing is directly related to cell fate decisions such that stem cells displaced from the soft crypt environment are ‘triggered’ to differentiate. The clinical implications of this pathway are highlighted by the demonstration that piezo1 inhibition with GsMTx4 increases the stem cell pool in organoid-based models of intestinal injury^[14], suggesting that piezo channels are drug targets for inflammatory bowel diseases.

The microfluidic systems of gut-on-chips have also shown that luminal flow and peristalsis affect the mechanics of the ISC niche as follows: when subjected to physiological flow, the mechanical properties of the ISC niche vary dynamically with the contraction–relaxation cycle, and the response of the Piezo channel reflects these dynamics in real time, as a function of the position of the niche^[36]. This aspect of mechanosensing, the kinetics of the application of forces rather than their intensity, is a new frontier of organoids.

Brain organoids: Cortical mechanics and the physics of folding

The human brain represents an exceptional mechanobiological system that is among the softest tissue types in the body, possessing an elastic modulus of ~0.1–1 kPa. Yet the brain’s

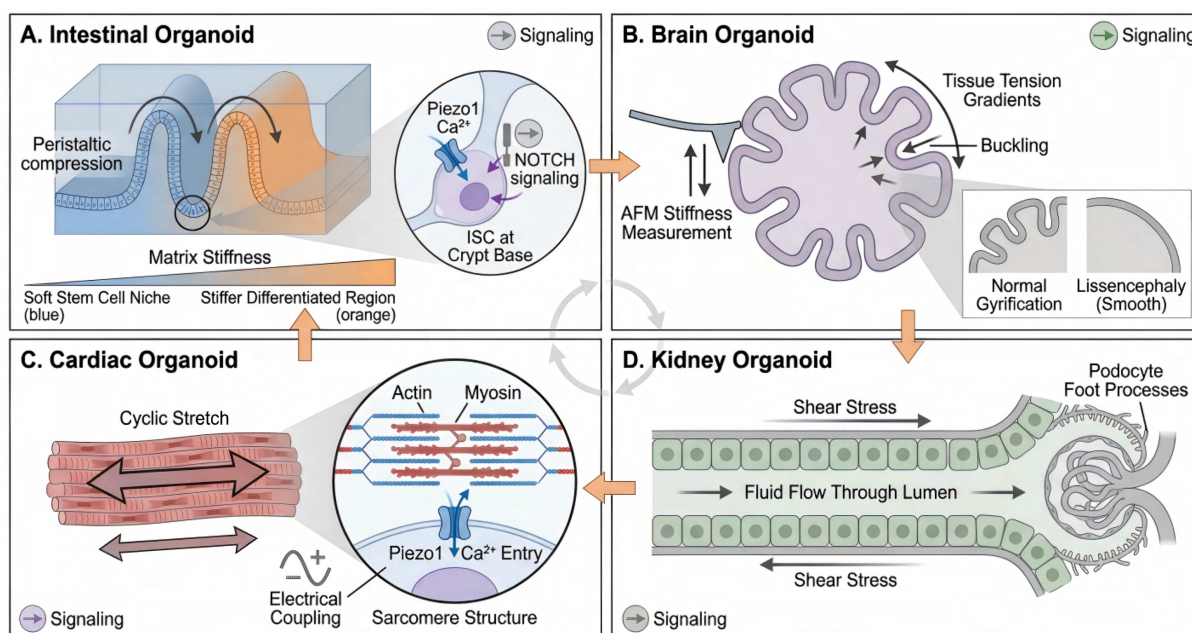


Figure 2. Organ-specific mechanobiology in intestinal, brain, cardiac, and kidney organoids. Each organoid system integrates distinct mechanical inputs with specific signaling pathways to achieve tissue-appropriate development. (Upper left) Intestinal organoids integrate ECM stiffness gradients (soft stem cell niche, stiffer villus domain) with Piezo1/2-mediated calcium signaling and NOTCH pathway modulation to regulate ISC fate at the crypt base. (Upper right) Brain organoids exhibit differential cortical plate growth, generating compressive instabilities that drive gyrification; disease states such as LIS1 mutation elevate tissue stiffness and impair folding. (Lower left) Cardiac organoids require cyclic electromechanical stretch to achieve sarcomere maturation, adult-like calcium handling, and contractile force development. (Lower right) Kidney organoids benefit from physiological tubular flow shear stress, which drives podocyte and tubular epithelial maturation, enhances vascularization, and activates mechanosensitive transport channels.

development is subject to precise mechanical instability events that govern the formation of the gyrencephalic folds that define the brain's cognitive capacity. Brain organoids have been demonstrated to be an exceptionally powerful tool in the study of the brain's mechanobiology because they naturally undergo the differential growth and physical instability events that govern the brain's folding without the need for any exogenous physical stimulation^[31].

