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REVIEW

How cells sense their own shape – mechanisms to probe cell geometry and their implications in cellular organization and function

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ABSTRACT

Cells come in a variety of shapes that most often underlie their functions. Regulation of cell morphogenesis implies that there are mechanisms for shape sensing that still remain poorly appreciated. Global and local cell geometry features, such as aspect ratio, size or membrane curvature, may be probed by intracellular modules, such as the cytoskeleton, reaction–diffusion systems or molecular complexes. In multicellular tissues, cell shape emerges as an important means to transduce tissue-inherent chemical and mechanical cues into intracellular organization. One emergent paradigm is that cell-shape sensing is most often based upon mechanisms of self-organization, rather than determinism. Here, we review relevant work that has elucidated some of the core principles of how cellular geometry may be conveyed into spatial information to guide processes, such as polarity, signaling, morphogenesis and division-plane positioning.

KEY WORDS: Cell shape, Cytoskeleton, Cell polarity, Cell division

Introduction

Any biologist would acknowledge that cells are beautiful objects. The range of forms they span is not only aesthetic, but reveals the complexity and diversity of intracellular systems that serve to construct cell shape and, in most instances, reflects the function of the cell. Long polarized nerve cells make distant connections in brains and muscles, the small and flat shape of red blood cells may enhance flowing capacities needed to navigate in thin blood vessels, cuboidal epithelial cells serve as brick units for the walls of our organs, and cork-screw like bacteria can bore their way through the surface of epithelia. Besides the cell-type-specific relevance of cell shape, an emergent concept is that both the regulation and the functional use of cell shape necessarily implicate geometry-sensing mechanisms. A cell that grows into a rod-shape must come with designs that informs on the straightness of its long axis, or with signaling systems that detect any unwanted curvature. A symmetrically dividing cell needs to precisely locate its geometrical center and orient the division plane accounting for its global surface morphology.

According to their specific shapes, sizes and functions cells may, thus, be equipped with internal systems to monitor global, local or dynamic geometrical features (Fig. 1). Those could confer robustness to cell shape or act as means to amplify a small surface deformation when shape changes are needed. Mechanisms that sense the straightness or curvature of the cell surface may be important to stabilize elongated cell shapes or to detect local 3D membrane geometries, such as protrusions or cilia (Cannon et al., 2017). Monitoring of the surface-to-volume ratio is thought to be important for timing cell division or as means to locally titrate molecular reactions around cells (Harris and Theriot, 2016; Schmick and Bastiaens, 2014). Furthermore, the global aspect ratio of the cell has key relevance for the positioning and orientation of the division plane, and in the definition of internal polarity axes (Minc et al., 2009, 2011) (Fig. 1).

Biologists have long recognized the relevance of feedback mechanisms that allow cells to probe their shapes and dimensions as a basal property of all cells, even the roundest one (Gerhart, 1989; Hertwig, 1884; Moseley and Nurse, 2010; Wilson, 1925). Recent work has begun to decipher the generic designs and molecular mechanisms implicated. Dissecting specific mechanisms of geometry sensing *in vivo* may prove difficult, given the contributions from both chemical and mechanical cues that also affect cell shapes in tissues. *In vivo*, for instance, processes – such as polarity or division orientation – have most often been linked to external signals, rather than as direct consequences of cell shape (Minc and Piel, 2012). However, it is becoming increasingly evident that cellular components, such as the cytoskeleton and reaction–diffusion systems have self-organizing properties that can probe cellular boundary conditions (Karsenti, 2008). In addition, the advent of microfabrication methods in order to control and manipulate shapes independently of external cues in cells – ranging from microbes to mammalian cells (Lautenschläger and Piel, 2013) – has served as a driving force to unequivocally demonstrate the profound impact that shape has on the spatial organization and function of most cells.

We will here focus on key questions underlying the mechanisms of shape-sensing, and on the functional interplays between shape and internal organization: How do molecules and/or molecular assemblies probe cellular shapes? How do they use such information to control cell behavior and morphogenesis? Is cell-shape sensing a conserved trait in evolution that is needed for fitness? We will introduce the different geometrical parameters that may be sensed in different cells, and discuss mechanisms that link shape-sensing to the spatial control of processes, such as polarity, signaling and division positioning. Although cell size is another important geometrical feature, we will not cover it here and refer the readers to recent reviews on this topic (Amodeo and Skotheim, 2016; Levy and Heald, 2015).

Cell-shape sensing and polarity

Microtubules as cell-shape sensors for cell polarity

Cell polarity underlies the ability of cells to define subcellular domains of activity at their surface, generally referred to as polarity

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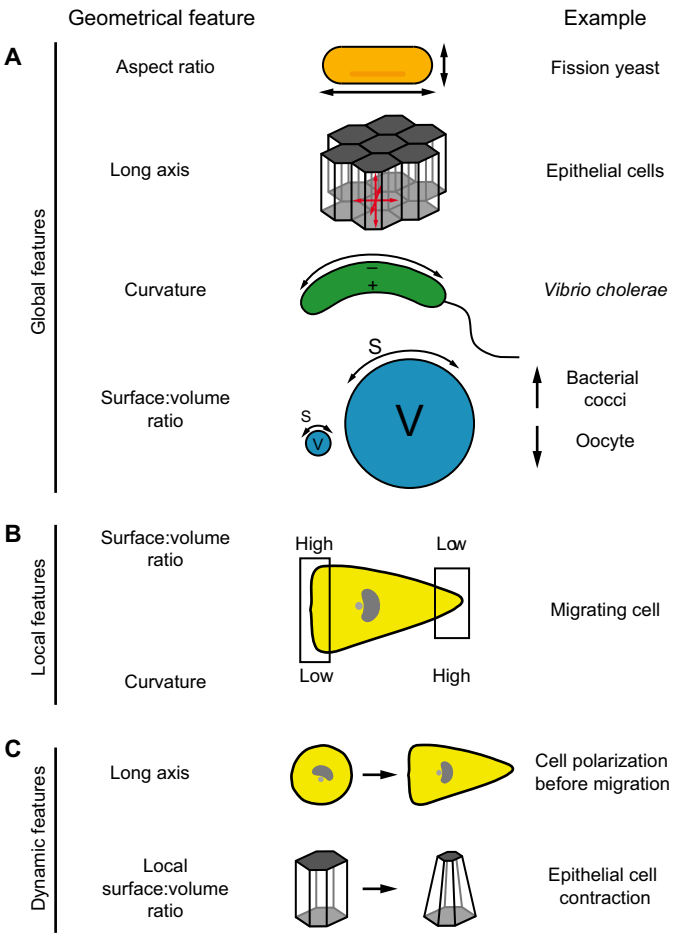

