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Review

Cell division geometries as central organizers of early embryo development

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ABSTRACT

Early cellular patterning is a critical step of embryonic development that determines the proper progression of morphogenesis in all metazoans. It relies on a series of rapid reductive divisions occurring simultaneously with the specification of the fate of different subsets of cells. Multiple species developmental strategies emerged in the form of a unique cleavage pattern with stereotyped division geometries. Cleavage geometries have long been associated to the emergence of canonical developmental features such as cell cycle asynchrony, zygotic genome activation and fate specification. Yet, the direct causal role of division positioning on blastomere cell behavior remain partially understood. Oriented and/or asymmetric divisions define blastomere cell sizes, contacts and positions, with potential immediate impact on cellular decisions, lineage specification and morphogenesis. Division positions also instruct daughter cells polarity, mechanics and geometries, thereby influencing subsequent division events, in an emergent interplay that may pattern early embryos independently of firm deterministic genetic programs. We here review the recent literature which helped to delineate mechanisms and functions of division positioning in early embryos.

1. Introduction

Early embryonic divisions occur in most cases without cellular growth, migration and apoptosis [1]. In addition, the rapid cell cycles and the not fully reactivated zygotic genome, are leaving very limited possibilities for signaling and genetic feedbacks [2–4]. Therefore, prior to gastrulation onset, the initial multicellular organization of the embryo is almost entirely defined by its cleavage geometry. This explains why the description of division positioning has been an early endeavor of embryology [5,6]. Division patterns come with a remarkable diversity, from orthogonal, rotational, to spiral patterns. They are stereotyped and typically invariant in large groups of species, and have been proposed to feature specific traits that could provide fitness to animal development with respect to their environment [5]. This argues in principle for the existence of deterministic genetic programs patterning early embryonic development. However, multiple lines of evidences suggest that these divisions are not firmly hard-coded. First, cleavage sequences can completely reorganize in response to physical manipulations like *e.g.* egg centrifugation, bisection or shape modulations [7–11]. Second, maternal-effect genetic screens for cleavage defects have failed to identify general "organizers", and rather support that early embryo development relies on the proper functioning of division regulators, like centrosomes and microtubule asters, or blastomere adhesion and shape [12,13]. And, third, many features of cleavages, including cell cycle progression, cell size regulation and division geometries may spontaneously emerge from egg cytoplasm extracts lacking gene expression or even DNA [14].

These choreographies of organized reductive divisions are not only aesthetic, but have crucial functions for development [15]. They impact the size, morphology, and arrangements of all early blastomeres. For instance, whether a cell is positioned at the embryo surface or more internally as well as the length and numbers of its contacts with neighboring cells are critically dependent on the orientation of cell divisions. Division orientation also often prescribe daughter cell polarity by determining if a cell inherits a cortical polar domains (Fig. 1). Importantly, many of these features are commonly concomitant with near-immediate alterations in cellular properties and decisions, including nuclear/cytoplasm (N/C) ratios, cell cycle length, fate specification and zygotic genome activation (ZGA). For instance, during echinoderm development, vegetal micromeres which result from a

Abbreviations: MTs, Microtubules; ZGA, Zygotic Genome Activation; N/C, Nucleus/Cytoplasm; pER, perinuclear endoplasmic reticulum; ICM, Inner Cell Mass; : MBT, Mid Blastula Transition.

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marked asymmetric division at the 8-cell stage, significantly slow down cell cycle, and relocate β-catenin in their nucleus to become fated as future endoderm and mesoderm [16]. Similar events also mark the early development of many vertebrates and mammals [17]. Whether these commitments may be driven by cell size, division asymmetry, cell position, the length of a cell-cell contact, the inheritance of a maternal polar domain, or a fine-tuned combination of all, is an outstanding problem in development. Dissecting causal links requires means to control division positioning in intact embryos.

These considerations raise two fundamental questions that are crucial to the understanding of early embryo development: How are division geometries specified by different cues in the egg, and how do they instruct important cellular decisions, such as e.g. fating or ZGA? These fascinating questions have been tackled in different species in the last decades and even if conserved principles have been proposed, a significant part of the mechanisms remain to be elucidated. Using examples from various models, we here review mechanisms of division plane specification, methods to study, alter or control them, and discuss how specific embryonic features may directly result from the position and the orientation of cell divisions.

