nature biotechnology

Perspective

https://doi.org/10.1038/s41587-026-03161-w

Decoding the origins of cellular self-organization for engineered biology

Received: 30 July 2025

Accepted: 5 May 2026

Published online: 01 June 2026

Check for updates

Qi Chen [1,2] ✉ & Magdalena Zernicka-Goetz [3] ✉

Cellular self-organization reflects an evolutionary leap in which multicellular coordination became essential. Driven by fundamental constraints like oxygen and nutrient transport, physical laws generate inevitable collective behaviors such as cavitation, folding and branching. These behaviors couple mechanics, signaling and gene regulation to build tissues and organs with spatiotemporal precision through the iterative layering of simple rules. Stem cell-based models of embryogenesis and organogenesis make these principles experimentally tractable, revealing canonical developmental routes and alternative trajectories and failure modes that expose bottlenecks and constraints. In this Perspective, we trace self-organization from evolutionary origins to biophysical inevitability and discuss how emerging tools in stem cell biology and bioengineering are beginning to translate these insights into regenerative strategies. Decoding the rules of morphogenesis will open possibilities to reimagine, simulate and rationally engineer the architecture of living tissues.

The question of how genetically identical cells organize themselves into the intricate, spatially ordered structures that form tissues, organs and, ultimately, entire organisms lies at the heart of developmental biology, fueling decades of inquiry into the choreography of natural embryogenesis. Today, this inquiry is being reimagined through the lens of stem cell-based models of development[1], a transformation that lets us not only watch but also reconstruct, guide, manipulate and even redesign embryonic processes in vitro. Paired with advances in imaging, single-cell technologies and synthetic biology, these models offer opportunities to uncover the fundamental principles of development, with implications for understanding both normal biology and disease.

Self-organization was once viewed as an inscrutable black box but now is emerging as a tractable, experimentally accessible phenomenon[2,3]. Its study is beginning to illuminate the generative logic underlying tissue architecture, organ formation and developmental plasticity, linking the principles of patterning to the regenerative potential of living systems.

In this Perspective, we propose a conceptual framework: self-organization is not a byproduct of biological complexity but a foundational principle emerging from the transition from unicellularity to multicellularity and the physical inevitability of intercellular interactions, refined through evolutionary selection. These principles are evident in animal development and in simpler systems such as bacterial biofilms, where adhesion, intercellular forces and diffusion gradients spontaneously generate multicellular communities with emergent properties[4]. We trace how early multicellular organisms evolved mechanisms for spatial coordination, which were later co-opted and elaborated upon by animal embryos to enable precise patterning and morphogenesis. By integrating gene expression, mechanical forces and biochemical signaling, we illustrate how cells acquire identity, communicate and assemble into increasingly complex forms. Stem cell-based systems (through the coculture of distinct progenitors or the incorporation of guiding signals) demonstrate how emergent spatial organization arises from reciprocal signaling, compartmentalization and physical self-assembly. We argue that uncovering the logic of self-organization holds promise for understanding development and guiding advances in synthetic biology, tissue engineering and regenerative medicine.

[1]Molecular Medicine Program, Department of Human Genetics, University of Utah School of Medicine, Salt Lake City, UT, USA. [2]Division of Urology, Department of Surgery, University of Utah School of Medicine, Salt Lake City, UT, USA. [3]Developmental Plasticity and Self-Organization Group, Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, CA, USA. ✉e-mail: qi.chen@hsc.utah.edu; magdaz@caltech.edu

https://doi.org/10.1038/s41587-026-03161-w

BOX 1

Evolving theories of multicellularity

At its core, multicellularity emerges from a fundamental challenge: how single cells overcome physical limits like nutrient diffusion to form cooperative collectives. Traditional theories provide the foundation, whereas emerging views highlight intracellular asymmetries as the spark igniting this transition[5].

The Colonial Theory (Haeckel, 1874)[139] envisions multicellularity arising when unicellular ancestors, such as choanoflagellates (animals' closest relatives), remained adherent after division, forming simple aggregates. Pre-existing mechanisms, like extracellular matrix synthesis and incomplete cytokinesis, enabled adhesion and basic coordination, evolving into differentiated forms through selective pressures.

The Synzoospore Theory (Zakhvatkin, 1949)[140] proposes aggregation of temporally or spatially differentiated single cells, which fuse or coordinate to create a unified entity, emphasizing predivision specialization as a precursor to multicellular labor division.

Both frameworks underscore aggregation and emergent cooperation, supported by ancient genes such as cadherins and integrins for adhesion that predated multicellularity[141,142]. Transcription factor expansions later drove cell-type diversification. Yet these models converge with a unifying insight: multicellularity may originate from intracellular asymmetries triggered by environmental cues, such as mechanical compression or spatial crowding. In confined spaces, uneven distribution of gene products polarizes cells, compartmentalizing reactions and altering biophysical properties like membrane tension, which could ignite the interactions of individual cells.

We call this the Asymmetric Initiation Hypothesis, wherein localized cues, including physical constraints (for example, compression and adhesion gradients) and intrinsic polarity cues (for example, spindle migration), ignite molecular imbalances within single cells. These asymmetries catalyze self-organization, ultimately paving the way for colonial or aggregative evolution (Fig. 1). This perspective may synchronize ancient origins with modern self-assembly (where cell–cell contacts negotiate fates via mechanical signals, such as Yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ) pathways[143]), suggesting multicellularity not as a rare leap but as an inevitable response to environmental pressures, as seen in recent examples showing archaea under pressure forming tissue-like structures[6]. In addition to spatial and molecular asymmetries, shifts in metabolism, such as the transition from fermentation to respiration, may have further reinforced group-level coordination[144]. Because respiration is more efficient in clustered cells that can share metabolites and oxygen, this metabolic asymmetry may have favored the emergence and stabilization of multicellular assemblies. Together, the ideas we propose here will stimulate new experimental approaches, such as bioengineered models to study evolutionary transitions and for synthetic multicellular life forms.

From multicellularity to the principles of cellular self-organization

The evolutionary transition from unicellular to multicellular life represents a profound leap that reshaped life's possibilities by enabling cellular specialization, structural complexity and coordinated behavior[5]. This shift set the stage for self-organization, which, once underway, unfolds with a kind of inevitability, driven by physical laws, dynamic biomechanical–biochemical feedback loops and spatially and temporally controlled gene expression. These processes collectively guide tissue architecture and function.

The onset of multicellularity

Two primary models for the transition from unicellular to multicellular life, the Colonial Theory and the Synzoospore Theory, propose that multicellularity arose either through retention of daughter cells after division or aggregation of free-living cells, respectively (Box 1 and Fig. 1)[5]. Although both models emphasize the role of cell adhesion and cooperation, increasing evidence suggests intracellular asymmetries as potential initiating factors for new multicellular forms to arise. In what we call the 'Asymmetric Initiation Hypothesis' (Box 1 and Fig. 1), we propose that uneven distribution of gene products or organelles within single cells may serve as the initial spark for polarization and functional divergence. These asymmetries, potentially triggered by external mechanical forces or spatial constraints such as crowding, could set the stage for multicellular organization.

Intracellular asymmetries in molecular components can compartmentalize biochemical reactions, alter biophysical properties like membrane rigidity and generate spatial biases in signaling. These conditions foster emergent behaviors such as polarization, cavitation and folding that drive higher-order structure. The formation of internal cavities, for example, may enhance fitness by supporting nutrient storage, long-range signaling and division of labor. These are all features evident in early multicellular organisms like *Volvox* and sponges, which form hollow, spherical morphologies.

Support for the biophysical origin of multicellularity has also emerged from recent studies in archaea. In Haloarchaea, mechanical compression alone induces a clonal multicellular state, resulting in tissue-like assemblies with eukaryotic characteristics. When confined under pressure, these cells cease division but continue growing, forming a multinucleate, coenocyte-like stage with multiple DNA copies. At a critical size, elevated membrane tension triggers cellularization, where membranes grow inward to form a polygonal network of smaller cells. This process yields two distinct cell types: tall, narrow central cells and flatter, broader peripheral cells. Actin-based 'pillars' support these structures, imparting elasticity reminiscent of animal tissues[6].

Additional evidence from Asgard archaea (close relatives of eukaryotes) reveals a complex actin cytoskeleton in single cells[7], suggesting that molecular machinery for multicellularity may have preceded eukaryotic evolution. Together, these findings position mechanical forces, particularly compression, as potential drivers of early multicellular evolution. These forces may have created selective pressures that favored genetic innovations, ultimately embedding multicellularity into developmental programs, without eliminating the individual cells' autonomy.

The role of physical laws

Once multicellularity is established, physical principles inevitably drive self-organization through processes such as cavitation, folding and branching (Fig. 2a), as elaborated below.