Fig. 1. Examples of cell-shape features that can be used by cells to control behavior and organization. (A) Global, cell-level features, such as aspect ratio, long axis, curvature and surface-to-volume ratio, may be monitored by a cell to ensure proper polarization, signaling or timing, and positioning of cell division. Examples include microorganisms, epithelial cells and oocytes. (B) Differences in local, subcellular geometrical features, such as curvature or surface-to-volume ratio, could be important to sustain cellular states, for instance during cell migration. (C) Geometric features can dynamically change over time. During polarized cell migration, an initially isotropic cell has to develop a long axis. Another example is in the course of epithelial cell contraction, where the apical surface-to-volume ratio of a cell changes.

domains. This allows cells to grow or migrate directionally, specify a front and a rear or position internal organelles, such as the nucleus, the centrosome or the Golgi relative to each other (Etienne-Manneville, 2004). Polarity domains can spontaneously assemble as a result of positive feedbacks between interacting proteins and cytoskeleton elements that amplify local fluctuations into mature polarity domains (Irazoqui et al., 2003; Wedlich-Soldner et al., 2003). Extrinsic or intrinsic chemical, mechanical or electrical cues can then orient or stabilize those domains along specific directions (Casamayor and Snyder, 2002; Etienne-Manneville, 2004; Haupt et al., 2014; Ladoux et al., 2016).

As polarity ultimately directs processes, such as cell growth or migration, it serves as a key input to define cell shape over time. This has been extensively studied in fission yeast. These cells grow into a rod by targeting polarity and growth factors, such as the Rho-GTPase Cdc42, actin and cell-wall-remodeling enzymes, to cell tips (see Chang and Martin, 2009 for a detailed review). Key to the tip localization of polarity zones are dynamic microtubule (MT) bundles, which emanate from the nucleus and grow near-parallel to the long cell axis in order to deposit MT-plus-end-associated landmark proteins at cell tips, which then recruit downstream elements. Mutants with defective MT organization have abnormally bent or branched shapes, and the MT organization of many mis-shaped mutants is defective, which has long suggested the existence of interplays between shape, MT organization and polarity (Verde et al., 1995).

Studies in which the shape of fission yeast cells was manipulated by physically bending them in microfabricated devices have been instrumental in deciphering feedbacks between shape and polarity (Minc et al., 2009; Terenna et al., 2008). In response to cell bending, MT organization dramatically changes – with most MTs not reaching the cell extremities anymore but, instead, touching cell sides, yielding the formation of ectopic polarization sites (Fig. 2A). In a reciprocal manner, round mutants with defective MT organization that were forced into a straight shape, recovered to almost wild-type MT orientation and polarization at cell tips (Terenna et al., 2008). Thus, through their dynamic properties and straightness, MTs serve as robust shape-sensors to promote polarization along a linear geometrical axis. This feedback between shape, MT orientation and polarity, may confer robustness to polarized growth and ensure the maintenance of rod-shape morphogenesis through generations of dividing cells (Drake and Vavylonis, 2013). Yet, polarizing spores or spheroplasts can readily elongate an – initially straight – rod-shaped cell, even in the absence of MTs and landmarks, which suggests the existence of other systems that promote directed growth (Bonazzi et al., 2014; Kelly and Nurse, 2011).

Work on epithelial cells in fly embryonic tissues has suggested a similar influence of cell shape on MT organization (Fig. 2B) (Gomez et al., 2016), with plausible implications on the definition of the planar polarity axis (Butler and Wallingford, 2017). Alignment of MTs along the long axis has also been documented in adherent cells, and was proposed to serve as a mechanism to limit the length of spreading cells (Levina et al., 2001; Picone et al., 2010). This effect may also contribute to guide the polarization of the nuclear–centrosome axis, to enhance persistent directional migration of cells which migrate along their long axis, although patterns of adhesion could serve as dominant spatial cues when cell geometry is mostly isotropic (Fig. 2B,C) (Jiang et al., 2005; McWhorter et al., 2013; Théry et al., 2006; Vignaud et al., 2012). Thus MT-based geometry-sensing might have a broad relevance to polarity establishment and maintenance of eukaryotic cells in general.

Sensing of subcellular micron-scale curvature

The rod-shape morphogenesis is also a common feature of many bacteria, including *E. coli* (Chang and Huang, 2014). In those cells, insertion of cell-wall material occurs along the sides of the cylinder and not at cell poles, a process that is mediated by the actin homolog MreB (Furchtgott et al., 2011). A recent study found that MreB polymers tend to preferentially bind to regions of positive curvatures along the cylinder (Ursell et al., 2014). This observation supports a model, in which curvature detection, and consequent local promotion of cell-wall insertion and growth by MreB, allows cells to actively straighten their shape (Fig. 2D). However, a recent paper indicates that this feedback is not be sufficient to account for cell straightening upon greater deformation (Wong et al., 2017). Thus, bacterial cells, which lack long-range cytoskeletal systems, might ensure rod-shape maintenance through local curvature sensing that is likely to be encoded in the structural properties of MreB polymers (Colavin et al., 2014).