The foundational study by Karzbrun et al. established the biophysical model that the differential tissue forces between the tissue contraction of the core and the nucleus expansion of the proliferating tissue of the organoid lead to the wrinkles that define the brain organoid's morphology at a critical threshold^[31]. The wavelength of the wrinkles scales linearly with tissue thickness according to classical shell theory, thus establishing that brain organoids indeed represent a physical system that is subject to the laws of elastic tissue properties. Heterozygous LIS1 organoids were demonstrated to have an elastic modulus and folding defects that mimic the smooth brain of lissencephaly patients^[31]. More recently, Karlinski Zur et al. carried out detailed mechanical characterization of LIS1-null iPSC-derived brain organoids at various developmental stages using AFM, demonstrating significant and progressive stiffening in comparison to controls^[12]. Proteomics and imaging studies identified abnormal deposition and remodeling of the ECM, and its impact on mechanical instability during gyrification. Importantly, pharmacological correction of ECM abnormalities with MMP9 reduced the stiffness and partially restored folding in the organoids, demonstrating for the first time a mechanotherapeutic approach in a cortical malformation organoid model^[12].

The growing field of brain organoid mechanics can also be

informed by Brillouin microscopy, which allows for the non-contact assessment of the viscoelastic characteristics of organoid volumes in their entirety, and computational simulations of cortical folding with organoid material properties derived from experimental studies^[27]. These techniques collectively position brain organoids as uniquely positioned in the growing field of the physical biology of human cortical development and neurological disease.

Cardiac organoids: Cyclic stretch and electromechanical maturation

The heart is defined by mechanical function: it must generate sufficient contractile force to circulate blood throughout life, and its cardiomyocytes are exquisitely attuned to the cyclic electromechanical environment in which they develop and operate. Recapitulating this environment *in vitro* is therefore not merely desirable but obligatory for achieving physiologically meaningful cardiac organoid models^[7].

While human iPSC-CMs are impressively differentiated by existing differentiation protocols, they are still developmentally immature, as static cultures display fetal-like gene expression profiles, disorderly sarcomere structures, and low contractile forces. However, when exposed to a gradually increasing magnitude of cyclic stretch that reflects the rising mechanical demand imposed by developing hearts, maturation is greatly accelerated^[7]. At a cellular level, cyclic stretch activates Piezo1-mediated calcium signaling that enhances SERCA-mediated calcium reuptake and Ryanodine receptor sensitization, thus enhancing the rate and magnitude of calcium transients and thus advancing electrophysiological maturation. In parallel, mechanosensing of cardiac muscle cells by titin and muscle LIM

protein (MLP) enhances alignment and lengthening of myofibrils into adult-like structures. Cardiac organoids that are exposed to cyclic stretch and electrical stimulation display adult-like action potential profiles, force-frequency relationships, and drug responses, making them significantly more predictive of drug responses compared to static cultures^[7].

Although human iPSC-derived cardiomyocytes have been remarkably derived using existing differentiation protocols, these cells remain developmentally immature in static culture systems with fetal-like gene expression, disorganized sarcomeres, and low contractile force. However, using progressively increasing cyclic stretch—similar to the rising hemodynamic pressures during development of the myocardium—has a dramatic effect on advancing the maturation of cardiomyocytes^[7]. At the molecular level, cyclic stretch activates Piezo1 calcium signaling pathways, which in turn augment calcium uptake through SERCA and ryanodine receptor sensitization. These processes significantly advance electrophysiological maturation. At the same time, sarcomere mechanosensing through the action of titin and MLP enhances myofibril organization and length toward adult-like phenotypes. Cardiomyocytes grown in organoids with cyclic stretch and electrostimulation show adult-like action potential characteristics, force-frequency relations, and drug responses and are therefore significantly more predictive in cardiotoxicity and drug efficacy studies compared with static culture systems without electrostimulation^[7].

Kidney organoids: Flow, filtration, and podocyte mechanics

The kidney has a constant blood filtration rate of 200 L/day. The tubular epithelial cells and podocytes are exposed to significant fluid shear stress (~ 0.1 – 1 dyn/cm² for tubules; pulsatile hemodynamic forces for glomeruli). These mechanical forces are important regulators of tubular cell maturation, polarity, and function, as well as glomerular filtration function. In static cultures of kidney organoids, tubular cell maturation is always incomplete, podocytes are immature, and filtration barrier function is absent^[41].