2. Division plane specification in early embryos

2.1. Cleavage geometries at the intersection between self-organization and determinism

Division plane positioning is a fundamental process for animal cell behavior and tissue architecture. For division plane specification, the nucleus and/or mitotic spindles are first positioned and oriented from forces and torques from microtubules (MTs), and cytokinesis then bisects the spindle axis in anaphase [18,19]. MTs are organized in star-shaped structures, called asters that radiate from centrosomes attached to nuclei and spindles. Polymerizing astral MTs can push against the cortex [20], be pulled by motors such as dyneins that interact with cortical or cytoplasmic elements [21,22], or generate forces when depolymerizing [23]. How astral MT forces are regulated in space and time by different cues in zygotes and blastomeres to position and orient centrosome pairs is thus key to understand cleavage patterns.

Cell shape is one fundamental cue for aster and division positioning. As described more than 150 years ago in Hertwig's rules, many zygotes and blastomeres divide in their middle and orthogonal to their long shape axis [7]. Shape sensing is now known to be regulated in large part by mechanisms that allow MTs to generate forces that scale to their length, though detailed mechanisms are still lacking and may vary between systems [24–29]. Integration of these forces at the scale of asters that grow to fill the cell volume, yield global forces and torques that center and orient centrosome pairs with respect to aster shape anisotropies [30,31]. In many embryos, aster shape is solely dictated by cell shape. In others, asters also grow against dense yolk layers or neighboring asters, that may block MT growth, generating effective excluded volumes and aster shape anisotropies, to orient, for instance, centrosome pairs and cell division parallel to yolk-cytoplasm interfaces [30,32,33]. These geometrical designs may work in iterative manners over early embryogenesis: Cell shape influences division position and division influences blastomere cell shapes and thus division orientation in the next cycle, and so on. Such iterations can account for classical features such as orthogonal patterns of successive division orientation seen in many invertebrate and vertebrate species [24,34,35], but is likely also relevant to more sophisticated cleavage like spirals [36,37]. Cell shape regulation by acto-myosin contractility, cell-cell adhesion or confining egg enveloping layers, thus emerge as central elements to the specification of division positioning and embryo morphogenesis [34,38–41].

Cortical polar domains at the surface of many zygotes or blastomeres are also important regulators of division positioning [42–44]. They can bias geometrical rules to generate asymmetric or oriented divisions. They may be inherited maternally, form *de novo* or maturate through embryo development [45]. Polar domains typically recruit or activate dynein or depolymerizing kinesins to a subcellular location at the cortex, yielding net forces that decenter or reorient asters and spindles [42–44, 46]. Polar domains may be aligned with the cell's long axis, or oriented