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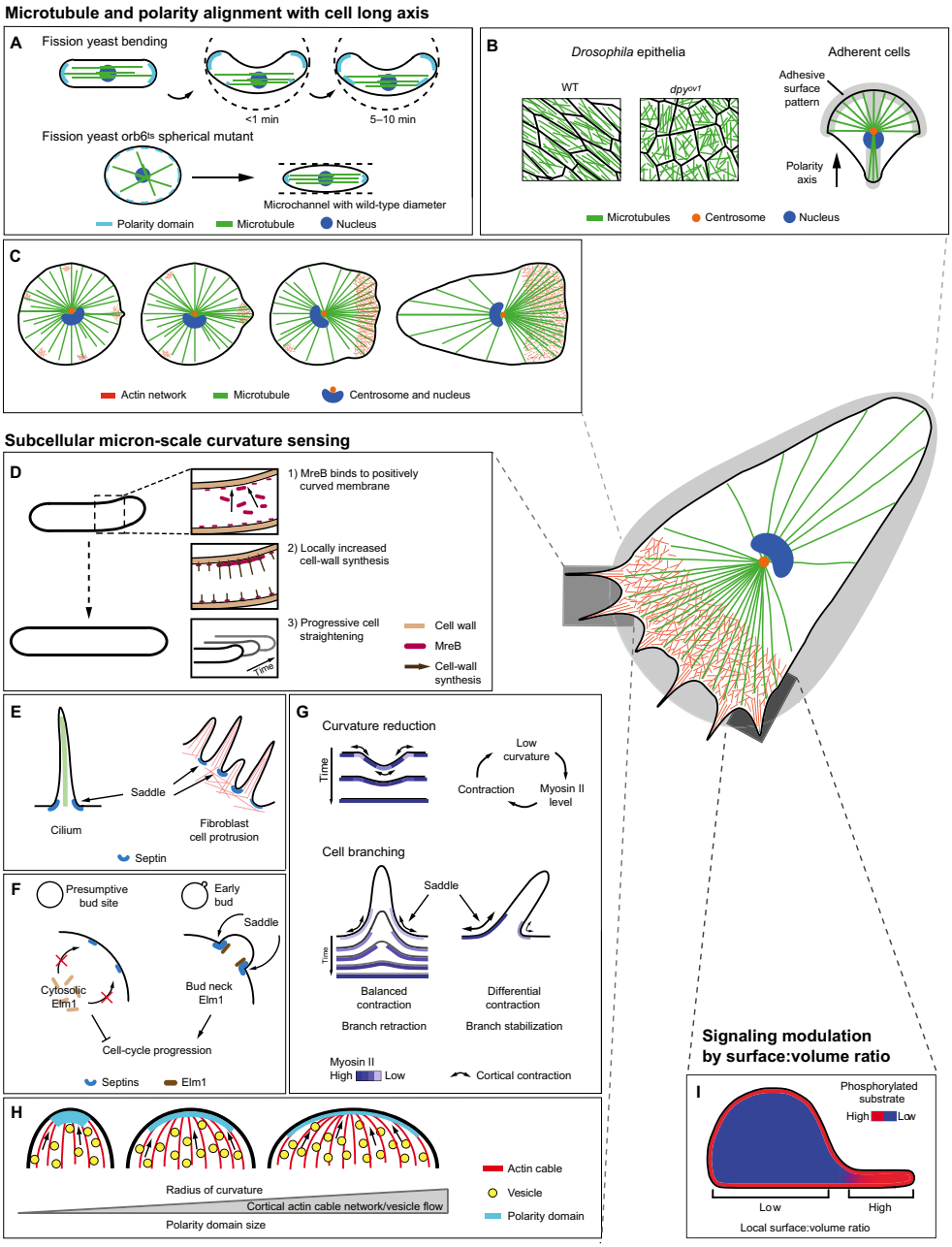

Fig. 2. Mechanisms of cell-shape sensing that are relevant for cell polarity, migration and signaling. (A) Fission yeast shape-sensing through MTs directly inputs on the positioning of polarity domains. Wild-type fission yeast bending (top); round mutant forced into straight shape (bottom). (B) Cell shape, MT alignment and polarization in animal cells. Left: Subapical MT alignment according to cell shape in *Drosophila* epithelia. Right: In adherent cells, MTs organize along the long cell-shape axis, defining the main polarity axis. The right panel has been modified from Thery et al., 2006 (copyright 2006 National Academy of Sciences). (C) MTs dynamically align along the long axis that is established after symmetry breaking during initiation of cell migration. (D) Shape-sensing and shape maintenance in bacteria. *E. coli* cells detect shape defects through the preferential binding of MreB to positively curved membranes; subsequent localized cell growth enables the cell to straighten again. (E) Curvature sensing by septins through preferential binding to 'saddle-like' membrane geometries, as found at the base of cilia or cell protrusions. (F) Geometry-dependent septin organization through curvature sensing may allow yeast cells to monitor bud emergence. (G) Binding of myosin II to curved areas of endothelial cells is stabilized by a positive feedback loop, resulting in an overall reduction of curvature and in selective branch stabilization. (H) In fission yeast spores, the size of actin networks and concomitant vesicle flow increases with the radius of the curvature, thereby ensuring adaptation of polarity domain size to local curvature. Modified from Bonazzi et al., 2015 (with permission from Elsevier). (I) Variations in surface-to-volume ratio can influence the kinetics of reactions between membrane-bound and cytoplasmic factors, thereby creating biochemically distinct states, e.g. with regard to the phosphorylation status of a factor, within a cell.