As cell aggregates expand, physical constraints like limited diffusion of nutrients and oxygen create central regions of hypoxia and nutrient deprivation. These stresses promote the emergence of internal spaces through cavitation, a conserved biophysical strategy that

https://doi.org/10.1038/s41587-026-03161-w

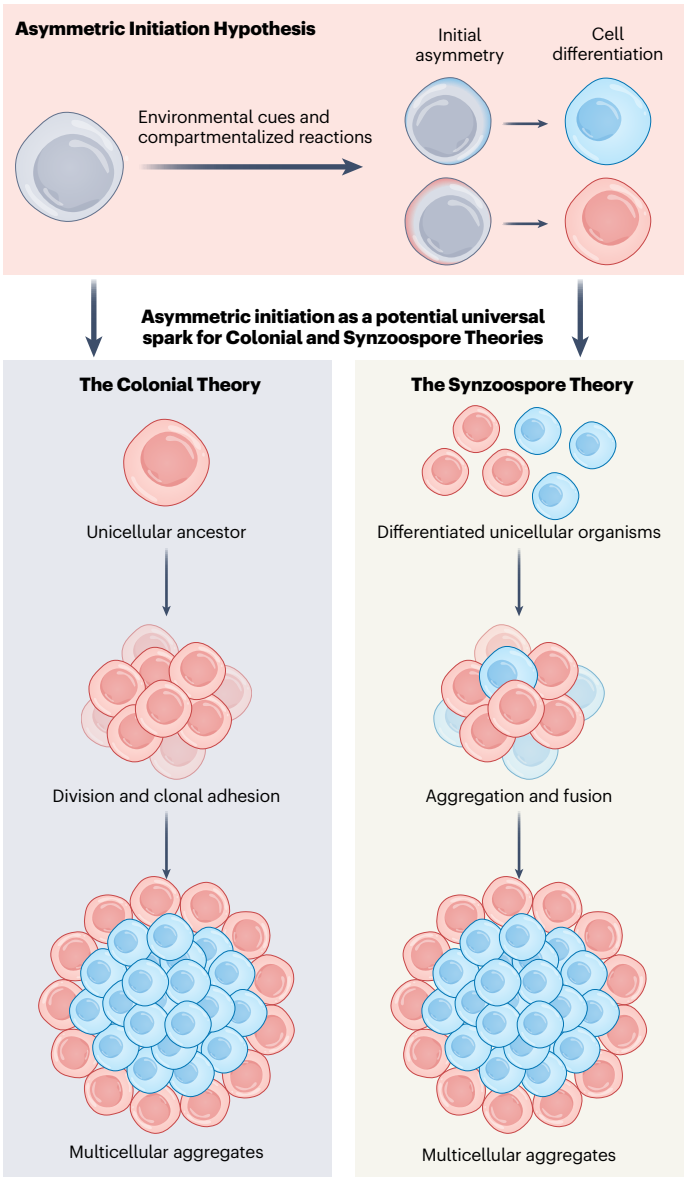

Fig. 1 | The Asymmetric Initiation Hypothesis for the origin of multicellularity. Classical theories explain multicellularity through either clonal retention after cell division (the Colonial Theory) or aggregation of distinct unicellular states (the Synzoospore Theory). We propose that these routes can be unified by an earlier initiating event: the emergence of intracellular asymmetry within a single cell. In this model, local physical constraints and intrinsic polarity cues can generate unequal distributions of molecules, organelles and mechanical tension, creating the first spatial biases in function and fate. These initial asymmetries may create the conditions for polarized behavior, stable adhesion, division of labor and ultimately self-organized multicellular architecture through either clonal (the Colonial Theory) or aggregative (the Synzoospore Theory) routes. In this view, multicellularity can be understood as a physical and evolutionary consequence of asymmetry under constraint. This framework connects the origin of multicellularity with the same principles that continue to govern morphogenesis in embryos, organoids and engineered living systems.

enhances nutrient exchange and waste removal (Fig. 2b). Cavitation underlies a wide variety of morphogenic solutions across taxa, from blastocoel formation in externally developing fish and amphibians[8,9] to blastocyst formation in internally developing mammals[10]. Mechanistically, cavitation can arise through apoptotic hollowing, directed secretion, coalescence of intercellular spaces or membrane remodeling, offering versatile means to increase the surface area-to-volume ratio and enable tissue specialization.

Following the initial cavitation event that generates the blastocyst cavity, subsequent cavitation can further sculpt embryonic architecture. One mammalian example is lumenogenesis in the pluripotent epiblast. After implantation, an unpolarized group of epiblast cells undergoes synchronized apical–basal polarization into a rosette stage, followed by asymmetric vesicular trafficking and apical secretion to open a central lumen. In stem cell-derived embryo models, as in mouse and human embryos, this process is coupled with the naive-to-primed pluripotency transition; when this transition is blocked, lumen formation stalls[11,12]. Thus, epiblast lumenogenesis offers an epithelial instantiation of the broader principle of cavitation, illustrating how coordinated mechanical and biochemical signals can convert an initially disordered cell mass into a spatially organized, tissue-like structure.

Folding emerges from differential growth rates between adjacent cells and the geometric limitations imposed by confined space (Fig. 2c). This physical process increases the surface area-to-volume ratio, enhancing nutrient and oxygen diffusion, optimizing spatial configurations and allowing for more intricate interactions between cells and their environment. As such, folding is a fundamental strategy for forming structurally and functionally complex tissues.

Folding is evident across development, from the transformation of the blastocyst into a cylinder-like structure[13,14] when the trophoblast folds in the process of extraembryonic ectoderm formation to the folds formed during organogenesis, like the formation of the neural tube[15], brain gyri and sulci[16,17] and intestinal villi[18]. At the cellular level, folding generates mechanical heterogeneity[19] (cells located at curved regions experience heightened tension and compression compared to those in flatter regions). These mechanical differences can alter cell shape and the distribution of cellular components, influencing gene expression, cell behavior and fate, which in turn shape subsequent developmental steps and tissue architecture.

Branching allows tissues to increase surface area while penetrating surrounding environments, as seen in the lungs, vasculature and glands (Fig. 2d). This architecture supports efficient nutrient and gas exchange and energy distribution by optimizing the interface between tissues and their external environment[20].

Many biological branching systems (such as blood vessels, lung alveoli and tree roots) display fractal patterns[21], where self-similar structures repeat at different scales. This organization maximizes exposure to nutrients and oxygen using minimal material investment. A recent study suggests that these fractal patterns emerge from a balance of global guidance cues dictating branch alignment and space-filling efficiency and local interactions[22], which regulate tissue density within the structure. Beyond transport efficiency, many branching systems can be viewed as compact developmental programs. In this view, simple recursive generative rules produce self-similar, fractal geometries that maximize interface with minimal 'instructional' cost (an information-theoretic view related to the principle of minimum description length), a property that may favor robustness and evolvability[23].

Collectively, cavitation, folding and branching illustrate how physical laws govern the self-organization of multicellular systems by optimizing morphogenesis and function under constraint. These 'hard-wired' rules reduce the informational burden on genetic programs, conferring robustness by buffering fluctuations. In doing so, they reveal how complexity can emerge from simple local interactions and global constraints achieved not through elaborate blueprints but through simplicity. These relatively simple self-organizing principles can be layered atop one another, enabling both increasing structural and functional complexity and the correct temporal sequence of events. These two features, complexity and chronology, are interlinked, with each layer setting the stage for the next in a self-reinforcing developmental cascade.

https://doi.org/10.1038/s41587-026-03161-w

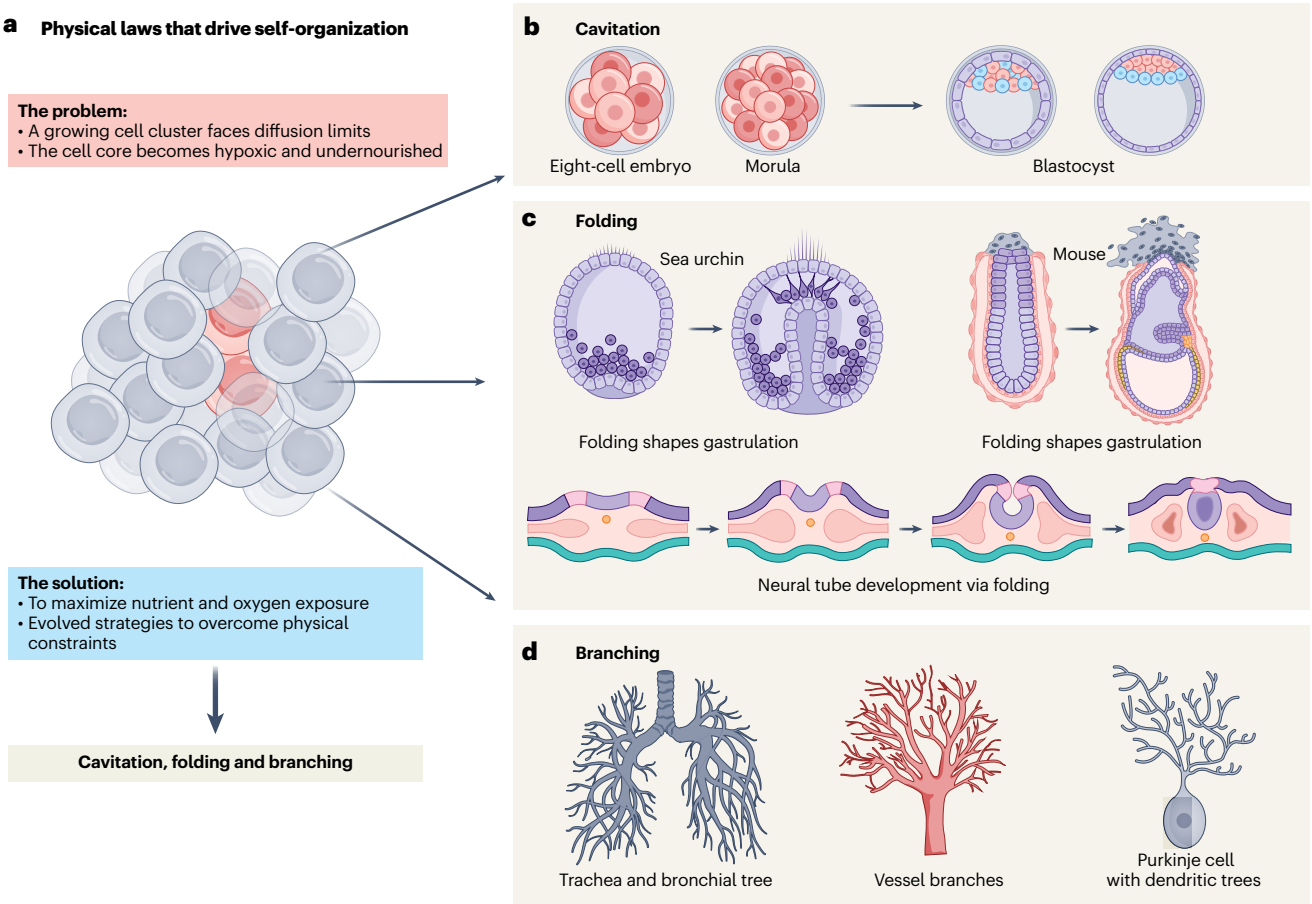

Fig. 2 | Physical laws governing multicellular self-organization: cavitation, folding and branching as drivers of nutrient and oxygen optimization. **a**, Schematic showing how physical constraints in growing cell masses lead to morphogenic solutions (cavitation, folding and branching) that maximize surface exposure for enhanced nutrient and oxygen transport. **b**, Cavitation: the progression from compact cell clusters to hollow forms, alleviating central anoxia. Top, natural embryonic stages, from an eight-cell embryo to a morula to a blastocyst with fluid-filled blastocoel (cavity formation is conserved across species like fish, amphibians and mammals). **c**, Folding: differential growth increases the surface area-to-volume ratio for efficient exchange. Left, sea urchin gastrulation via invagination. Right, mouse gastrulation shaping the egg cylinder (first mammalian morphogenetic fold). Bottom, illustration of neural tube development through progressive folding of the neural plate, generating mechanical biases that influence gene expression and cell fate. **d**, Branching: fractal patterns maximize the interface for gas/nutrient distribution. Left, trachea and bronchial tree in the lungs. Center, vessel branches in the vasculature. Right, Purkinje cell dendritic trees (neuronal example of self-similar branching). These processes collectively optimize form and function under physical constraints, as seen in developmental scaffolds and organ architectures.

