Most remarkably, they found that depletion of GEFH1 prevents accumulation of active RhoA, while depletion of Ect2 does not. These results, obtained via biochemical analysis, were confirmed and extended by direct imaging of RhoA activity during cytokinesis: following GEFH1 depletion, a relatively minimal amount of active RhoA is observed at the equatorial plasma membrane, and it often fails to persist. Following Ect2 depletion, in contrast, robust RhoA activation occurs but is not confined to the equatorial plasma membrane and instead the fire spreads, resulting in abnormal contraction and abnormal or failed cytokinesis.

Clearly, these findings are not consistent with Ect2 serving as the major RhoA activator during cytokinesis, and instead argue that its primary role is to keep the fire restricted to the equator. How could this work? One possibility is that a small pool of RhoA activated by Ect2 somehow primes more extensive RhoA activation by GEFH1. Birkenfeld et al. (2007) make an even more provocative suggestion, and argue that Ect2 doesn't serve as GEF in the usual sense at all, but instead acts as part of a scaffold that ensures localization of other players critical for local RhoA activation. Whatever the mechanistic explanation turns out to be, this study and the three that use chemical genetics to disrupt Plk1 function, suggest that it is time to revise our model for how RhoA is activated during cytokinesis.

REFERENCES

Barr, F.A., Sillje, H.H., and Nigg, E.A. (2004). Nat. Rev. Mol. Cell Biol. *5*, 429–440.

Bement, W.M., Benink, H.A., and von Dassow, G. (2005). J. Cell Biol. *170*, 91–101.

Birkenfeld, J., Nalbant, P., Bohl, B.P., Pertz, O., Hahn, K.M., and Bokoch, G.M. (2007). Dev. Cell *12*, this issue, 699–712.

Brennan, I.M., Peters, U., Kapoor, T.M., and Straight, A.F. (2007). PLoS ONE *2*, e409. 10.1371/journal.pone.0000409.

Burkard, M.E., Randall, C.L., Larochelle, S., Zhang, C., Shokat, K.M., Fisher, R.P., and Jallepalli, P.V. (2007). Proc. Natl. Acad. Sci. USA *104*, 4383–4388.

Eggert, U.S., Mitchison, T.J., and Field, C.M. (2006). Annu. Rev. Biochem. *75*, 543–566.

Mishima, M., Kaitna, S., and Glotzer, M. (2002). Dev. Cell *2*, 41–54.

Petronczki, M., Glotzer, M., Kraut, N., and Peters, J.-M. (2007). Dev. Cell *12*, this issue, 713–725.

Piekny, A., Werner, M., and Glotzer, M. (2005). Trends Cell Biol. *15*, 651–658.

Somers, W.G., and Saint, R. (2003). Dev. Cell *4*, 29–39.

Yoshida, S., Kono, K., Lowery, D.M., Bartolini, S., Yaffe, M.B., Ohya, Y., and Pellman, D. (2006). Science *313*, 108–111.

Cell Polarity from Cell Division

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Apical-basal polarity of epithelial cells is critical for their symmetric versus asymmetric division and commonly thought to be established in interphase. In a novel type of cell division termed "mirror-symmetric", apical cell constituents accumulate during M-phase at the cleavage furrow, resulting in epithelial daughter cells with opposite apical-basal polarity.

Neurulation in vertebrates is an ideal system to study the cell biological and genetic basis regulating the coordination of cell shape changes, cell divisions, and cell polarity during morphogenesis of an epithelium, which ultimately results in the formation of a tube. Primary neurulation in mammals occurs via invagination of the neural plate, during which the neuroepithelial cells maintain apical-basal polarity, independent of the phase of the cell cycle (Figures 1A and 1B). Neuroepithelial cell number is increased by symmetric divisions, with the cleavage plane oriented parallel to their apical-basal axis, resulting in the equal distribution of polarized apical and basal constituents to the daughter cells (Figure 1B). Cleavage planes deviating from the apical-basal axis result in an unequal inheritance of polarized constituents and, consequently, different fates of the daughter cells; in the most extreme (albeit rare) case of these asymmetric divisions, the cleavage plane is oriented perpendicular to the apical-basal axis (Figure 1B) (Götz and Huttner, 2005).