Eukaryotic cells might also possess micron-scale curvature sensing systems. Septins are conserved oligomeric protein complexes that can assemble into non-polar filaments and bind to the cell cortex. They are important for many processes, including those controlling cell shape, protein scaffolding and disease (Bridges and Gladfelter, 2015; Cannon et al., 2017). Septins in yeast and mammalian cells have recently been demonstrated to have an intrinsic affinity to bind surfaces with a defined positive curvature at the micron scale. Even though individual oligomers exhibit selective curvature binding, they require polymerisation to bind curved membranes within cells (Bridges et al., 2016). In cells, positive curvature at micron scale can be found on edges between spheres and protrusions (a topology often referred to as 'saddle'; see Box 1), such as at the base of dendritic spines, axons and cilia, in the yeast bud neck or in branches of fungal hyphae – all structures where septins have been found to localize (Fig. 2E) (Bridges and Gladfelter, 2015). The function of septins at some of these sites has been linked to that of a diffusion barrier or scaffold (Hu et al., 2010; Merlini and Piatti, 2011). Thus, the inherent anisotropic curvature of saddle structures might promote the formation of specific higher-order septin organization, which is important for their biological functions.

This curvature-dependent septin recruitment might be used as a cellular readout. In budding yeast, the formation of a bud is monitored through the morphogenesis checkpoint that delays mitosis onset until bud emergence (Kang and Lew, 2017). The presumptive bud site is labelled by a septin ring that might rearrange into higher-order structures that are aligned along the saddle that is formed upon bud emergence. This alignment might trigger the recruitment of Elm1, a kinase that influences mitotic entry (Fig. 2F) (Kang et al., 2016). Therefore, septin-mediated curvature sensing could also serve cells to monitor shape changes and time them with cell cycle progression.

Another prime example of local curvature sensing was recently proposed in the context of tip-branching regulation during endothelial cell migration. Branching and general curvature formation in these cells was shown to be limited by actomyosin cortex contraction (Elliott et al., 2015; Fischer et al., 2009). Myosin II was found to, preferentially, bind to flat (or less curved) membrane regions with a binding efficiency that negatively correlates with the absolute curvature. This generates a positive feedback loop, in which myosin II may promote its own binding by actively reducing the curvature of bent membrane regions. In the context of branching morphogenesis, this feedback allows myosin II to stabilize branches that form at small angles to pre-existing protrusions, while suppressing those that arise perpendicular to existing protrusions, thus polarizing branching along the direction of migration (Fig. 2G). Curvature sensing of myosin there was, again, proposed to be encoded in the elongated morphology of filaments, which could favor their binding to actin on flat membranes (Elliott et al., 2015). Curvature dependence of actomyosin forces has also been proposed to be important in the context of cytokinesis to promote faithful centripetal ring closure (Dorn et al., 2016; Zhou et al., 2015).

Evidence that cells developed ways to probe their local curvature on a micron scale through means other than direct polymer recognition of curved surfaces, has recently been obtained in fission yeast. In that system, the width of functional polarity domains scales with the local radius of curvature in rounded spores and rod-shaped cells (Bonazzi et al., 2015). This scaling was shown to rely on actin-dependent vesicle transport and fusion that may dilute and spread polarity domains in a manner dependent on the local curvature. According to this model, local geometry constrains limit the volume that cortical actin cable networks can probe, yielding different cargo flux to dilute the cap (Fig. 2H). As the size of polarity domains that are built around conserved small GTPases, such as Cdc42, usually adjusts to cell sizes varying from small yeast cells to large egg cells (Bonazzi et al., 2015; Jost and Weiner, 2015), it will be interesting to test whether this curvature-sensing mechanism is based on similar actin-dependent transport processes in other cell types. Thus, the ability of actin or actin-homologues and their interactors to probe local micron-scale curvatures could serve as an important conserved shape-sensing design in morphogenesis.

Box 1. Geometrical terms

Curvature: Defines how much a surface deviates from being flat. Throughout this review, we look at curvature from within the cell interior. For a spherical cell this means that its inner surface has a negative curvature. A tube-shaped protrusion of this sphere also has a negative curvature along its transverse section but, furthermore, generates a region of positive curvature at its base in the direction pointing away from the sphere into the protrusion. The topology at the base is called a 'saddle', where the curvature along two orthogonal axes is opposite.

Aspect ratio: Defines the proportional relation of width and height of a two-dimensional object. It can be applied to cells when depth is similar to width or when width has an approximately rotational symmetry along the height axis.

Surface-to-volume ratio: Defines the amount of surface area per unit volume of an object. For an object with a given geometry, as it gets bigger, volume increases faster than the surface area. A spherical cell has the lowest surface-to-volume ratio, compared to for example, flat or tube-like shapes.