Signal feedback in time and space

In addition to physical constraints, self-organization is shaped by dynamic feedback between cellular behaviors, biochemical signals and gene expression. Together, these form a continuous loop. The intrinsic properties of cells, set by their gene expression at a given time, determine how they interact with their environment and neighboring cells[24]. These interactions then reshape the physical and biochemical landscape, feeding back to modify gene expression and cellular behavior in return. This ongoing, reciprocal relationship is both spatially and temporally controlled, guiding the organization of cells into higher-order structures.

For instance, when cultured in vitro, mouse embryonic stem (ES) cells form clusters via intrinsic adhesive properties, driven by cadherin-family proteins[25–29]. By contrast, cancer cells, with different surface protein profiles, tend to spread and migrate[30–34]. In three-dimensional (3D) culture, ES cell clusters undergo lumenogenesis, forming so-called lumenoids[11,35], whereas cancer cells typically form dispersed or invasive networks. These distinct outcomes show that intrinsic cellular programs, interacting with external physical forces, dictate the spatial organization of a cell population.

A compelling example is the self-organization of skin-derived organoids[36], where a 'mechano–chemical circuit' transforms multiple spheroidal units into a flat epithelial sheet, mirroring in vivo skin architecture. Here, the intrinsic ability of cells to sense mechanical cues, such as dermal stiffness, activates the YAP1 signaling pathway, which then triggers Wnt/matrix metalloproteinase signaling to degrade the basement membrane[37,38]. This process, rooted in the cells' genetic and molecular programming, enhances tissue fluidity, enabling the organoid to coalesce into a planar form. Similarly, intestinal adult stem cells self-organize into organoids that recapitulate intestinal architecture, complete with crypt–villus structures, cavitation, folding and branching. This occurs through their inherent genetic instructions that direct stem cells to diversify into multiple cell types and arrange into functional patterns, even without external tissue scaffolds.

These examples highlight how cellular programs, operating in conjunction with mechanical and chemical feedback, enable self-organization in both in vivo and in vitro contexts. As cells proliferate and differentiate, their gene regulatory networks coordinate with environmental cues, shaping cell fate and positioning in real time. This dynamic process reveals the nature of self-organization: not a preordained outcome, but a real-time negotiation (Fig. 3a). Through coupled feedback between gene expression, signaling and mechanics, cells translate intrinsic programs into coordinated local behaviors that scale to form coherent, functional structures.

https://doi.org/10.1038/s41587-026-03161-w

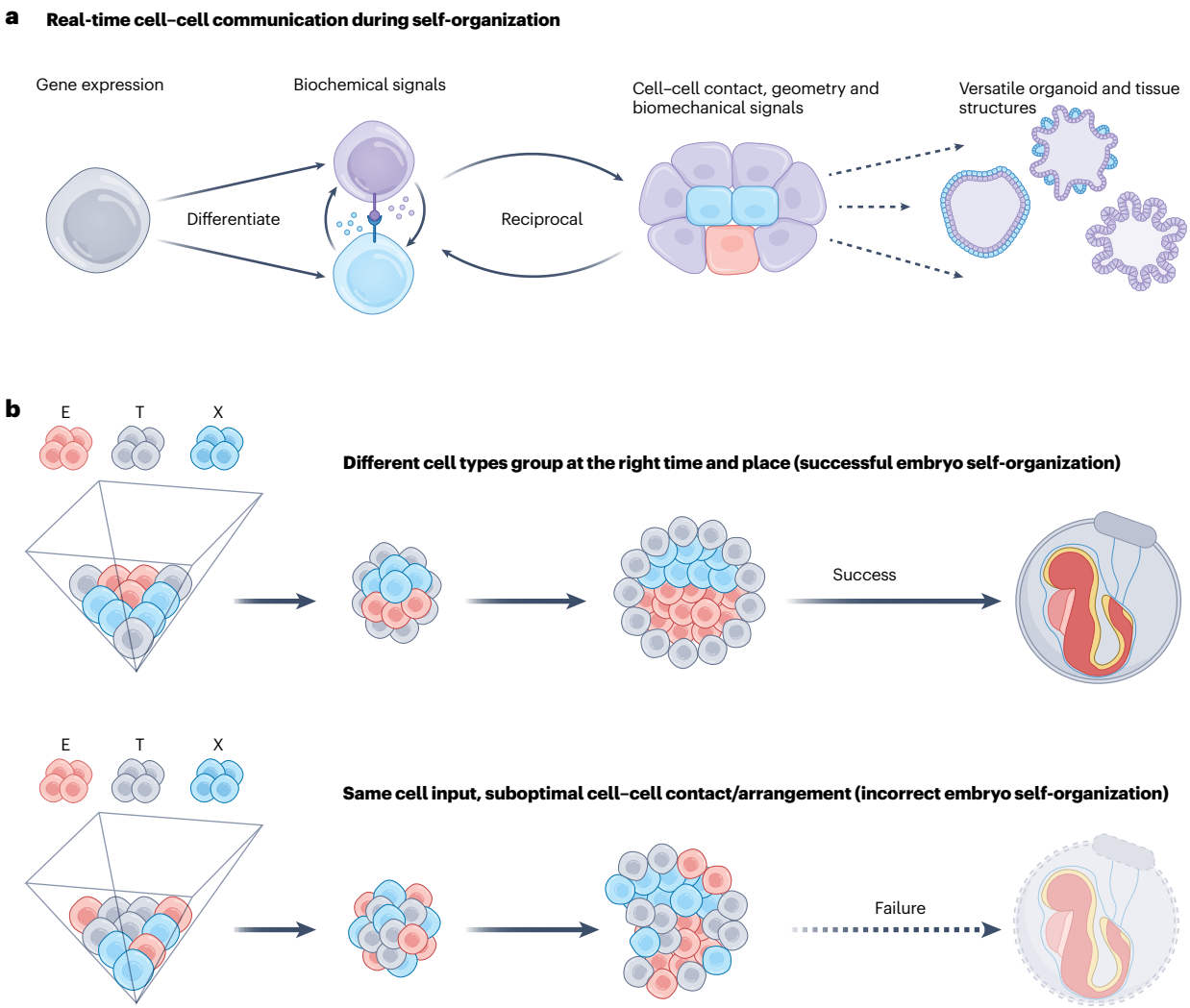

Fig. 3 | Mechanical–biochemical–gene expression feedback loops driving self-organization in organoids and embryo models. a, Schematic depicting dynamic feedback loops in cellular self-organization. Starting from gene expression inducing differentiation (left, single cell), reciprocal biochemical signaling enables initial interactions of different cell types (center left, signaling molecules exchanged). These evolve into cell–cell contacts shaped by geometry and biomechanical forces (center right, clustered cells with different tension and geometry), yielding versatile organoid and tissue structures (right). **b**, Precise cell-type arrangement and timing in the early growth window enable successful self-organization in stem cell-derived embryo models. The schematic illustrates the critical role of spatial–temporal coordination in self-organization of embryo-like structures, such as ETX models. Top, successful assembly occurs when different cell types (red, gray and blue spheres) group at the right time and place, enabling optimal cell–cell contacts and arrangement to form a structured embryo. Bottom, with the same cell inputs but suboptimal contact or arrangement, self-organization fails, resulting in disorganized or malformed structures. This principle extends to induced models like EiTX and EiTiX, where trophectoderm-like and/or extraembryonic endoderm-like cells are induced from epiblast-like cells (either through transgene or chemical approaches[61,65,102,135–138]). Induced types must emerge at precise positions and timings through regulated cell interactions (for example, cytoskeletal tension or adhesion codes) to ensure robust morphogenesis, as misalignment during early growth windows prevents self-correction.

Cell fate diversification and the coordinated logic of self-organization

A key feature of self-organization is not only how cells arrange themselves in space but also how they diversify into distinct cell types and how these differentiated cells interact to shape complex tissue structures. This diversification emerges from a combination of intrinsic genetic programs and extrinsic physical or biochemical cues, which vary across species and developmental contexts. In embryos of flies, frogs, sea urchins and fish, prepatterning of the oocyte (before fertilization) or zygote (after fertilization) is prominent, with asymmetrically deposited maternal morphogens that dictate the fates of descendant blastomeres as they create the diverse tissues. By contrast, mammalian embryos are likely to rely on subtler cues to bias cell fate specification[3]. Such biases can be seeded by spindle migration to the cortex during oocyte maturation[39–41], mechanical and molecular inputs at sperm entry[42,43], uneven inheritance of sperm-borne RNAs or mitochondrial proteins[44,45], mechanical compression within the elliptical zona pellucida and cleavage patterns that bias RNAs and protein distribution[3,46]. When amplified over time, these early cues help cells interpret their uniqueness and predisposition to make context-sensitive fate decisions where Turing's reaction–diffusion principles[47] and Wolpert's positional information[48] can act in concert to guide pattern formation[3].

Asymmetric events at fertilization such as egg–sperm fusion can trigger cytoplasmic reorganization, redistributing maternal transcripts and proteins. In the mouse, cytoplasmic flows emanate from the sperm entry site and persist in coordination with calcium spikes for hours[43], potentially initiating the first cellular asymmetries. This might explain why sister blastomeres at the two-cell stage already differ

BOX 2

Mechanotransduction: translating physical forces into biological responses

Mechanotransduction is the process by which cells convert mechanical stimuli (such as substrate stiffness, shear stress or cell crowding) into biochemical signals that influence gene expression, cell behavior and fate[19]. This mechanism is central to self-organization, enabling cells to sense their physical environment and adapt during development, tissue homeostasis and disease. Key pathways link force detection at the cell membrane to intracellular responses, often through cytoskeletal remodeling and nuclear signaling.