In contrast to mammals, most teleosts, including the zebrafish *Danio rerio*, undergo what is called secondary neurulation (Kimmel et al., 1995). The neural plate folds inward at the midline to build the neural keel, a solid structure, which shortly after rounds up and detaches from the overlying epidermis to form the lumenless neural rod. Cavitation finally results in the formation of the lumen of the neural tube (Figure 1C). Cleavage plane orientation differs during these stages: it is perpendicular to the neuroectodermal surface in the neural plate and to the

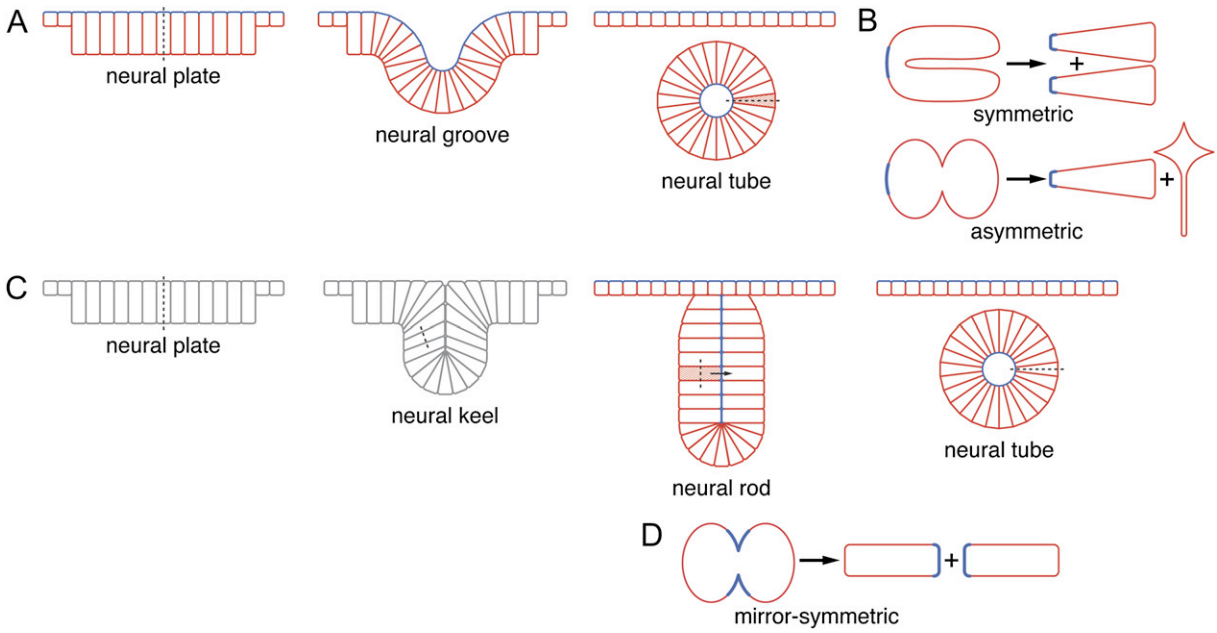

Figure 1. Neural Tube Formation in Mammals and Zebrafish

(A) Neural tube formation in mammals. Neuroepithelial cells exhibit apical-basal polarity at the neural plate, groove, and tube stage, and cleavage planes are oriented parallel to their apical-basal (long) axis (symmetric division, shaded cell in neural tube). (B) Symmetric and asymmetric divisions of neuroepithelial cells. In symmetric division (top; corresponding to the shaded cell in panel A, neural tube), the cleavage furrow ingresses in a polarized fashion from basal to apical; this results in the inheritance of apical constituents by both daughter cells, which remain neuroepithelial. In asymmetric division (bottom; not depicted in panel A), the cleavage furrow may ingress, in a concentric fashion, perpendicular to the apical-basal (long) axis; this results in inheritance of apical constituents by only one the daughter cells, which remains neuroepithelial, whereas the other differentiates. (C) Neural tube formation in zebrafish. Cleavage planes are oriented parallel to the long axis of cells in the neural plate and neural tube stage, and perpendicular to it in the neural keel and neural rod stage. Full apical-basal polarity is established at the neural rod stage. Following mirror-symmetric division (shaded cell in neural rod, see panel D), the daughter cell located more medially crosses the midline (arrow), and the daughter cells whose apical surfaces are initially aligned at the midline move apart, resulting in neural tube lumen formation. (D) Mirror-symmetric division of neuroepithelial cells (corresponding to the shaded cell in panel C, neural rod). Apical constituents accumulate at the cleavage furrow, resulting in daughter cells with opposite apical-basal polarity. (A–D) Blue, apical plasma membrane and cell cortex; red, basolateral plasma membrane and cell cortex; dashed lines, cleavage planes.

lumenal surface in the neural tube. Strikingly, during neural keel/rod stages, when the two halves of the neural anlage are in apposition to each other, the cleavage plane is oriented parallel to the midline (perpendicular to the cell's long axis). It has been previously demonstrated by elegant transplantation experiments and in vivo analysis that division of a cell on one side of the neural keel/rod results in two daughter cells populating both sides (Geldmacher-Voss et al., 2003; and references therein). This unusual behavior poses several questions. By which mechanisms are the two daughter cells distributed to either side of the midline? What controls mirror-image polarity in the daughter cells? What controls the separation of the closely adjacent apical surfaces during cavitation, i.e., how does the lumen arise? And how is all of this related to apical-basal polarity, cleavage plane orientation, molecular composition of the cleavage furrow, and symmetric versus asymmetric cell division?