Local surface-to-volume ratio as a cue for polarization and signaling

One interesting implication of the existence of flat, curved or narrow regions inside cells is that they may affect the local surface-to-volume ratio. The global surface-to-volume ratio, set by cell size, has been well-documented to influence division timing or the scaling of internal organelles to cell size, but local effects are still poorly appreciated (Harris and Theriot, 2016; Wilbur and Heald, 2013). The impact of the local surface-to-volume ratio on local cell biochemistry was first explored theoretically by using a membrane-bound kinase that could phosphorylate a cytoplasmic substrate (Meyers et al., 2006). Competition between kinase reaction rate and substrate diffusion results in a gradient of phosphorylation from the membrane to the cell center. A cell with a protruding flat front would, in that context, be able to set a different cytoplasmic biochemical activity, simply as a result of the increased local surface-to-volume ratio. This could, in principle, serve as a 'ruler' to measure cell shape and size (Fig. 2I) and might even recognize small membrane deformations. Yet, one important limitation of this model is that the lateral diffusion of the kinase within the membrane rapidly disperses this gradient. As a consequence, this effect can only serve as a transient shape sensor, unless the kinase is continuously maintained in a polarized subcellular localization through reinforcements by cytoskeletal elements or other external cues (Schmick and Bastiaens, 2014). A recent study explored this mechanism in a systematic manner for reactions that occur within the membrane, by using an enzyme that diffuses in the cytoplasm or the extracellular space, and proposed that a transient localized increase in reaction products can be achieved theoretically and experimentally, purely as a result of cell deformation – which even influenced signaling globally (Rangamani et al., 2013). Pioneering studies, in which micropatterned islands were used, have long demonstrated that cell geometry can influence important processes, such as differentiation, growth and death (Chen et al., 1997; Kilian et al., 2010; McWhorter et al., 2013). However, in this context, geometry was thought to indirectly affect the mechanical state of cells, which then influenced its fate (Chen et al., 1997). Thus, while the above-mentioned concept that cell shape directly modulates signaling reactions awaits further generalization, it supports the provocative view that, at least in certain cell types, geometry per se serves as a hub to mediate key cellular decisions during tissue development and homeostasis (Rangamani et al., 2013; Ron et al., 2017; Schmick and Bastiaens, 2014).

Cell shape and division plane positioning

Cell shape and division in evolution

Cell shape also has an important influence on the positioning and orientation of the cell division plane, processes with profound implications for cell size control, stem cells and tissue morphogenesis (Minc and Piel, 2012). While some cells exhibit marked asymmetric divisions, most tend to divide in a symmetric manner through bisection of the mother cell into two halves of almost the same volume. Symmetric division is inherently linked to cell geometry, as cells need to locate their geometrical center. In addition, apart from rare exceptions (Leisch et al., 2012), most elongated prokaryotic and eukaryotic cells tend to bisect their longest axis during symmetric division. This conserved behavior is fascinating in terms of evolution because mechanisms that position cytokinesis or septation vary largely (Oliferenko et al., 2009). In animal cells, the position at which cytokinesis occurs depends upon spatial cues that are provided by the mitotic spindle towards anaphase. In most fungi, cytokinesis and septum ingression are pre-specified from the position of the nucleus, and the spindle usually

aligns orthogonal to the septum. In plants, the pre-prophase band also forms around the nucleus and serves as a landmark for spindle orientation and cell plate growth. In bacteria and other prokaryotes, septum positional information arises from protein gradients that are mostly independent of DNA or any cytoskeletal structure (reviewed in Oliferenko et al., 2009).

These considerations raise the question of what kind of evolutionary pressure could have driven cells of various sizes and shapes, and within different environments, to divide along their long axes. One possibility is that this geometrical design provides the largest cytoplasmic space for DNA segregation (Cadart et al., 2014; Lancaster et al., 2013). Another proposed idea is that this design promotes the stability of ring positions during ingression, at least in some cell types (Mishra et al., 2012). We also foresee that such a setting minimizes the impact of an error in detecting the geometrical center on the repartition of cell volumes between daughter cells. Finally, cell division along the long axis could just reflect inherent geometry-sensing properties of division-positioning machineries that, naturally, tend to self-organize along the longest axis (Karsenti, 2008). Recent evolutionary developmental biology (evo-devo) studies suggest that variations in asymmetric division plane position depend on the cell size, thereby ensuring a stable volume ratio between daughter cells (Farhadifar et al., 2015). Further evo-devo approaches investigating variations in position and orientation of symmetric division as a function of cell shape in closely related species should help to address those important questions.

Microtubule forces as geometrical rulers to target the cell center

Historically, the relevance of cell shape for division positioning was first appreciated in large dividing eggs and blastomeres, such as those of frog or marine invertebrates, leading to the formulations of early empirical ‘geometrical’ rules for cell divisions (Hertwig, 1884, 1893, and reviewed in Minc and Piel, 2012). Indeed, most invertebrate and vertebrate zygotes cleave exactly in the cell center. This is challenging, because eggs can be very large (≤1 mm in amphibian species) and because fertilization, which brings centrosomes attached to the sperm pro-nucleus into the egg, is dramatically asymmetric. The question, thus, arises of how the nucleus and centrosome move to the exact geometric center of those large cells (Wühr et al., 2009)? Apart from rare exceptions (see below), nuclear centration in animal cells is mediated by MT-mediated forces, with actin being mostly dispensable. MTs nucleate around the centrosome and grow to form an aster, which then exerts forces to move the nucleus and centrosome to the cell center (Reinsch and Gonczy, 1998; Wühr et al., 2009).

While much debate is still ongoing on the exact nature and regulation of MT-mediated forces, one common well-accepted aspect of shape sensing and aster centration is that MT-exerted forces depend on the length of astral MTs. The combination of aster-like geometry with the dynamic growth and shrinkage properties of MTs, and their length-dependent forces provides a simple, yet extremely robust, design for the cell to probe the cellular volume and center the centrosome (Fig. 3A) (Bornens, 2012; Holy et al., 1997; Kimura and Onami, 2005; Tanimoto et al., 2016; Wühr et al., 2010). Length-scaling may arise from compressive pushing forces owing to MT-plus-end polymerization against the cell surface. Because of dynamic instabilities, more MTs will push on the centrosome as it is being brought closer to the cortex. Additionally, pushing may be limited by buckling in a length-dependent manner, so that longer MTs will buckle more than shorter ones and will, thus, exert comparatively more pushing forces on the centrosome (Fig. 3A) (Howard, 2006; Howard and Garzon-Coral, 2017). Indeed, such a mechanism has been demonstrated to promote nuclear centering in small yeast cells (Daga et al., 2006; Tolić-Nørrelykke et al., 2005; Tran et al., 2001) and was proposed to contribute to spindle centration in *Caenorhabditis elegans* (Garzon-Coral et al., 2016; Howard and Garzon-Coral, 2017). *In vitro* work and simulations suggest, however, that pushing yields unstable situations that tend to decenter asters when, for instance, MTs are allowed to pivot around centrosomes (Letort et al., 2016; Pinot et al., 2009). Whether those situations are relevant to cells remains to be tested.