A prime example is the YAP/TAZ pathway, which integrates mechanical cues to regulate transcription[145]. YAP and TAZ are coactivators that shuttle between the cytoplasm and nucleus. Force sensing begins at focal adhesions, where integrins bind the extracellular matrix and transmit tension via talin and vinculin unfolding, activating Rho GTPases[145]. This promotes actin polymerization and contractility, inhibiting the Hippo pathway kinase LATS, which normally phosphorylates YAP and TAZ to retain them in the cytoplasm. Dephosphorylated YAP and TAZ translocate to the nucleus, binding TEAD transcription factors to activate genes involved in proliferation (for example, CTGF and CYR61) and differentiation (for example, trophectoderm specification in blastocysts)[146]. In embryos, YAP and TAZ respond to uterine compression or cell density, determining inner cell mass versus trophoblast fates. In addition, mechanical forces alter cellular shape, leading to compartmentalized biochemical reactions. Stretching or compression deforms the cytoskeleton, redistributing proteins and creating local signaling hubs. For instance, force-induced membrane curvature activates RhoA in specific compartments, driving localized actin assembly and kinase cascades (for example, FAK/ERK)[147]. Nuclear deformation under tension opens pores, facilitating transcription factor import or chromatin reorganization, directly linking shape to gene expression[148]. Recent work directly links shape to gene expression, including osmotic stress-induced condensate remodeling that primes pluripotency exits[149].

Mechanical cues are interpreted not only through YAP/TAZ but also within a network involving FGF, Notch and Wnt pathways, converting local forces into tissue-scale patterns. FGF signaling, via the RAS–ERK cascade, modulates YAP/TAZ transcriptional programs via MAPK signaling[150], influencing proliferation and epithelial-to-mesenchymal transition, while integrating with biomechanical inputs. Mechano-sensitive Wnt/β-catenin signaling converges with YAP/TAZ, where YAP can stabilize or cooperate with β-catenin–TCF complexes to enhance proliferative and patterning responses, and Wnt gradients inform force-dependent decisions[151]. Contact-dependent Notch signaling senses cell geometry and tension, interfacing with YAP and Wnt to drive lateral inhibition and sharpen fate boundaries[152,153]. These pathways form reinforcing loops that amplify mechanics into robust patterning, as seen in organoid morphogenesis[154].

These processes highlight self-organization's plasticity and robustness, with implications for bioengineering: manipulating shape via scaffolds or specific molecular pathways such as YAP/TAZ[155] may enhance embryo model fidelity and regenerative therapies.

in developmental potential: one contributing more to the epiblast (future fetus) and the other to the trophectoderm (future placenta) when separated and cultured individually[42,49–51].

Mechanical cues from the embryo's environment, such as the zona pellucida, blastomere to blastomere contact and uterine tissues at implantation, are also likely to be sensed during early embryogenesis. These cues can shape gene expression through mechanotransduction pathways, such as the Hippo pathway, which responds to tension by driving YAP into the nucleus[52–55] (Box 2). In the embryo, these mechanisms help specify whether a cell adopts inner cell mass or trophectoderm fate, illustrating how biomechanics and gene regulation are intertwined in guiding cell identity.

As development progresses and cell types diversify, the embryo becomes an exercise in arrangement: which cells are located next to each other and which cells communicate starts to matter as much as identity itself. Stem cell-based embryo models make this principle experimentally tractable by recapitulating early developmental events in controlled systems.

Stem cell-based embryo models as developed by us and others now span a wide developmental range from simple implantation- and early postimplantation-stage epiblast-like spheroids/lumenoids[11]; amnion-like amniotic sac embryoids[56]; two-dimensional (2D) micropatterned ES cell cultures[57,58]; epiblast- and trophectoderm-like ETS models (combining epiblast-like (E) and trophectoderm-like (T) stem cells)[59,60]; epiblast-, extraembryonic trophectoderm- and extraembryonic endoderm-like ETX models (combining epiblast-like (E), trophectoderm-like (T) and extraembryonic endoderm-like (X) stem cells) and induced (i) EiTiX variants wherein extraembryonic stem cell types are induced from ES cells[59,61–69] and bilaminoids[70], capturing early disc-like organization, to preimplantation stage blastoids[71–73]. In all these systems, correct proportions, positioning and timing of each stem cell type (epiblast-like, trophectoderm-like and extraembryonic endoderm-like) are critical for successful self-organization[74]. It is not enough to have the right components; they must interact in the right context (Fig. 3b). Their potency state matters too. For example, it appears that it helps if ES cells are in a naive, expanded or totipotent-like state to generate blastoids[75–78].

In lumenoids, ETS, ETX and EiTiX embryoids, successful formation of the amniotic cavity and the symmetry-breaking events that initiate gastrulation depend on the correct mechanical alignment of epiblast-like, trophoblast-like and extraembryonic endoderm-like tissues. This alignment is influenced by both intrinsic properties (cytoskeletal tension or apical domain formation) and extrinsic mechanical cues (stiffness of the surrounding environment[25]). This alignment can be imperfect during the early growth window, when cells still have motility and can be rearranged, but once cells become tightly packed they lose the ability to rearrange. As a result, cells become jammed, and the embryo fails to self-correct[25]. This illustrates how timing and spatial arrangement are just as critical as cell identity in enabling successful development.

Tissue and organ formation are not a linear unfolding of fate decisions but a dynamic choreography in which cells interpret signals, respond to mechanical and chemical cues and adjust their behavior in real time. As distinct cell types emerge, they influence one another through paracrine signaling, cell–cell contact and mechanical forces, creating a constantly evolving feedback network. Much like a choreographer guiding dancers through an unfolding performance, the initial instructions guiding cells are often imprecise and shaped through local

interactions, mechanical constraints and adaptive responses, gradually giving rise to an organized, functional structure. It is this ongoing dialog between intent and possibility, constraint and discovery, that brings biological form to life.

Species-specific adaptations in postimplantation self-organization

While self-organization of the embryo before implantation shares similarities across mammals, self-organization after implantation varies across species, driven by both external cues and intrinsic programming[79]. In mice, the implanting embryo transforms from a ball to an elongated egg cylinder, a structure that adapted to the slit-like uterine environment's mechanical constraints[80], which guides its postimplantation development. Conversely, human and monkey embryos become a flat bilaminar disc following implantation, reflecting a uterine wall with fewer lateral constraints, perhaps better suited to their implantation process[81]. These morphological differences are underpinned by spatial–temporal variations in critical gene expression, such as *Cdx2* and *Oct4*, which dictate lineage patterning with species-specific precision[82–85] and may have contributed to the observed species-specific features of the embryonic models regarding growth timing and spatial arrangements[86–92].

These morphological and molecular differences can have direct implications for stem cell-based embryo models. For instance, optimizing in vitro culture systems by incorporating mechanical constraints that mimic the uterus might be able to improve their developmental fidelity and long-term developmental success rates.

Self-organization failure in developmental disorders and disease

When the self-choreography of assembly goes off script, the consequences can range from subtle developmental changes to severe disease. The precise coordination of timing, position and interaction among cells is not only a feature of development but also its foundation.

An example comes from teratomas, which are tumors that arise from ES cells when they are allowed to differentiate without guidance of cell numbers or constraints of time and mechanical cues[93–96]. While their microstructures are impressively organized, their overall architecture is chaotic. This reveals a critical point: self-organization is not only about forming the right parts but also about putting them together at the right time, in the right place and in the right context.

Similar principles apply to congenital disorders (for example, Down syndrome[97]) where an extra copy of chromosome 21 alters gene expression. The resulting shifts in developmental timing and interaction lead to consistent features, like craniofacial changes and altered brain morphology[98]. What is remarkable is that the self-organization program still runs, but it does so in a slightly altered direction due to the gene dosage imbalance, enough to be recognized across individuals.

These cases reveal that self-organization is robust, but not infallible. Understanding these missteps is influential for developmental biology but also offers clues into how we might prevent or correct them. We might be able to enhance developmental plasticity.

Stem cell-based models of mammalian embryos

Recent breakthroughs have transformed how we investigate the self-organization of cells during early human embryo development. Rather than relying solely on human embryos, we can now model key stages of human embryogenesis and organogenesis using stem cell-derived systems. These models mimic aspects of development in vitro, and they also allow a degree of experimental control that was previously unattainable.

Systems such as lumenoids[11,12,35,99], stem cell-derived embryo-like structures[59,61,64–66,100–102] (for example, ETS, ETX, ETiX and EiTiX), human embryoids[67,68], gastruloids[103–105] and blastoids[63,71,72,106] have emerged as tools to explore symmetry breaking, germ layer specification, morphogenesis (including lumenogenesis, folding and branching) and the physical constraints that influence developmental trajectories. These models are, by their nature, simplified and incomplete, but they demonstrate that a limited number of stem cell types, when assembled under the right conditions, can spontaneously organize into structures that echo critical aspects of natural development.

The field of embryo-like structure formation in 3D (once termed 'synthetic embryology' to emphasize the concept of synthetic-like interactions between different types of stem cells) began with the development of spheroids/lumenoids, gastruloids and 2D micropatterns. Developed by the laboratory of M.Z.-G., a lumenoid can initiate self-organization from a single ES cell (dividing to generate a small epiblast-like population), mirroring how a compact group of pluripotent stem cells builds structure of the embryo. Embedded in Matrigel, which partially substitutes for missing extraembryonic cues[11,12,107], these cells undergo coordinated polarization, rosette formation, lumenogenesis and symmetry breaking, progressing toward early postimplantation-like states and mesoderm specification. This makes lumenoids a tractable model for implantation-stage morphogenesis, a stage that is difficult to observe directly, especially in humans. However, because lumenoids lack extraembryonic tissues, their developmental progression depends on Matrigel as a critical biochemical and mechanical surrogate rather than on embryo-derived tissue interactions.