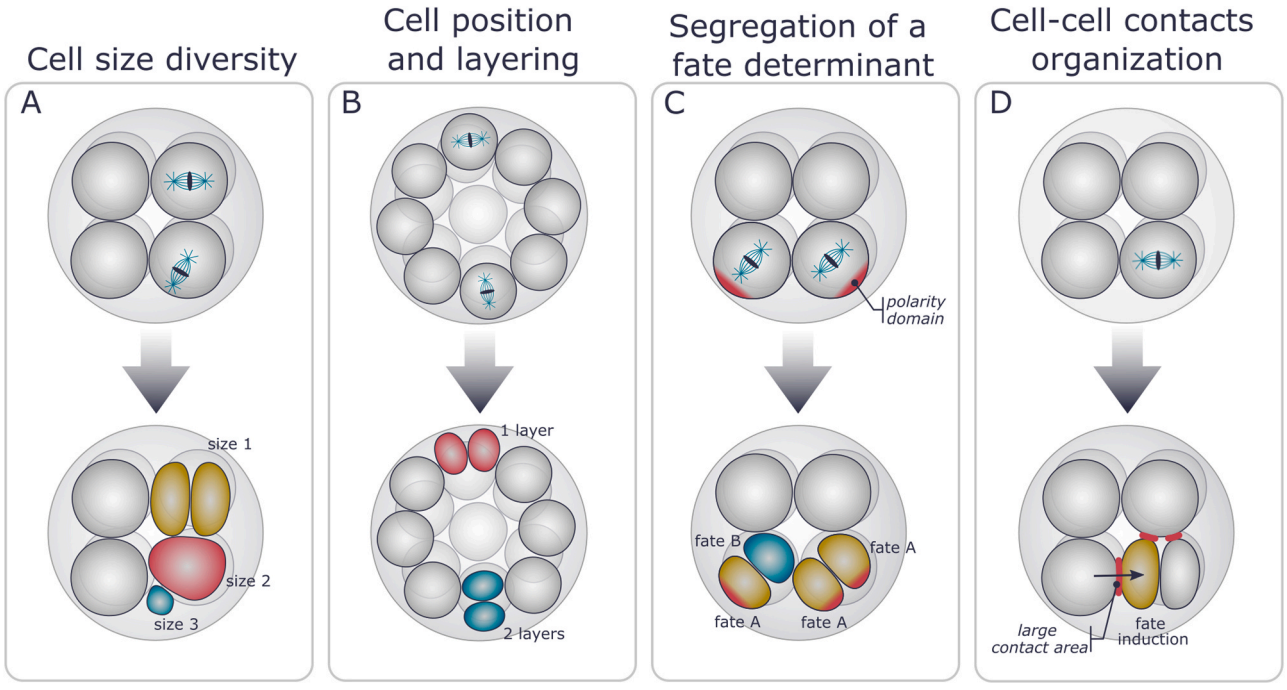

Fig. 1. Schematic view of the impact of division plane position and orientation in early embryos. (A) An asymmetric cell division produces two daughter cells with different sizes contributing to cell size diversity. (B) Orientation of cell divisions define important aspects of morphogenesis, including embryo layering and cell internalization. (C) Specific position of the division plane can either result in the equal segregation of a polarity domain or its exclusive segregation in one daughter cell influencing sibling cells fates. (D) Daughter cells position after division influences cell-cell contact area which can modulate fate induction.

in orthogonal manner generating competing cues that asters integrate to define division orientation in different cells [9,34,47–49]. This interplay between deterministic asymmetric cues such as polar domains or yolk layers, and self-organizing geometrical rules may thus be at the heart of the regulation of most cleavage geometries.

2.2. Imaging and tracking early embryo development

Understanding division specification and embryo morphogenesis requires proper methods to image, for instance, MT asters and associated motors, cell membranes or cortical polarity in live developing embryos. While this has become trivial for small cells in culture, the large size of eggs and early blastomeres and their inherent three-dimensional configurations pose challenges for quantitative imaging and reconstitution. Eggs of model invertebrate marine species like sea urchins, star fish, ascidians or mollusks range from 80 to 300 μm in diameters. Eggs of fish and frogs are in the millimeter range. Classical confocal microscopy is mostly restricted to few tens of microns above the coverslip, often limiting the *in toto* imaging of subcellular structures like MTs and their regulators, in these large cells. Light-sheet microscopy has emerged as a powerful solution, to detect cellular membranes, and thus compute with great precisions shapes and sizes [50–53], but is not fully adapted for detailed sub-cellular imaging at high magnification. Multiphoton microscopy is an important alternative, and has been used in seminal work to image the full cleavage process of extremely large early zebrafish embryos, providing unprecedented 3D information on cleavage geometries, blastomere lineage and mitotic spindles [32]. Recent efforts have also been dedicated to develop robust and reliable segmentation methods that can extract cellular features within a complex developing embryo [48,54–56]. Such "digital embryos" generated from experimental data have become a powerful tool to study division plane positioning, not only for the unambiguous 3D quantitative description of cell divisions, lineage trajectories, and embryogenesis, but also as a critical input to understand single-cell expression profiles and for modelling early development [57,58].