Perfusion of kidney organoids using microfabricated chips at physiological shear stress levels greatly enhances maturation of the organoids. Homan et al. demonstrated that kidney organoids under flow develop vascular networks, tubular structures with lumen sizes and transporter expression profiles similar to adult nephron segments, and enhanced podocyte foot process formation compared to static controls^[40]. The mechanistic rationale for flow-enhanced kidney organoid maturation is the activation of primary cilia-based mechanosensing. Renal tubular cells possess the longest primary cilia of any cell type. Shear stress-induced bending of the cilia activates intracellular calcium mobilization through polycystins PC1/PC2. Disruption of mechanosensing in the kidney, as seen in autosomal dominant polycystic kidney disease (ADPKD), leads to cyst formation. This disease phenotype was successfully recapitulated using the kidney on chip platform^[41]. The combination of mechanobiology and kidney organoids provides not only enhanced maturation strategies but also mechanistic insight into important renal diseases.

Disease modeling through pathological mechanics

A common thread in fibrosis, cancer, cardiovascular disease, and neurological disorders appears to be that alterations in tissue

mechanics are not only a consequence of disease processes but also a contributing cause of disease progression. Organoids represent a new paradigm in which these processes can be carefully controlled in human cell systems.

Fibrosis. Fibrotic diseases, including cirrhosis of the liver, pulmonary fibrosis, and inflammatory bowel disease, are associated with increased ECM cross-linking and stiffening. These processes enhance fibrosis through increased signaling of YAP/TAZ pathways, TGF- β signaling, and epithelial-to-mesenchymal transition (EMT). Organoids of cholangiocyte cells in stiff hydrogels have increased YAP and fibrosis markers in a stiffness-dependent manner that mimics primary sclerosing cholangitis^[19]. Importantly, organoids of fibrotic disease have shown that pharmacologic antagonism of cellular tension using inhibitors of the Rho kinase or myosin pathways can rescue normal organoid phenotypes.

Cancer. Tumors represent an archetypal example of pathological mechanical reprogramming, in which tumor cell cross-linking of the tumor ECM through desmoplastic processes, increased interstitial fluid pressure, and solid stress all play roles in tumor progression, invasion, angiogenesis, and immune evasion^[42]. Tumors grown in 3D matrices that are stiffer or anisotropic in nature have increased invasive bud formation and drug resistance, and these models more closely mimic *in vivo* conditions than traditional culture models^[44]. This emerging concept in pharmacology, mechanopharmacology, in which drugs are believed to have responses that are modulated in accordance with a mechanical context, suggests that improved accuracy in clinical models can be achieved.

Neurological disorders. Abnormal ECM mechanics in LIS1 brain organoids induce failure of brain cortical folding through purely mechanical mechanisms^[12]. In a broader context, abnormal brain tissue mechanics, i.e., tissue stiffness, are increasingly understood as a unifying aspect of Alzheimer's disease, glioblastoma, and multiple sclerosis, and brain organoids are proving themselves as a tool for exploring the mechanisms by which abnormal brain tissue mechanics are induced and, further, by which abnormal brain tissue mechanics induce cell-type specific abnormalities^[27].

Cardiovascular disease. Cardiac organoids subjected to abnormal mechanical regimes, i.e., abnormally high cyclic stretch simulating hypertension due to pressure overload, or abnormally low stretch simulating cardiomyopathy due to dilated heart, display disease-type gene expression signatures, i.e., BNP upregulation, β -MHC/ α -MHC switching, and structural abnormalities that mimic clinical cardiomyopathy phenotypes. These models are being used to identify mechanically induced therapeutic targets, i.e., Piezo1 inhibitors, which may alleviate hypertrophic remodeling.

Translational perspectives and future directions

Mechanically instructive scaffolds for transplantation

For organoids to be translated from research tools to therapeutics, there are critical hurdles that must be overcome, including organoid engraftment efficiency and post-transplant vascularization, which are significantly impacted by the mechanical properties of the scaffold used to carry these cells. Biomaterial scaffolds with mechanical properties similar to those of target tissue, degradability consistent with organoid expansion,

and presentation of angiogenic factors have been shown to significantly improve organoid engraftment efficiency in preclinical models^[45]. Synthetic hydrogels are increasingly being used over animal-derived materials due to their well-defined mechanical properties and lack of xenogenic contaminants, making them well suited for clinical translation.

Mechanopharmacology and drug discovery

The understanding that drug responses are mechanically contextual, i.e., that a drug may have different effects depending on the substrate stiffness or flow conditions calls for a paradigm shift in drug screening strategies. The term mechanopharmacology has started to gain popularity as evidence is gathered that indicates that 2D or soft Matrigel screens may miss important drug resistance mechanisms that are relevant to clinical situations^[46]. New strategies are now being developed to utilize organoid-on-a-chip devices that allow for simultaneous mechanical stimulation during drug screening strategies^[36].