In larger cells, such as eggs and early blastomeres of marine invertebrates, amphibians and fish, mounting evidence suggests that MT pushing is not very efficient in promoting aster centration (Hamaguchi and Hiramoto, 1986; Tanimoto et al., 2016; Wühr et al., 2010). Length-scaling in these cells is thought to be driven from dynein motors that directly pull on MTs from sites in the cytoplasm (Barbosa et al., 2017; Hamaguchi et al., 1986; Kimura and Kimura, 2011; Longoria and Shubeita, 2013). The mechanical coupling of dyneins to the cytoplasm is thought to be mediated by the friction of cargos or endo-membranes that are moved by dyneins to the aster center. Accumulation of dynein–cargo complexes onto MTs in a length-dependent manner naturally results in MT-pulling forces that scale to the length of MTs; but even when those complexes are diluted in the aster, the pulling forces are still predicted to scale to the length of MTs – although in a non-linear manner (Fig. 3A). It is still unclear, though, whether there are types of endo-membrane or cargo that are more suitable for MT forces in bulk cytoplasm, and how these cytoplasmic anchors may be recycled back to the surface to be able to continuously sustain this effect.

MT-based centering systems have remarkable abilities in tracking the geometrical confines of a cell. For instance, sperm asters, which nucleate on the side of the egg at fertilization, can precisely target the center of large eggs in tens of minutes without any prior positional information. This is because they can continuously monitor the local cell geometry through MT growth, length-limitation by the cortex and length-dependent forces. This has clearly been demonstrated by manipulating the egg shape and the sites of sperm entry, which led to aster-centering paths with sharp turning points that reflected the local cell geometry explored by the aster during centration (Fig. 3B) (Tanimoto et al., 2016; Tanimoto and Minc, 2017). Another property of length-dependent MT forces is that they act as elastic springs with respect to the geometry of the cell. In recent work, magnetic beads attached to centrosomes in *C. elegans* metaphase spindles allowed to apply external calibrated forces to asters (Garzon-Coral et al., 2016). Centrosomes moved away from the cell center to stop at a position that depended on the applied force and rapidly repositioned to the center after force cessation, much like a spring (Fig. 3C). The stiffness value of this spring is of key biological significance. A low stiffness value would permit aster fluctuations, rotations or displacement owing to other cellular cues (e.g. an asymmetric cortical domain), whereas a high stiffness value would tend to ‘freeze’ the aster at the cell center (Howard and Garzon-Coral, 2017). How stiffness and overall mechanical properties of centering machineries vary with shape, size and among different cell types, and how they relate to aster dynamics and division phenotypes is an exciting future research direction.

Finally, it is worth noting that some cells may promote nuclear or centrosome centration relative to cell shape by using systems that do not solely rely on MT forces. Actomyosin contraction might produce forces that directly influence MT dynamics, aster motion

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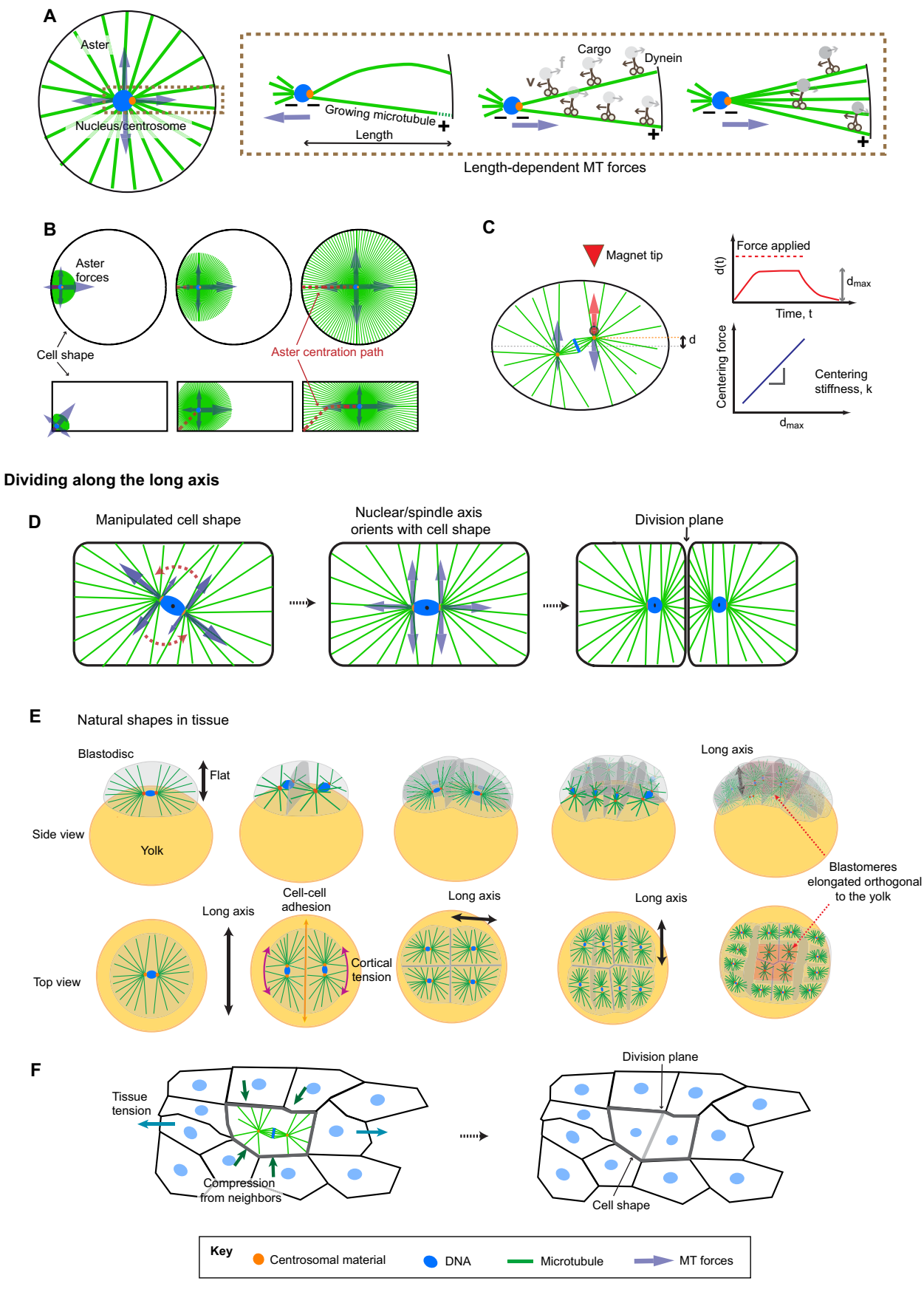