2.3. Models for cleavage geometries

Aster and spindle positioning is a fruitful area for interactive frameworks between experiments and mathematical models [24,33,47,59–62]. Two recent studies have provided modelling platforms to predict details of the cleavage patterns in 3D [34,36]. The first one is based on: (i) a mechanical model to predict centrosome/aster positioning and orientation based on the distribution of MT forces and (ii) a model of surface minimization that defines blastomere cell shapes and arrangements that unfold as a result of the division in the previous cycle. Starting from initial conditions such as the position of a polar domain or a confining egg envelope, these modelling layers iterate to predict rounds of divisions allowing to delineate generic regulatory layers of cleavage features in different embryos [34]. A second study uses a simulation platforms that describes blastomere cells as a network of surface nodes that can deform and rearrange as a result of cell division or adhesion for example. These simulations incorporate a set of rules such as division along the long axis, cell polarization or cell-cell adhesion, and demonstrate that altering the weight of each rule allows to predict the diversity of spiral cleavages [36]. Direct interaction between these models and experiments in live embryos should allow to discover or refine important hypotheses for how cleavage geometries are controlled.

2.4. Methods to control division plane position

The ability to modulate division positioning is essential to test mechanisms and functions of cell division geometries for embryo development. Given the near-universal impact of cell shape on division positioning, a powerful method to reorient division is to alter zygote and/or blastomere geometries. This can be achieved by physical or more biological/chemical means. Older physical methods include the use of glass plates, microneedles or ligatures [6,63,64], and more recent ones make use of microfabricated wells or actuated flattening devices [65–68]. For instance, a seminal study using the ligature of the Xenopus zygote to form an "hourglass" shaped zygote allowed to generate an asymmetric division at the four-cell stage that developed into two independent "twin" embryos with the same total volume but different cell numbers and cell sizes, providing key experimental tests for the role of cytoplasmic volume on ZGA [64]. Importantly, in response to the new cell topology, the position of the spindle will often be modified independently of cell or embryo polarity. This has allowed to disentangle the role of cortical polarity and cell shape anisotropies for division orientation and fate specification in different embryos [9,48] (Fig. 2A). Finally, cell shapes can also be modified by affecting cadherins based cell-cell adhesion or acto-myosin cortical contractility, in a global or even more local manner by localized injection in a sub-set of cells (Fig. 2B) [40,69].

A more direct means of manipulating cell division is to act directly on MT forces in asters and spindles. Spindles have been moved in large zygotes with microneedles impacting cell divisions, but with poor control and some invasive effects [70]. As such, more recent developments have exploited the relocation of dynein forces to indirectly pull on MTs and control asters/spindle positions. Using injected magnetic beads which presumably capture dynein or dynein-associated regulators [71], we recently developed the use of magnetic polar domains that can be assembled at any location in eggs/blastomeres with magnetic tweezers [44]. These domains pull on MTs to decenter and/or tilt asters and spindles, allowing to control division orientation and position throughout early embryogenesis. Optogenetics is another emerging avenue to control cortical dynein activity in space and time [72,73]. Light-induced recruitment of NuMA a dynein regulator to specific locations at the cortex has for instance been used to generate defined spindle tilts [72], or to equalize the normally asymmetric division of *C. elegans* zygotes and address consequences on early development [74] (Fig. 2C). Overall these methods for altering cell divisions, which are becoming more acute and less invasive, are starting to repopulate the field bringing key insights into the specific role of division positioning for early embryo development.

3. General impact of division geometry on embryonic features

3.1. Cortical domain partitioning

Asymmetric division is a common strategy to promote cell diversity during both development and homeostasis [74–77]. This process requires polar domains that are then segregated according to the orientation of the division plane. The inheritance of these domains in one of the two daughter cells is often responsible for fate acquisition (Fig. 1) [78–80]. Exclusive partitioning of polar domains requires the alignment of the spindle with the cortical polarity axis, which in many cells is achieved by recruiting MT pulling motors to the domain [42–44,46]. However, in several instances, the presence of a polarity domain alone is not sufficient to influence division orientation and fate decision. For instance, in early mammalian embryo, an elongated shape overrides polarity to dictate the division axis while a spherical cell is more prone to divide along the polarity axis [81] (Fig. 2A). The balance between these two division modes plays a key role in fate patterning in trophectoderm cells and ICM (Inner Cell Mass) cells [81]. In addition, proper segregation of fate determinants is also not always sufficient to ensure correct fate decisions. A recent report shows how the long term fate outcome of the first oriented asymmetric division of the *C. elegans* embryo, with normal segregation of cortical domains, can be altered if the relative size of the two daughter cells is equalized [74]. Thus, while partitioning of polar fate determinants plays a central role to define early cellular identities, other outputs of division plane positioning like cell volume asymmetries or cell positions may contribute to modulate