Convergence with computational mechanics and AI

Computational modeling of organoid mechanics is developing in parallel with experimental studies. Vertex models, continuum elastic models, and phase-field models have all been successful in reproducing organoid gyrification, crypt budding, and lumen formation from first principles. These predictions are now being compared with live imaging data from experimental systems^[32]. The next step in the development of a comprehensive understanding of organoid development will be the integration of the mechanical models with the biochemical signaling models (multiscale mechanochemical models), which will allow us to understand how organoids are able to robustly pattern despite cell-type heterogeneity and stochasticity. Ultimately, the development of machine learning approaches on large datasets from mechanically defined organoid cultures may reveal novel and unanticipated mechanical parameters that predict organoid quality, disease phenotype severity, and drug sensitivity.

Standardization and toward clinical-grade platforms

The scientific community is in need of standardization of mechanical parameters for organoid research. At the moment, the elastic modulus and viscoelastic properties of batches of Matrigel differ significantly from lot to lot, which makes it difficult to compare results from different labs, and it may be a reason for conflicting data in existing organoid mechanobiology studies^[8]. Artificial matrices are a promising alternative, and their

application requires the validation of existing and future formulations, as well as quality control of matrices, which will be a step forward for the scientific community. Creating reference standards for the mechanical properties of organoid substrates, similar to reference standards for cell culture medium and antibodies for flow cytometry, will be a step forward for the scientific and regulatory communities.

Key challenges and emerging opportunities

Table 1 summarizes the primary technical and conceptual challenges facing organoid mechanobiology and the most promising emerging solutions.

Conclusions

From being an interesting frontier to being one of the main pillars of organoid biology, mechanobiology has come of age. The evidence gathered and discussed in the present review article proves beyond doubt that physical forces, as quantified by the stiffness and viscoelastic properties of the extracellular matrix, fluid flow, cyclic stretch, and spatial confinement, are not merely modulators of organoid biology but rather the main regulators of the same. This is now known to be true for the cell fate decisions of ISCs in the intestinal crypt, the folding of the brain cortex, the electromechanical maturation of the heart tissue, and the tubular function of the kidney.

The development of synthetic hydrogel technology, microfluidic organ-on-a-chip technology, and bioreactor technology has given us the experimental tools necessary to explore these relationships. Recent advances in brain organoid mechanics^[12], Piezo channel biology in ISCs^[11], and the use of viscoelasticity to control neural progenitor cell fate^[22] have given us the tools to explain the power of the mechanobiological approach to organoid research. One of the most powerful tools to come out of the combination of organoids and organ-on-a-chip technology is the combination of the two. This technology provides the power of biology and the power of microfluidics to better predict outcomes than either technology could on its own^[39].

Looking forward, the field is poised to resolve the many open questions related to the multiscale nature of mechanotransduction, from how molecular force sensing is integrated across cells to give rise to tissue-level mechanical responses, and is poised to advance the next generation of organoid systems that incorporate chronic mechanical conditioning, vascularization, and innervation. In doing so, mechanobiology is poised to take a leading role in accelerating the

Table 1. Key challenges and future priorities in organoid mechanobiology.

Challenge	Current Limitations	Promising Solutions	Timeline
Standardization	Matrigel batch variability; undefined mechanics	Synthetic tunable hydrogels; mechanical reference standards	Near-term
3D mechanosensing complexity	YAP/TAZ stiffness correlations break down in 3D	Decoupled viscoelastic/stiffness matrices; live mechanosensing reporters	Near-term
Multiscale force integration	No system integrates solid stress+shear+matrix remodeling simultaneously	Multiphysics OOC with tunable ECM; coupled mechanical modeling	Mid-term
Long-term culture	Most experiments span days–weeks; chronic adaptation inaccessible	Perfusion bioreactors with <i>in situ</i> monitoring; slow-degrading matrices	Mid-term
Vascularization and innervation	Organoids lack vasculature/nerves, key mechanical elements	Coculture with endothelial/neural organoids; <i>in vivo</i> implantation	Mid-term
Clinical translation	Undefined matrices; lot variability; scale-up challenges	GMP synthetic hydrogels; modular bioreactor design	Long-term
Patient heterogeneity	Individual variation in tissue stiffness not captured	Patient-matched stiffness profiling with AFM; personalized matrices	Long-term

development of better disease models, better drug testing systems, and better regenerative therapeutics—by applying the physics of life to better human health.

Research ethics and patient consent

Not applicable.

Declaration of conflicting interests

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Wenbo Qian contributed to conceptualization, visualization, writing original draft, as well as writing–review and editing. Feng Chen, Junle Zhu and Jinmao Gu were involved in visualization and writing–review. Qi Wang participated in conceptualization and supervision, and was responsible for writing–review and editing.

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