Fig. 3. See next page for legend.

Fig. 3. Cell-shape sensing for division positioning. (A) Astral microtubules (MTs) exert length-dependent forces to center nuclei and centrosomes. Length dependency may arise when MTs polymerize and buckle, or when they are pulled in the cytoplasm through dynein-cargo motions. (B) Aster growth and length-dependent forces provide dynamic shape-sensing abilities to MT asters, and result in aster-centering paths that depend on cell shape. Modified according to Tanimoto et al., 2016. (C) The cellular response to external forces (magnetic tweezers) on centered asters suggests that asters behave like elastic springs to maintain the spindle in the cell center. Red curve: Upon force application, the distance to the cell center (d) increases over time [d(t)], reaching a plateau value (d_{max}) at which aster forces balance the external magnetic force. When the force is released, d(t) relaxes exponentially to 0. Blue curve: By varying externally applied forces and measuring d_{max}, the stiffness of the 'centering spring' can be computed. (D) When an egg is shaped into a rectangular microwell, the torques and forces generated through length-dependent MTs align nuclei and spindles along the long axis of a cell. (E) Cleavage patterns of zebrafish embryos exemplify the iterative influence of cell shape on division orientation and vice versa. (F) Cells in tissues can be exposed to external mechanical forces, such as tissue tension or compression from neighboring cells, which may influence cell shape and resulting spindle orientation with respect to external forces (left). As a consequence cells will divide according to those mechanical forces; which could in turn relax tissue stress or influence the topology of cell–cell contacts (right).

and position (Burakov et al., 2003; Zhu et al., 2010). Remarkably, large mouse oocytes, which lack centrosomes and asters, are capable of moving nuclei to their center, albeit much slower than similar-sized egg cells of other species, such as sea urchins embryos – as discussed above (Almonacid et al., 2015). This is thought to be mediated by a gradient of actin-driven cytoplasmic agitation, with more agitation close to the cell cortex. As a result of this gradient, a nucleus positioned off-center experiences more 'kicks' on the cortex-facing side, which will move it to the center of the cell. Thus, in some cases, actin may contribute to geometry-sensing in order to move large structures and organelles to the center of cells.

Orienting division with cell shape

After the nucleus has reached the center, the centrosome duplicates and defines an orientation axis for the mitotic spindles. As observed almost 150 years ago, this axis most often correlates with the long axis of the cell, but how cells probe their geometry in order to orient cell division accordingly remains mysterious. Recent studies of the cleavage patterns of early embryos suggested that length-dependent MT forces also function in orientating the division axis with respect to cell shape anisotropies (Minc et al., 2011; Wühr et al., 2010). In essence, the distribution of MT lengths around two sister asters generates torques that rotate the centrosome pair, with a favored minimal-energy configuration that corresponds to the long axis of the cell (Fig. 3D). This model has been validated in multiple studies, including those in which the shape of embryos was manipulated, or those that exploited the natural changes in the shape of 3D blastomeres that occur in different cleaving embryos (Bjerknes, 1986; Minc et al., 2011; Mitchison et al., 2012; Pierre et al., 2016; Wühr et al., 2010). One prime example is the cleavage pattern of fish embryos, which entails a choreography of successive cell divisions with precise 3D angular settings (Fig. 3E). The one-cell fish egg consists of a flat blastodisc located on a large yolk sac. Because the yolk blocks aster growth, the aster adopts a flat 3D shape and, as a consequence, the first division axis lies parallel to the yolk interface. At telophase, asters and centrosomes are duplicated and elongate along the long axis of sister asters perpendicular to the first division axis, giving rise to a division that is orthogonal to the previous plane (Wühr et al., 2010). This alternating orthogonal sequence of division axis and cell/aster shapes continues until the 16-cell stage, at which point the four most-centered blastomeres, which are squeezed by their neighbors, elongate perpendicular to the yolk and orient division along this shape axis, thereby ensuring tissue layering in the 3rd dimension (Olivier et al., 2010) (Fig. 3E). Strikingly, 3D models that are solely based on shape sensing from length-dependent MT forces were able to account for this cleavage pattern in fish and other species (Pierre et al., 2016). Thus, the interplay between shapes and division can serve as an iterative design to produce complex patterns of oriented divisions that are instrumental to the morphogenetic development of embryos and tissues (Pierre et al., 2016; Xiong et al., 2014).