A so-called 'gastruloid', like an embryoid body[108], is formed from about 100 or more ES cells aggregated under defined conditions, specifically Wnt activation, which induces elongation and axial patterning with regionally restricted gene expression, including Hox clusters[103,105,109,110]. This model is used for studying axis elongation and posterior development, despite that it does not recapitulate true gastrulation as it lacks a primitive streak, cell intercalation and anterior structures. As such, these models are valuable for probing posterior patterning but are limited as complete embryo models[57,58].

More recent models such as somitoids, segmentoids and trunk-like structures[111–114] take these models further by recapitulating key features of the embryonic trunk, including somite formation and early mesodermal patterning. Focusing on specific processes, they enable insight into high-resolution analysis of segmentation dynamics. However, they lack the global architecture and complex tissue interactions of an intact embryo.

Developed alongside lumenoids and gastruloids, 2D micropatterns confine ES cells to defined geometries[57], enabling reproducible studies of symmetry breaking and germ layer patterning. After BMP4 stimulation, cells self-organize into concentric rings that mimic ectoderm, mesoderm and endoderm, depending on position and density. Two-dimensional micropatterns are highly effective for probing the logic of fate decisions but lack morphogenetic movements and 3D architecture, limiting their ability to capture dynamic tissue organization.

The realization that reconstructing embryos with both anterior and posterior structures requires more than ES cells alone prompted the laboratory of M.Z.-G. to combine ES cells with trophoblast stem (TS) cells, leading to assembly of ETS embryoid[59] models: integrated structures that allowed for modeling critical cross-talk between embryonic and extraembryonic compartments. These models uncovered distinct lumenogenesis mechanisms in embryonic and extraembryonic compartments and how their cavities merge, as well as symmetry-breaking events that lead to mesoderm and primordial germ cell specification. However, ETS embryos lack the visceral endoderm, a second key extraembryonic lineage required for anterior–posterior patterning and anterior signaling center formation in natural embryos.

To overcome this issue, our group built so-called complete embryo models through coassemby of ES cells, TS cells and extraembryonic endoderm cells (XENs), which led to ETX embryoids[64]. These models continue to develop for 8.5 days, mimicking several hallmarks

https://doi.org/10.1038/s41587-026-03161-w

of postimplantation development, including symmetry breaking, anterior–posterior axis formation, anterior signaling center emergence, primitive streak formation and epithelial-to-mesenchymal transition, defining features of gastrulation previously seen only in natural embryos. More recent extensions of these models, such as ETiX and EiTiX structures, replaced TS cells and XENs with ES cells reprogrammed to generate both trophectoderm- and visceral endoderm-like lineages[101]. These advanced models progress to neurulation, forming anterior neural tissue and beating heart-like structures, and exhibit coordinated spatial and temporal patterning that closely mirrors embryonic development[61,65,66,101,102].

The efficiency and fidelity of models integrating multiple stem cell types hinge on the precise ratio, timing and biophysical interactions among the constituent stem cell types[115]. These systems revealed that differential expression of cadherins among ES cells, TS cells and XENs and regulation of cortical actin guide their ability to self-assemble into correct configurations[25]. Enhancing cadherin expression substantially boosts the success of ETX-embryoid formation, emphasizing how cell adhesion codes and mechanical tension governs self-organization.

Alongside ETX models emerged blastoids, stem cell-derived structures that mimic the architecture and lineages of the blastocyst[71]. Blastoids formed by combining ES cells and TS cells self-organize into an inner cell mass-like core, a trophectoderm-like shell and a blastocoel-like cavity. They offer a scalable system to study preimplantation lineage segregation.

While all these stem cell-derived models are far from being perfect replicas and differ in fidelity from natural embryos, they offer numerous advantages: control over cell composition, organization and signaling; scalability and compatibility with advanced tools. Live imaging enables real-time 3D visualization of morphogenesis, while single-cell and spatial multiomics[116] (transcriptomics, epigenomics and proteomics) allow for detailed molecular profiling of developing cells. CRISPR–Cas-based perturbation screens[117] (Fig. 4a), layered onto these systems, enable functional dissection of gene regulatory networks. Importantly, environmental toxicants and drug screens applied to embryo models allowed for testing of their impact on development and teratogenicity[118,119] (Fig. 4b), potentially identifying vulnerable windows and bottlenecks. When scaled up with organ-on-a-chip systems (Fig. 4c), these systems can complement efforts like the US National Institute of Environmental Health Sciences Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription program[120] and the National Institutes of Health new initiative promoting organoid-based alternatives to animal use[121]. Combined with artificial intelligence (AI)-based analysis[115], they bring a powerful lens into the earliest determinants of developmental success or failure, well before the human eye can detect.

As stem cell-based models are extended to human development, structures composed solely of human ES cells programmed to different fates have begun to mimic some key postimplantation events, such as amnion and yolk sac formation, primordial germ cell induction and the appearance of anterior hypoblast-like centers to induce anterior–posterior axis specification[67–70,122]. Some models reveal unexpected dynamics, such as the apparent dispensability of the trophoblast for amnion and primordial germ cell induction, challenging assumptions based on mouse development[67,123] and promoting further investigations. These advances open up exciting possibilities to identify which building blocks are essential, which are supportive and how early developmental programs might be substituted or rerouted through alternative mechanisms, setting the stage for engineering and optimization.

Engineering self-organization

The transition from understanding the evolutionary origins of self-organization to harnessing them represents the next frontier in developmental biotechnology. The same physical laws that drive cavitation, folding and branching in the embryo can be repurposed as design constraints to transform stem cell biology from a descriptive science into a robust engineering discipline.

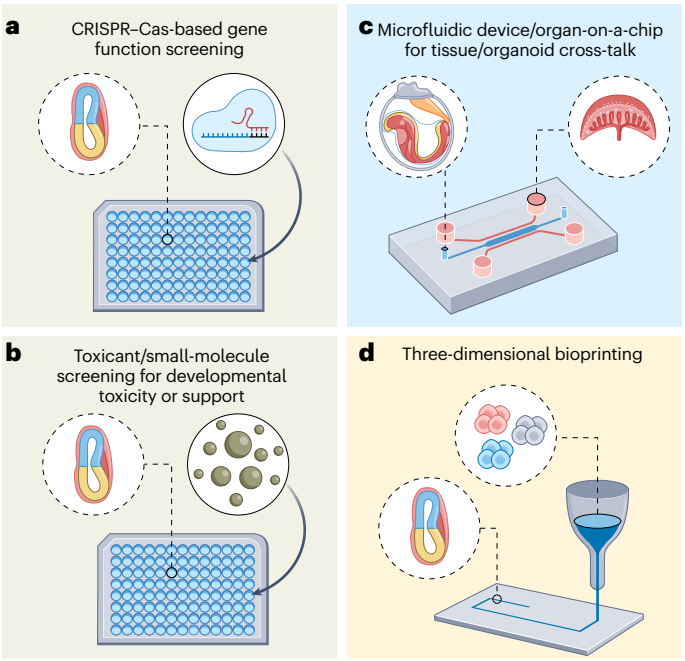

Fig. 4 | Emerging technologies enhancing the application of embryo models. Schematic overview of emerging biotechnological tools to advance stem cell-derived mammalian embryo models, enabling deeper insights into self-organization, developmental robustness and regenerative applications. **a**, CRISPR–Cas-based gene function screening enables systematic perturbation of developmental gene networks in stem cell-derived embryo models, revealing genetic hierarchies and regulatory nodes critical for self-organization. **b**, Small-molecule screening identifies compounds that either support or disrupt developmental progression, enabling interrogation of environmental cues, teratogens or candidate therapeutics. **c**, Microfluidic devices and organ-on-a-chip systems recapitulate spatial patterning, tissue–tissue cross-talk and mechanical constraints, offering a dynamic in vitro environment to simulate implantation or organogenesis. **d**, Three-dimensional bioprinting technologies allow spatially defined placement of different stem cell types, enabling architectural assembly of embryo-like structures and providing a platform to test the minimal requirements for self-organization. Together, these approaches transform embryo models from passive mimics to programmable systems, tools not only to observe but also to experimentally dissect, manipulate and even prototype multicellular organization.

For example, a major bottleneck in embryoid and organoid technology is batch heterogeneity. The rules of self-organization described above, particularly regarding the dependence on geometric confinement and mechanical feedback, offer a potential solution. For example, by using micropatterning and defined hydrogel stiffness to impose precise boundary conditions, we can restrict the growing space of the cells, forcing them to adopt a more defined, deterministic trajectory rather than a stochastic distribution. In this context, the physical parameters of self-organization become the intrinsic quality control metrics in the culture system needed for clinical-grade biomanufacturing.

Bioengineering innovations like microfluidic chips, organ-on-a-chip systems and 3D bioprinting[99,124–126] (Fig. 4c,d) offer further refined opportunities to decode the ‘design logic’ of life. They allow us to explore not only how embryos choreograph their own morphogenetic ‘dance’ but also why evolution selected certain forms and pathways over others. In practice, these programmable platforms when coupled with high-content perturbation libraries (for example, CRISPR and small molecules) can be used for automated imaging and AI-based phenotyping to learn predictive maps from inputs to morphogenetic

trajectories and outcomes and then used in closed-loop optimization to improve yield and fidelity.

An emerging direction to elevate stem cell-derived embryo models is the engineering of the embryo–uterine interface. A wave of recently developed 3D coculture and 'implantation-on-chip' systems has reinforced the idea that self-organization at implantation is a reciprocal morphogenetic event[127–130]. These models reveal that the uterine niche is not a passive substrate but an active driver: it reconstructs complex luminal, glandular and stromal compartments to guide implantation and actively accelerates lineage maturation, specifically extravillous trophoblast emergence, through critical human chorionic gonadotropin signaling and ligand–receptor cross-talk[129,130]. Complementing this biochemical dialog, biomimetic studies have identified that the mechanical properties of the niche, particularly stress relaxation and matrix degradability via embryo-secreted matrix metalloproteinases[127], are essential physical prerequisites for focal adhesion formation and developmental progression. This reciprocal logic also enables disease modeling: by deriving endometrioids from individuals with recurrent implantation failure, a recent work has recapitulated a 'failure-to-implant' phenotype in vitro and used this as a platform for high-throughput screening of US Food and Drug Administration-approved compounds to identify agents that rescue implantation defects[128].