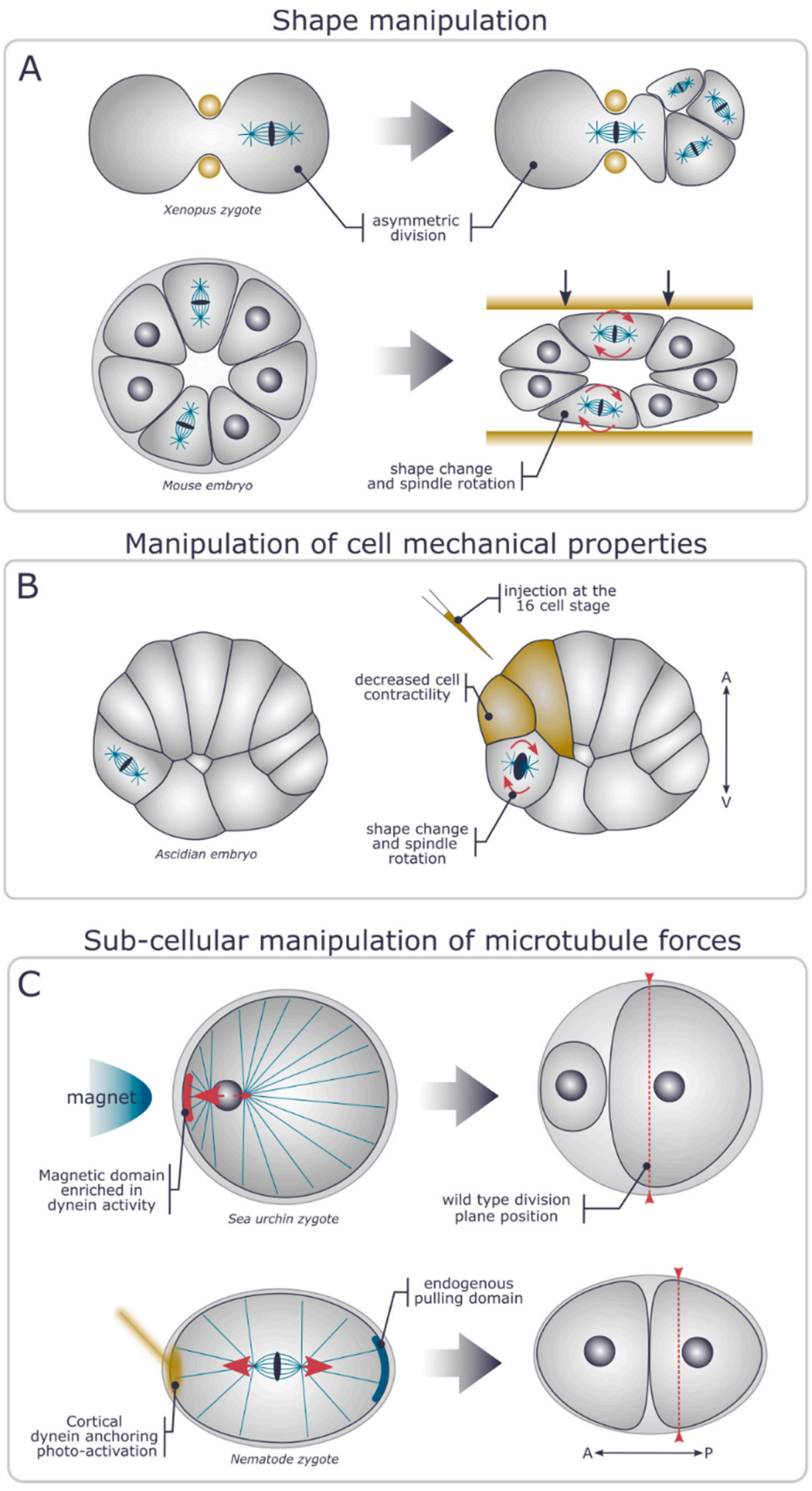

Fig. 2. Experimental approaches to alter or control division position in embryos. (A) Local shape changes in zygotes has been used in Xenopus to "trap" the spindle in a small cytoplasmic volume to manipulate cell size. Global embryo shape manipulations has been used in mouse embryo to reorient spindle along the long axis of the cell, potentially overriding other positioning cues (B) In Ascidian embryos, injection of a constitutively active form of myosin phosphatase in some blastomeres can reduce cell contractility changing the shape of neighboring blastomeres and their consequent spindle orientation. (C) Subcellular control of spindle position using magnetic tweezers and optogenetic tools allows a fine control of subcellular dynein/microtubule forces and consequent position and/or orientation of asters, spindles and division plane
(A) (adapted from [64,81]), (B) (adapted from [40]), (C) (adapted from [44,74,109]).

fate decision.

3.2. Cell-cell contact reorganization

Relative position of cells is another important output of cleavage geometries [74,82,83]. The location of the cell, as well as its size, will determine the number of neighbors and the contact area with surrounding cells (Fig. 1D). Cell contacts established during cleavages can form a signaling network crucial to determine fate diversity in a robust manner [57,83–85]. As an illustration of this, a modification of the division geometry at the four cell stage of the *C. elegans* embryo causes the ABp cells not to be exposed to Notch signaling from the P2 cell thereby failing to adopt the correct fate [74,86,87]. Similarly, in mouse embryo, Hippo signaling pathway is specifically activated in internalized cells by the adherent junction-associated Angiomotin proteins Amot and Amotl2 and participates to the specification of ICM cells [88]. In a recent study, potential cell-cell signaling in the whole ascidian embryo has been mapped in a systematic manner [57]. The authors combined the early embryo 3D geometry with an *in situ* hybridization database to generate the spatial expression map of ligands, receptors and antagonists for canonical signaling pathways including FGF, ephrin, Wnt, Bmp, Nodal and Notch [57,89]. With this model, they showed how the different active pathways are modulated by the contact