In light of these models, the factors that contribute to shaping cells are, thus, key to understand division positioning in multicellular tissues. Cortical tension and cell–cell adhesion are prime cell-shape regulators in tissues, but tissue tension or compression forces from neighboring cells might contribute as well (Fig. 3E,F). In return, the orientation of cell division along the cell shape axis also has functional implications in tissues. It may serve to relax stresses in epithelial monolayers (Campinho et al., 2013; Wyatt et al., 2015) or as the basis of a homeostatic mechanism regulating the topology of cell contacts (Gibson et al., 2011). One important current debate is to discern whether division orientation in tissues under tension or compression is caused by the direct effect of external forces on the division machinery (Fink et al., 2011), or whether it is the sole result of deformed cell shapes that orient division (Minc et al., 2011; Pierre et al., 2016).

Cell shape can also change during mitosis. Rounding is prominent in adherent vertebrate cells and in epithelia, and appears to be an important mechanism to, temporarily, erase the contribution of geometry to the determination of the division axis (Théry and Bornens, 2008). Yet, in many instances, the mitotic spindle in the rounded cell still aligns with the preceding interphase long axis. Seminal work, in which cells were seeded on micro-patterns, showed that this memory is provided by actin fibers that read the geometry of the adhesive pattern and influence polarity cues inside the round mitotic cell to orient the spindle (Théry and Bornens, 2006; Théry et al., 2007, 2005). Studies of the protein Mud in fly epithelia (Numa in vertebrates) have recently suggested similar shape-memory mechanisms in *Drosophila* tissues (Bosveld et al., 2016). An interesting recent study also revealed that, when rounding is inhibited in the fly embryo epithelium, cell shape will largely override cortical polarity cues, yielding division orientations that are often orthogonal to the epithelial layer (Chanet et al., 2017). Thus, a tentative speculation is that any significant anisotropy in cell shape dominates over other signals in symmetrically dividing cells.

Cells lacking centrosomes, such as the early blastomeres of many rodent embryos (Courtois et al., 2012), can still orient their division to cell shape by mechanisms that, thus far, remain mostly mysterious (Gray et al., 2004). Actin may be involved at some level, but the geometrical features that allow the actin cytoskeleton to read cell shape in this context are not known (Chaigne et al., 2016). Cortical and/or cytoplasmic protein gradients may also contribute to division positioning relative to cell shape. For instance, in adherent cells, gradients of Ran-GTP that emanate from chromosomes, and diffusible signals from polo-like kinase at spindle poles could serve as rulers to monitor and control the position and orientation of the spindle (Kiyomitsu and Cheeseman, 2012). In bacterial cells, dynamic gradients of Min proteins serve as geometry sensors to promote medial bacterial fission (see

Kretschmer and Schwille, 2016 for a recent review). Bacterial systems have self-organized membrane-associated patterns that are built around a core set of three proteins – Min C, Min D and Min E – that exhibit pole-to-pole oscillations as a result of specific rules of biochemical interactions and diffusion properties. Through time-averaging, this system defines a narrow mid-cell zone, in which the septum machinery is allowed to assemble in order to divide the cell. Remarkably, the Min proteins can self-assemble into dynamic patterns *in vitro* and probe the geometry to define a long axis, even in triangular or squared shapes (Schweizer et al., 2012; Wu et al., 2015; Zieske and Schwille, 2014). Thus, a system based on reaction–diffusion can generate specific positional protein patterns with respect to the geometry of a cell and may represent an additional important feature to connect cell shape with division position (Xiao et al., 2017).

Conclusion and future directions

The 'morphobiological' mechanisms that allow cells to probe their geometry are still at their premise stage. However, by summarizing recent efforts in the literature, we identified several generic design principles that appear to have been repeatedly used in evolution. The first one is based on MT networks, which can convert cellular geometries into defined modes of polarization or oriented division. MTs serve as prominent rulers, primarily owing to the long-range and dynamic nature of MT polymers and the forces they exert on the cortex, the cytoplasm and on nuclei and spindles. A second, more local design feature is based on the differential curvature recognition that is encoded in the structural properties of molecular assemblies, such as septins, MreB filaments and myosin filaments. The final feature is based on reaction–diffusion and its ability to form self-assembled patterns relative to cell geometry. An intriguing realization is that the above-mentioned systems exist in most cells, raising the question of how they may be tuned down to allow a more deterministic cue, such as a chemical gradient, to override them.

Up to date, however, many of the relevant studies have only been performed at the single-cell level, often in model cell types, such as yeast, HeLa cells or invertebrate zygotes, with only few studies recognizing the contribution of cell-shape sensing in multicellular tissues. This is because tissues come with a plethora of cues that are frequently orienting cell behavior as well as cell shape, making it difficult to disentangle them. In addition, cell shapes within tissues have complex 3D features that are a challenge to analyze. The standardization of novel microscopy methods, such as selective plane illumination microscopy (SPIM) or two-photon microscopy, could circumvent this limitation by allowing analysis of cell shapes in 3D, deep inside of developing tissues and organs.

Finally, one area that is lagging behind in this field has been the systematic identification of the gene products specifically affected by cell shape or required for shape-sensing. Given the advent of microfabrication methods, recent studies are now beginning to describe methods to systematically screen genes required for shape sensing, for instance during spindle orientation (Burri et al., 2017). Another way to approach this question is by exploiting cell-shape variations, which are widespread in diseases such as cancer. To this end, the recent development of large-scale profiling of gene expression and image analysis has begun to establish dose-dependent correlations between geometry and the activation of specific pathways in some cancers (Sailem and Bakal, 2017; Sero et al., 2015). Therefore, further investigation of morphobiological mechanisms might also be relevant in understanding the contribution of cell geometry to the pathophysiological behavior of cells under disease conditions.

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Competing interests

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