The ability to reconstruct interfaces between tissues, such as the embryo–endometrial boundary, should allow us to move one day from observing development to correcting it. As demonstrated by these recent models, failures of self-organization in disease often reflect specific mechanical or signaling mismatches, such as disrupted hormonal feedback or aberrant matrix mechanics, which can be predicted and treated ex vivo. This enables a closed-loop strategy: measure trajectories, perturb systematically, learn predictive models and tune inputs to maximize developmental success while minimizing variance. The corresponding engineering 'control knobs' follow directly from the principles discussed above, specifically boundary conditions (geometry, confinement and hydrogel stress relaxation), transport fields (oxygen and nutrient delivery, waste removal) and cell–cell/extracellular matrix interaction codes (adhesion, ligand specificity and cortical tension). Applying these inputs within defined time windows, when the system can still self-correct, could pave the way for precision therapeutics in reproductive medicine that harness the logic of life.

Future perspectives

As we uncover the fundamental principles that guided the transition from single cells to structured, multicellular organisms, we are entering an era in which these rules can be reverse engineered, simulated and, in some cases, deliberately rewritten. This might be seen as marking a shift from observing biology to prototyping it.

Stem cell-derived models allow us to explore alternative trajectories of multicellular organization, raising evolutionary questions that were previously unsolvable. What is the minimal set of interactions sufficient to produce an embryo-like structure? Could there have been other paths to life? What changes if we tweak the timing, geometry or lineage logic? Although current stem cell-based models remain imperfect, with structural heterogeneity and low efficiency still common[100], these very imperfections make them powerful exploration tools because their failure modes expose gaps in our understanding and point to new experimental ways to address them.

Looking ahead, these systems offer opportunities to illuminate why so many human pregnancies fail and how such losses might one day be prevented as well as to derive progenitor cell populations for organ repair. As self-organization principles are integrated into engineering designs and interfaces, it will allow for distinguishing which cellular and mechanical building blocks are essential, which are supportive but dispensable and which can be substituted or bypassed through alternative routes. AI will be instrumental in this endeavor, extracting compact rule sets of developmental success or failure from high-dimensional experimental datasets.

Beyond modeling disease or aiding tissue repair, these technologies serve as conceptual frameworks to allow us to travel backward and forward along the arc of evolution, reconstructing steps from the first cooperating cells to complex organisms and projecting possible futures. Integrating new methods for quantifying cell–cell mechanical forces[131] and positional information[132] lays the groundwork for innovations such as in vitro gametogenesis[133] and organoid systems that interact dynamically with their environments[134]. As we uncover the logic of self-organization, we edge closer to building entirely new forms of biological complexity.

References

1. Zhu, M. & Zernicka-Goetz, M. Principles of self-organization of the mammalian embryo. *Cell* **183**, 1467–1478 (2020).
2. Karsenti, E. Self-organization in cell biology: a brief history. *Nat. Rev. Mol. Cell Biol.* **9**, 255–262 (2008).
3. Chen, Q., Shi, J., Tao, Y. & Zernicka-Goetz, M. Tracing the origin of heterogeneity and symmetry breaking in the early mammalian embryo. *Nat. Commun.* **9**, 1819 (2018).
4. Squyres, G. R. & Newman, D. K. Biofilms as more than the sum of their parts: lessons from developmental biology. *Curr. Opin. Microbiol.* **82**, 102537 (2024).
5. Brunet, T. & King, N. The origin of animal multicellularity and cell differentiation. *Dev. Cell* **43**, 124–140 (2017).
6. Rados, T. et al. Tissue-like multicellular development triggered by mechanical compression in archaea. *Science* **388**, 109–115 (2025).
7. Rodrigues-Oliveira, T. et al. Actin cytoskeleton and complex cell architecture in an Asgard archaeon. *Nature* **613**, 332–339 (2023).
8. Kimmel, C. B., Ballard, W. W., Kimmel, S. R., Ullmann, B. & Schilling, T. F. Stages of embryonic development of the zebrafish. *Dev. Dyn.* **203**, 253–310 (1995).
9. Fleming, T. P., Papenbrock, T., Fesenko, I., Hausen, P. & Sheth, B. Assembly of tight junctions during early vertebrate development. *Semin. Cell Dev. Biol.* **11**, 291–299 (2000).
10. White, M. D., Zenker, J., Bissiere, S. & Plachta, N. Instructions for assembling the early mammalian embryo. *Dev. Cell* **45**, 667–679 (2018).
11. Bedzhov, I. & Zernicka-Goetz, M. Self-organizing properties of mouse pluripotent cells initiate morphogenesis upon implantation. *Cell* **156**, 1032–1044 (2014).
12. Shahbazi, M. N. et al. Pluripotent state transitions coordinate morphogenesis in mouse and human embryos. *Nature* **552**, 239–243 (2017).
13. Christodoulou, N. et al. Morphogenesis of extra-embryonic tissues directs the remodelling of the mouse embryo at implantation. *Nat. Commun.* **10**, 3557 (2019).
14. Weberling, A. & Zernicka-Goetz, M. Trophectoderm mechanics direct epiblast shape upon embryo implantation. *Cell Rep.* **34**, 108655 (2021).
15. Karzbrun, E. et al. Human neural tube morphogenesis in vitro by geometric constraints. *Nature* **599**, 268–272 (2021).
16. de Vareilles, H., Riviere, D., Mangin, J. F. & Dubois, J. Development of cortical folds in the human brain: an attempt to review biological hypotheses, early neuroimaging investigations and functional correlates. *Dev. Cogn. Neurosci.* **61**, 101249 (2023).
17. Karzbrun, E., Kshirsagar, A., Cohen, S. R., Hanna, J. H. & Reiner, O. Human brain organoids on a chip reveal the physics of folding. *Nat. Phys.* **14**, 515–522 (2018).
18. Huycke, T. R. et al. Patterning and folding of intestinal villi by active mesenchymal dewetting. *Cell* **187**, 3072–3089 (2024).
19. Heisenberg, C. P. & Bellaiche, Y. Forces in tissue morphogenesis and patterning. *Cell* **153**, 948–962 (2013).