area between signal sending and signal receiving cells and proposed this mechanism to be sufficient to explain all fate inductions in the early ascidian embryo [57]. Thus, cleavage geometry which directly instructs cell positions within the embryo may in turn define non-autonomous cell-cell signaling networks with major implication for lineage specification.

3.3. Cell size patterning

In an early embryo, the significant reduction of cell volume at each division supported by a fast cell cycle is a characteristic shared by most species [90,91]. Thus, the initial zygote volume together with the control of symmetric vs asymmetric divisions defines a global cell size patterns (Fig. 1A). Interestingly, while the alteration of the size of the one-cell zygote seems to shift the timing of certain developmental events such as the zygotic genome activation (ZGA), the overall embryogenesis remains unaffected [92–94]. In addition, the production of sibling cells with different sizes is almost systematically coupled with a different cell fate [95–97]. Rapidly reducing cellular volumes is also a challenge for basic cellular processes, such as mitosis or polarity [98]. How cellular functions may be maintained while the stoichiometry of structural components is modified as cells reduce in size, and what are the consequences of size modification on cell cycle and fate are critical questions, that have received a large attention recently.

In early embryos, organelles scale to the rapidly changing cellular dimensions through mechanisms that are currently not perfectly understood [90,99]. The impact of a modification of the cytoplasmic volume has been revealed in particular through alteration of the size of the egg/zygote using specific genetic background [100] or mechanical manipulations [92,101]. The mitotic spindle together with its chromosomes and centrosomes, are prominent examples of structures that scale to cell size [100,102–104]. Several evidences suggest that such scaling may be achieved through the progressive depletion of key diffusible regulators, of e.g. microtubule dynamics or centrosome growth [100,105–107]. Rapid scaling of these processes may ensure a constant spindle assembly timing and accurate chromosome segregation, thereby safeguarding the fidelity of cell division across cellular dimensions [100,108].