20. Ochoa-Espinosa, A. & Affolter, M. Branching morphogenesis: from cells to organs and back. *Cold Spring Harb. Perspect. Biol.* **4**, a008243 (2012).
21. Losa, G. A. The fractal geometry of life. *Riv. Biol.* **102**, 29–59 (2009).
22. Ucar, M. C. et al. Theory of branching morphogenesis by local interactions and global guidance. *Nat. Commun.* **12**, 6830 (2021).
23. West, G. B., Brown, J. H. & Enquist, B. J. A general model for the origin of allometric scaling laws in biology. *Science* **276**, 122–126 (1997).
24. Hannezo, E. & Heisenberg, C. P. Mechanochemical feedback loops in development and disease. *Cell* **178**, 12–25 (2019).
25. Bao, M. et al. Stem cell-derived synthetic embryos self-assemble by exploiting cadherin codes and cortical tension. *Nat. Cell Biol.* **24**, 1341–1349 (2022).
26. Niwa, H., Burdon, T., Chambers, I. & Smith, A. Self-renewal of pluripotent embryonic stem cells is mediated via activation of STAT3. *Genes Dev.* **12**, 2048–2060 (1998).
27. Larue, L. et al. A role for cadherins in tissue formation. *Development* **122**, 3185–3194 (1996).
28. Redmer, T. et al. E-cadherin is crucial for embryonic stem cell pluripotency and can replace OCT4 during somatic cell reprogramming. *EMBO Rep.* **12**, 720–726 (2011).
29. Foty, R. A. & Steinberg, M. S. The differential adhesion hypothesis: a direct evaluation. *Dev. Biol.* **278**, 255–263 (2005).
30. Hanahan, D. & Weinberg, R. A. Hallmarks of cancer: the next generation. *Cell* **144**, 646–674 (2011).
31. Thiery, J. P. Epithelial–mesenchymal transitions in tumour progression. *Nat. Rev. Cancer* **2**, 442–454 (2002).
32. Desgrosellier, J. S. & Cheresh, D. A. Integrins in cancer: biological implications and therapeutic opportunities. *Nat. Rev. Cancer* **10**, 9–22 (2010).
33. Lamouille, S., Xu, J. & Derynck, R. Molecular mechanisms of epithelial–mesenchymal transition. *Nat. Rev. Mol. Cell Biol.* **15**, 178–196 (2014).
34. Kessenbrock, K., Plaks, V. & Werb, Z. Matrix metalloproteinases: regulators of the tumor microenvironment. *Cell* **141**, 52–67 (2010).
35. Shahbazi, M. N. et al. Self-organization of the human embryo in the absence of maternal tissues. *Nat. Cell Biol.* **18**, 700–708 (2016).
36. Lei, M. et al. Self-organization process in newborn skin organoid formation inspires strategy to restore hair regeneration of adult cells. *Proc. Natl Acad. Sci. USA* **114**, E7101–E7110 (2017).
37. Lei, M. et al. The mechano–chemical circuit drives skin organoid self-organization. *Proc. Natl Acad. Sci. USA* **120**, e2221982120 (2023).
38. Ramos, R. et al. Parsing patterns: emerging roles of tissue self-organization in health and disease. *Cell* **187**, 3165–3186 (2024).
39. Dumont, J. et al. Formin-2 is required for spindle migration and for the late steps of cytokinesis in mouse oocytes. *Dev. Biol.* **301**, 254–265 (2007).
40. Plusa, B. et al. The first cleavage of the mouse zygote predicts the blastocyst axis. *Nature* **434**, 391–395 (2005).
41. Duan, X. et al. Dynamic organelle distribution initiates actin-based spindle migration in mouse oocytes. *Nat. Commun.* **11**, 277 (2020).
42. Piotrowska, K. & Zernicka-Goetz, M. Role for sperm in spatial patterning of the early mouse embryo. *Nature* **409**, 517–521 (2001).
43. Ajduk, A. et al. Rhythmic actomyosin-driven contractions induced by sperm entry predict mammalian embryo viability. *Nat. Commun.* **2**, 417 (2011).
44. Chen, Q., Yan, W. & Duan, E. Epigenetic inheritance of acquired traits through sperm RNAs and sperm RNA modifications. *Nat. Rev. Genet.* **17**, 733–743 (2016).
45. Luo, S. M. et al. Unique insights into maternal mitochondrial inheritance in mice. *Proc. Natl Acad. Sci. USA* **110**, 13038–13043 (2013).
46. Shi, J. et al. Dynamic transcriptional symmetry-breaking in pre-implantation mammalian embryo development revealed by single-cell RNA-seq. *Development* **142**, 3468–3477 (2015).
47. Turing, A. M. The chemical basis of morphogenesis. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* **237**, 37–72 (1952).
48. Wolpert, L. Positional information and pattern formation. *Curr. Top. Dev. Biol.* **117**, 597–608 (2016).
49. Gardner, R. L. Specification of embryonic axes begins before cleavage in normal mouse development. *Development* **128**, 839–847 (2001).
50. Morris, S. A., Guo, Y. & Zernicka-Goetz, M. Developmental plasticity is bound by pluripotency and the FGF and Wnt signaling pathways. *Cell Rep.* **2**, 756–765 (2012).
51. Iwamoto-Stohl, L. K. et al. Fertilization triggers early proteomic symmetry breaking in mammalian embryos. *Cell* **188**, 7428–7444 (2025).
52. Nishioka, N. et al. The Hippo signaling pathway components LATS and YAP pattern TEAD4 activity to distinguish mouse trophectoderm from inner cell mass. *Dev. Cell* **16**, 398–410 (2009).
53. Samarage, C. R. et al. Cortical tension allocates the first inner cells of the mammalian embryo. *Dev. Cell* **34**, 435–447 (2015).
54. Dupont, S. et al. Role of YAP/TAZ in mechanotransduction. *Nature* **474**, 179–183 (2011).
55. Wicklow, E. et al. Hippo pathway members restrict SOX2 to the inner cell mass where it promotes ICM fates in the mouse blastocyst. *PLoS Genet.* **10**, e1004618 (2014).
56. Shao, Y. et al. A pluripotent stem cell-based model for post-implantation human amniotic sac development. *Nat. Commun.* **8**, 208 (2017).
57. Warmflash, A., Sorre, B., Etoc, F., Siggia, E. D. & Brivanlou, A. H. A method to recapitulate early embryonic spatial patterning in human embryonic stem cells. *Nat. Methods* **11**, 847–854 (2014).
58. Heemskerk, I. et al. Rapid changes in morphogen concentration control self-organized patterning in human embryonic stem cells. *eLife* **8**, e40526 (2019).
59. Harrison, S. E., Sozen, B., Christodoulou, N., Kyprianou, C. & Zernicka-Goetz, M. Assembly of embryonic and extraembryonic stem cells to mimic embryogenesis in vitro. *Science* **356**, eaal1810 (2017).
60. Girgin, M. U. et al. Bioengineered embryoids mimic post-implantation development in vitro. *Nat. Commun.* **12**, 5140 (2021).
61. Lau, K. Y. C. et al. Mouse embryo model derived exclusively from embryonic stem cells undergoes neurulation and heart development. *Cell Stem Cell* **29**, 1445–1458 (2022).
62. Sozen, B. et al. Reconstructing aspects of human embryogenesis with pluripotent stem cells. *Nat. Commun.* **12**, 5550 (2021).
63. Sozen, B. et al. Self-organization of mouse stem cells into an extended potential blastoid. *Dev. Cell* **51**, 698–712 (2019).
64. Sozen, B. et al. Self-assembly of embryonic and two extra-embryonic stem cell types into gastrulating embryo-like structures. *Nat. Cell Biol.* **20**, 979–989 (2018).
65. Amadei, G. et al. Embryo model completes gastrulation to neurulation and organogenesis. *Nature* **610**, 143–153 (2022).
66. Amadei, G. et al. Inducible stem-cell-derived embryos capture mouse morphogenetic events in vitro. *Dev. Cell* **56**, 366–382 (2021).
67. Weatherbee, B. A. T. et al. Pluripotent stem cell-derived model of the post-implantation human embryo. *Nature* **622**, 584–593 (2023).
68. Oldak, B. et al. Complete human day 14 post-implantation embryo models from naive ES cells. *Nature* **622**, 562–573 (2023).

69. Pedroza, M. et al. Self-patterning of human stem cells into post-implantation lineages. *Nature* **622**, 574–583 (2023).
70. Okubo, T. et al. Hypoblast from human pluripotent stem cells regulates epiblast development. *Nature* **626**, 357–366 (2024).
71. Rivron, N. C. et al. Blastocyst-like structures generated solely from stem cells. *Nature* **557**, 106–111 (2018).
72. Yu, L. et al. Blastocyst-like structures generated from human pluripotent stem cells. *Nature* **591**, 620–626 (2021).
73. Liu, X. et al. Modelling human blastocysts by reprogramming fibroblasts into iBlastoids. *Nature* **591**, 627–632 (2021).
74. Gantner, C. W., Weatherbee, B. A. T., Wang, Y. & Zernicka-Goetz, M. Assembly of a stem cell-derived human postimplantation embryo model. *Nat. Protoc.* **20**, 67–91 (2025).
75. Guo, G. et al. Epigenetic resetting of human pluripotency. *Development* **144**, 2748–2763 (2017).
76. Takashima, Y. et al. Resetting transcription factor control circuitry toward ground-state pluripotency in human. *Cell* **158**, 1254–1269 (2014).
77. Theunissen, T. W. et al. Systematic identification of culture conditions for induction and maintenance of naive human pluripotency. *Cell Stem Cell* **15**, 471–487 (2014).
78. Ren, Y. et al. A continuous totipotent-like cell-based embryo model recapitulates mouse embryogenesis from zygotic genome activation to gastrulation. *Nat. Cell Biol.* **27**, 1993–2006 (2025).
79. Mole, M. A., Weberling, A. & Zernicka-Goetz, M. Comparative analysis of human and mouse development: from zygote to pre-gastrulation. *Curr. Top. Dev. Biol.* **136**, 113–138 (2020).
80. Chen, Q. et al. Navigating the site for embryo implantation: biomechanical and molecular regulation of intrauterine embryo distribution. *Mol. Aspects Med.* **34**, 1024–1042 (2013).
81. Carson, D. D. et al. Embryo implantation. *Dev. Biol.* **223**, 217–237 (2000).
82. Niwa, H. et al. Interaction between OCT3/4 and CDX2 determines trophectoderm differentiation. *Cell* **123**, 917–929 (2005).
83. Bou, G. et al. OCT4 expression transactivated by GATA protein is essential for non-rodent trophectoderm early development. *Cell Rep.* **41**, 111644 (2022).
84. Bi, Y. et al. Cell fate roadmap of human primed-to-naive transition reveals preimplantation cell lineage signatures. *Nat. Commun.* **13**, 3147 (2022).
85. Zhai, J. et al. Primate gastrulation and early organogenesis at single-cell resolution. *Nature* **612**, 732–738 (2022).
86. Zhai, J. et al. Neurulation of the cynomolgus monkey embryo achieved from 3D blastocyst culture. *Cell* **186**, 2078–2091 (2023).
87. Ma, H. et al. In vitro culture of cynomolgus monkey embryos beyond early gastrulation. *Science* **366**, eaax7890 (2019).
88. Ming, H., Scatolin, G. N., Ojeda-Rojas, O. A. & Jiang, Z. Establishment of bovine extraembryonic endoderm stem cells enables efficient blastoid formation. *Cell Rep.* **44**, 115707 (2025).
89. Pinzon-Arteaga, C. A. et al. Bovine blastocyst-like structures derived from stem cell cultures. *Cell Stem Cell* **30**, 611–616 (2023).
90. Niu, Y. et al. Dissecting primate early post-implantation development using long-term in vitro embryo culture. *Science* **366**, eaaw5754 (2019).
91. Gong, Y. et al. Ex utero monkey embryogenesis from blastocyst to early organogenesis. *Cell* **186**, 2092–2110 (2023).
92. Li, J. et al. Modelling late gastrulation in stem cell-derived monkey embryo models. *Nature* **649**, 161–172 (2026).
93. Stevens, L. C. The biology of teratomas. *Adv. Morphog.* **6**, 1–31 (1967).
94. Thomson, J. A. et al. Embryonic stem cell lines derived from human blastocysts. *Science* **282**, 1145–1147 (1998).
95. Lancaster, M. A. et al. Cerebral organoids model human brain development and microcephaly. *Nature* **501**, 373–379 (2013).
96. Simunovic, M. & Brivanlou, A. H. Embryoids, organoids and gastruloids: new approaches to understanding embryogenesis. *Development* **144**, 976–985 (2017).
97. Bull, M. J. Down syndrome. *N. Engl. J. Med.* **382**, 2344–2352 (2020).
98. Hasina, Z., Wang, N. & Wang, C. C. Developmental neuropathology and neurodegeneration of Down syndrome: current knowledge in humans. *Front. Cell Dev. Biol.* **10**, 877711 (2022).
99. Zheng, Y. et al. Controlled modelling of human epiblast and amnion development using stem cells. *Nature* **573**, 421–425 (2019).
100. Zernicka-Goetz, M. The evolution of embryo models. *Nat. Methods* **20**, 1844–1848 (2023).
101. Tarazi, S. et al. Post-gastrulation synthetic embryos generated ex utero from mouse naive ESCs. *Cell* **185**, 3290–3306 (2022).
102. Li, H. et al. A complete model of mouse embryogenesis through organogenesis enabled by chemically induced embryo founder cells. *Cell* **188**, 5912–5930 (2025).
103. Arias, A. M., Marikawa, Y. & Moris, N. Gastruloids: pluripotent stem cell models of mammalian gastrulation and embryo engineering. *Dev. Biol.* **488**, 35–46 (2022).
104. van den Brink, S. C. et al. Single-cell and spatial transcriptomics reveal somitogenesis in gastruloids. *Nature* **582**, 405–409 (2020).
105. Beccari, L. et al. Multi-axial self-organization properties of mouse embryonic stem cells into gastruloids. *Nature* **562**, 272–276 (2018).
106. David, L., Bruneau, A., Freour, T., Rivron, N. & Van de Velde, H. An update on human pre- and peri-implantation development: a blueprint for blastoids. *Curr. Opin. Genet. Dev.* **83**, 102125 (2023).
107. Langkabel, J. et al. Induction of rosette-to-lumen stage embryoids using reprogramming paradigms in ESCs. *Nat. Commun.* **12**, 7322 (2021).
108. Stevens, L. C. Embryonic potency of embryoid bodies derived from a transplantable testicular teratoma of the mouse. *Dev. Biol.* **2**, 285–297 (1960).
109. Deschamps, J. & Duboule, D. Embryonic timing, axial stem cells, chromatin dynamics, and the Hox clock. *Genes Dev.* **31**, 1406–1416 (2017).
110. Moris, N. et al. An in vitro model of early anteroposterior organization during human development. *Nature* **582**, 410–415 (2020).
111. Miao, Y. et al. Reconstruction and deconstruction of human somitogenesis in vitro. *Nature* **614**, 500–508 (2023).
112. Veenvliet, J. V. et al. Mouse embryonic stem cells self-organize into trunk-like structures with neural tube and somites. *Science* **370**, eaba4937 (2020).
113. Hamidi, S. & Alev, C. In vitro models of pre- and post-gastrulation embryonic development. *Curr. Opin. Genet. Dev.* **77**, 101985 (2022).
114. Makwana, K. et al. Modelling co-development between the somites and neural tube in human trunk-like structures. *Nat. Cell Biol.* **27**, 2049–2062 (2025).
115. Caldarelli, P. et al. AI-based approach to dissect the variability of mouse stem cell-derived embryo models. *Nat. Commun.* **16**, 1772 (2025).
116. Vandereyken, K., Sifrim, A., Thienpont, B. & Voet, T. Methods and applications for single-cell and spatial multi-omics. *Nat. Rev. Genet.* **24**, 494–515 (2023).
117. Li, K., Ouyang, M., Zhan, J. & Tian, R. CRISPR-based functional genomics screening in human-pluripotent-stem-cell-derived cell types. *Cell Genom.* **3**, 100300 (2023).
118. Huang, M. et al. Establishment of human gastrulating stem cells with the capacity of stable differentiation into multiple gastrulating cell types. *Cell Res.* **35**, 719–734 (2025).
119. Jorgensen, V. et al. Efficient stem cell-derived mouse embryo models for environmental studies. *Dev. Cell* **61**, 193–207 (2026).

120. Wang, T. et al. The NIEHS TaRGET II Consortium and environmental epigenomics. *Nat. Biotechnol.* **36**, 225–227 (2018).
121. NIH. Standardized Organoid Modeling Center to reduce reliance on animal modeling. *NIH Grants & Funding* https://grants.nih.gov/news-events/nih-extramural-nexus-news/2025/09/standardized-organoid-modeling-center-to-reduce-reliance-on-animal-modeling (2025).
122. Liu, L. et al. Modeling post-implantation stages of human development into early organogenesis with stem-cell-derived peri-gastruloids. *Cell* **186**, 3776–3792 (2023).
123. Hu, W. et al. Atlas of amnion development during the first trimester of human pregnancy. *Nat. Cell Biol.* **27**, 1175–1185 (2025).
124. Zheng, Y., Shao, Y. & Fu, J. A microfluidics-based stem cell model of early post-implantation human development. *Nat. Protoc.* **16**, 309–326 (2021).
125. Ingber, D. E. Human organs-on-chips for disease modelling, drug development and personalized medicine. *Nat. Rev. Genet.* **23**, 467–491 (2022).
126. Matai, I., Kaur, G., Seyedsalehi, A., McClinton, A. & Laurencin, C. T. Progress in 3D bioprinting technology for tissue/organ regenerative engineering. *Biomaterials* **226**, 119536 (2020).
127. Guo, J. et al. 3D biomimetic niche modulates embryo development in vitro. *Nat. Commun.* **17**, 1279 (2026).
128. Li, Q. et al. A 3D in vitro model for studying human implantation and implantation failure. *Cell* **189**, 70–86 (2026).
129. Mole, M. A. et al. Modeling human embryo implantation in vitro. *Cell* **189**, 87–105 (2026).
130. Song, J. et al. 3D post-implantation co-culture of human embryo and endometrium. *Cell Stem Cell* **33**, 58–72 (2026).
131. Campas, O. et al. Quantifying cell-generated mechanical forces within living embryonic tissues. *Nat. Methods* **11**, 183–189 (2014).
132. Tkacik, G., Dubuis, J. O., Petkova, M. D. & Gregor, T. Positional information, positional error, and readout precision in morphogenesis: a mathematical framework. *Genetics* **199**, 39–59 (2015).
133. Saitou, M., Nagano, M. & Mizuta, K. Mechanisms of human germ cell development. *Nat. Rev. Mol. Cell Biol.* **27**, 153–171 (2026).
134. Puschhof, J., Pleguezuelos-Manzano, C. & Clevers, H. Organoids and organs-on-chips: insights into human gut-microbe interactions. *Cell Host Microbe* **29**, 867–878 (2021).
135. Chen, C. et al. Signaling reprogramming via STAT3 activation unravels high-fidelity human post-implantation embryo modeling. *Cell Stem Cell* **32**, 1528–1544 (2025).
136. Liu, K. et al. Modeling post-gastrula development via bidirectional pluripotent stem cells. *Cell Res.* **35**, 954–969 (2025).
137. Oura, S., Li, L. & Wu, J. An inducible model of human post-implantation development derived from primed and naive stem cells. *Cell Stem Cell* **32**, 1509–1527 (2025).
138. Yilmaz, A. et al. Transgene-free generation of mouse post-gastrulation whole embryo models solely from naive ESCs and iPSCs. *Cell Stem Cell* **32**, 1545–1562 (2025).
139. Haeckel, E. Die Gastrea-Theorie, die phylogenetische Classification des Thierreichs und die Homologie der Keimblätter [The Gastrea theory, the phylogenetic classification of the animal kingdom and the homology of the germ layers]. *Jena. Z. Med. Naturwiss.* **8**, 1–55 (1874).
140. Zakhvatkin, A. A. Sravnitel'naya embriologiya nizshikh bespozvonochnykh [The comparative embryology of the low invertebrates]. *Sov. Nauka* (1949).
141. Murray, P. S. & Zaidel-Bar, R. Pre-metazoan origins and evolution of the cadherin adhesome. *Biol. Open* **3**, 1183–1195 (2014).
142. Sebe-Pedros, A., Roger, A. J., Lang, F. B., King, N. & Ruiz-Trillo, I. Ancient origin of the integrin-mediated adhesion and signaling machinery. *Proc. Natl Acad. Sci. USA* **107**, 10142–10147 (2010).
143. Dasgupta, I. & McCollum, D. Control of cellular responses to mechanical cues through YAP/TAZ regulation. *J. Biol. Chem.* **294**, 17693–17706 (2019).
144. Pfeiffer, T., Schuster, S. & Bonhoeffer, S. Cooperation and competition in the evolution of ATP-producing pathways. *Science* **292**, 504–507 (2001).
145. Panciera, T., Azzolin, L., Cordenonsi, M. & Piccolo, S. Mechanobiology of YAP and TAZ in physiology and disease. *Nat. Rev. Mol. Cell Biol.* **18**, 758–770 (2017).
146. Varelas, X. The Hippo pathway effectors TAZ and YAP in development, homeostasis and disease. *Development* **141**, 1614–1626 (2014).
147. Bade, N. D., Kamien, R. D., Assoian, R. K. & Stebe, K. J. Curvature and Rho activation differentially control the alignment of cells and stress fibers. *Sci. Adv.* **3**, e1700150 (2017).
148. Kalukula, Y., Stephens, A. D., Lammerding, J. & Gabriele, S. Mechanics and functional consequences of nuclear deformations. *Nat. Rev. Mol. Cell Biol.* **23**, 583–602 (2022).
149. McCreery, K. P. et al. Mechano-osmotic signals control chromatin state and fate transitions in pluripotent stem cells. *Nat. Cell Biol.* **27**, 1757–1770 (2025).
150. Reddy, B. V. & Irvine, K. D. Regulation of Hippo signaling by EGFR–MAPK signaling through Ajuba family proteins. *Dev. Cell* **24**, 459–471 (2013).
151. Azzolin, L. et al. YAP/TAZ incorporation in the β-catenin destruction complex orchestrates the Wnt response. *Cell* **158**, 157–170 (2014).
152. Engel-Pizcueta, C. & Pujades, C. Interplay between Notch and YAP/TAZ pathways in the regulation of cell fate during embryo development. *Front. Cell Dev. Biol.* **9**, 711531 (2021).
153. Stassen, O., Ristori, T. & Sahlgren, C. M. Notch in mechanotransduction—from molecular mechanosensitivity to tissue mechanostasis. *J. Cell Sci.* **133**, jcs250738 (2020).
154. Gjorevski, N. et al. Designer matrices for intestinal stem cell and organoid culture. *Nature* **539**, 560–564 (2016).
155. Dey, A., Varelas, X. & Guan, K. L. Targeting the Hippo pathway in cancer, fibrosis, wound healing and regenerative medicine. *Nat. Rev. Drug Discov.* **19**, 480–494 (2020).

Acknowledgements

We thank Y. Pilpel for stimulating feedback and X. Zhang for preparing the figure draft. Our laboratories are supported in part by the NIH (Director's Pioneer Award 5DP1HD104575-04 to M.Z.-G.; R01HD092431 and R01ES032024 to Q.C.).

Author contributions

Q.C. and M.Z.-G. contributed to the conceptualization and writing of this Perspective and approved the final version of the Perspective.

Competing interests

M.Z.-G. declares a patent 'Reconstructing human early embryogenesis in vitro with pluripotent stem cells'. Q.C. declares no competing interests.

Additional information

Correspondence should be addressed to Qi Chen or Magdalena Zernicka-Goetz.

Peer review information *Nature Biotechnology* thanks Jianping Fu, Alexandre Bisson and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.