As observed by Conklin and Wilson in the early 1900's interphasic nuclei also scale with cell volume through embryo development [91,109,110]. However, in difference with spindles, this scaling is partial or non-linear (allometric scaling), with reductions of nuclear volumes being generally slower than reduction in cell volumes, causing progressive increase in nuclear to cytoplasmic (N/C) volume ratio, as embryos develop (Fig. 3A). Several diffusible factors involved in nuclear import like importin α, NTF2 and nucleoplasmin have been linked to nuclear scaling to cell size [111–113]. In addition, accumulation of endomembranes around the nucleus via microtubules and dynein have also been shown to promote nuclear growth and size control [114,115]. For instance, a recent study suggests that the size of the nucleus is correlated with the volume of peri-nuclear endoplasmic reticulum (pER) [109]. As cells divide, this pER pool is gradually partitioned between divided nuclei, independently of cell size, providing one potential mechanism for the different rates of nuclear size and cell size reductions in early embryos. Importantly, as nuclear and cell size are uncoupled, an asymmetric division can yield to a net immediate difference in N/C ratios, a process potentially crucial for patterning fate or cell cycle (Fig. 3) [109].

Indeed, several studies across different species have established correlations between N/C ratio increase and ZGA onset (Fig. 3) [64,101,116,117]. Titration of Histone proteins, progressively depleted by the formation of new nucleosomes after each division, has been proposed to define a threshold to trigger transcription. As the quantity of Histones per DNA molecule decreases, transcription factors in competition with Histones can access gene loci and promote ZGA [117,118]. Recently, the cell autonomous nature of ZGA onset has been highlighted in Xenopus embryo in which a gradient of cell size along the A/V axis is established by the early cleavage geometry. The authors showed that, in small cells located close to the animal pole, ZGA is triggered precociously as compared to the large vegetally-located cells. In addition, changing the initial size of the embryo shifts this timing, making a clear connection between cytoplasmic volume and ZGA onset [92]. Together with ZGA, significant lengthening of the cell cycle, taking place in the similar time window, is the second landmark that is classically used to define the Mid Blastula Transition (MBT) (Fig. 3). Cell cycle lengthening is associated with drastic changes in cell identity [64,116,119]. Cell cycle duration is thought to be highly dependent on cytoplasmic volume as key regulators are becoming limiting as cell size decreases [120–123]. This effect is particularly striking during embryonic asymmetric divisions in sea urchins and ascidians in which cell cycle is immediately slower in the smaller sibling cells [57,123]. Consistently, a recent study in *C.elegans* showed that an artificial increase of the size of a blastomere leads to a faster cell cycle and extra-numbers of division rounds in the lineage of the blastomere [74]. Several models have been proposed to account for these observations such as a titration of cyclins or a crosstalk between allometrically scaling subcellular compartments but detailed molecular mechanisms remain to date largely unknown [121,124].

4. Conclusion and future directions

Based on our appreciation of the literature, we conclude by proposing that early embryogenesis may be in large part controlled by regulating layers that self-organize from initial conditions in the egg. Embryos control their division geometries with centrosomes and asters that use local rules of MT force-generation that propagate at the cellular scale to sense geometries and pre-patterned guiding cues such as polar domains or yolk asymmetric layers. If such cues and local MT rules are tightly controlled between individual embryos, this could explain the large robustness and reproducibility of cleavage patterns. Yet, at the same time, a small modulation in these parameters may become amplified through iterative divisions allowing to diversify cleavage geometries. Divisions then give a geometrical pattern of cell sizes, positions and contacts, that local signaling networks or organelle scaling mechanisms exploit to define lineage, fate maps and trigger major transition such as ZGA and cell-cycle lengthening at a temporal as well as spatial level within the embryo.

We note that many important feedbacks also exist between cell behavior and cell divisions. For instance, cell-cycle asynchrony, may generate asymmetric mechanical cues that influences shapes, polarities and divisions [34,40,125]. Allometric or more linear scaling of nuclei,

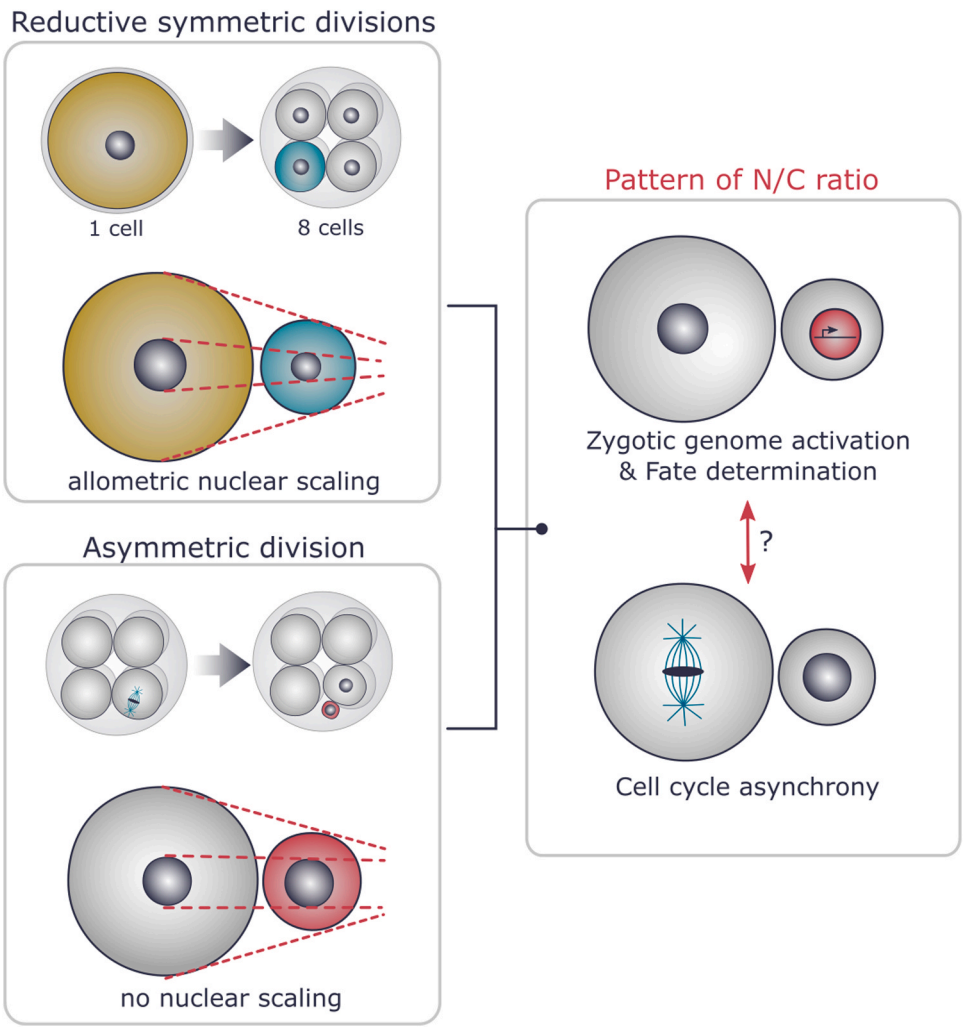

Fig. 3. Schematic view of general mechanisms controlling nuclear/cytoplasm (N/C) ratio and their implications for embryo development. Series of reductive symmetric divisions cause an allometric nuclear size scaling with cell sizes usually reducing faster than nuclei sizes. Because cell and nuclei size reduction are uncoupled, upon an asymmetric division both daughter cells will have a similar nuclear size, creating immediate spatial patterns of N/C ratio. This implies a direct relationship between the geometry of a division and the values of the N/C ratio between daughter cells. This may trigger critical embryogenesis events such as zygotic genome activation and cell cycle slow-down associated with the mid-blastula transition.

endomembranes or spindles to cell sizes, may also influence the length or forces of MTs, thereby impacting division phenotypes [25,44,108,128]. Lengthening of interphase duration may also extend the temporal window during which a cell can receive and respond to a signal. We envision that future breakthroughs will hinge on innovative experiments combining detailed *in vivo* imaging and precise control of cleavage geometry or cellular properties. In parallel, emerging methods allowing to correlate embryonic architecture with single-cell RNA sequencing, are setting new standards to study early development [58,129]. Their systematic use to study the development of uncommon organisms, not only model ones, will provide new insight on evolutionary rules governing cleavage pattern robustness and plasticity.

Declaration of Competing Interest

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

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