The recent paper in *Nature* by Clarke and colleagues (Tawk et al., 2007) confirms published data (Geldmacher-Voss et al., 2003; Concha and Adams, 1998) and adds intriguing observations on "mirror-symmetric" cell divisions in the zebrafish neural keel/rod, which lead us to propose the concept of "cell polarity from cell division". Tawk et al. (2007) concentrate on zebrafish Par3d, one of the Par proteins, which are known to form, together with an atypical protein kinase C (aPKC), an apically localized protein complex. This complex is a key player in the regulation of epithelial and neuronal cell polarity, spindle and cleavage plane orientation, asymmetric cell division, and directed cell migration in a variety of organisms (Macara, 2004). Strikingly, in the neural primordium of zebrafish embryos, Par3, aPKC, and junctional markers (ZO-1, β-catenin) become polarized for the first time during neural rod stages (Geldmacher-Voss et al., 2003), indicating that epithelial polarity is established only then.

The essence of the findings by Tawk et al. (2007) and their implications is as follows. They confirm the previous observation (Geldmacher-Voss et al., 2003) that during rod stage, apical Par3-GFP localization is lost during metaphase but is regained in the daughter cells after one of them has crossed the midline and integrated into the neuroepithelium on the contralateral side. Additionally, they now show that, during cytokinesis, cells concentrate Par3-GFP at the cleavage furrow (Figure 1D). Consequently, the resulting daughter cells are polarized, with Par3-enriched domains facing

each other, hence the term "mirror-symmetric" cell division (Figure 1D). Given that in other epithelial cells, Par3 is a constituent of the apical cell cortex (Macara, 2004), it follows that the surfaces of the daughter cells that face each other have apical character and that the mirror-symmetric cell divisions in the zebrafish neural keel/rod yield two epithelial daughters with opposite apical-basal polarity (Figure 1D). If formation of the neural keel and neural rod is slowed down due to delayed convergence-extension, as is the case in *trilobite/vangl2* mutants, cells already start mirror-image divisions when they are still in the neural plate, indicating a cell-autonomous timing of this particular kind of division in the neural primordium. As a consequence, two lumina (rather than one) form (Tawk et al., 2007). The results thus show that *trilobite/vangl2* does not abolish the polarization of the neural keel cells as previously suggested (Ciruna et al., 2006). Inhibiting mirror-image divisions in *trilobite/vangl2* mutant embryos by partial reduction of Par3d function prevents the formation of duplicated lumina in about half of the embryos and results in a single, medial, neural tube lumen.

The accumulation of Par3 at the cleavage furrow of zebrafish neural keel/rod cells is not the first example of a protein implicated in apical-basal polarity becoming concentrated at the cleavage furrow during M-phase. The somatic stem cell marker prominin-1 (CD133), a pentaspan membrane protein, is specifically localized to microdomains of the apical plasma membrane in mammalian neuroepithelial cells. During mitosis of hematopoietic progenitors, prominin-1 becomes concentrated at the cleavage furrow (Fargeas et al., 2006). Prominin-1 specifically interacts with membrane cholesterol. Interestingly, in dividing sea urchin eggs, cholesterol and the ganglioside GM1 accumulate along with glycoconjugates at the cleavage furrow (Ng et al., 2005). Given the role of lipid rafts and cholesterol-based membrane microdomains in apical-basal polarity (Schuck and Simons, 2004), the clustering of these microdomains at the cleavage furrow may well turn out to reflect a general mechanism by which the process of cell division is utilized to polarize the resulting daughter cells. In this regard, the findings by Tawk et al. (2007) are intriguing because such cleavage furrow-triggered daughter cell polarity is observed in the context of tissue morphogenesis during development.

Yet, important questions remain unanswered. How do apical polarity proteins become concentrated at the cleavage furrow? To what extent does the actomyosin-based contractile ring contribute to this process? Why do the cells on either side of the midline of the zebrafish neural rod separate from each other upon expression of apical features on their surfaces? Do certain apical surface molecules exert a repulsive function and how are they involved in lumen formation? And, above all, how widespread are cleavage furrow-triggered daughter cell polarity and mirror-symmetric cell divisions in tissue formation and maintenance?

REFERENCES

Ciruna, B., Jenny, A., Lee, D., Mlodzik, M., and Schier, A.F. (2006). Nature *439*, 220–224.

Concha, M.L., and Adams, R.J. (1998). Development *125*, 983–994.

Fargeas, C.A., Fonseca, A.-V., Huttner, W.B., and Corbeil, D. (2006). Future Lipidology *1*, 213–225. 10.2217/17460875.1.2.213.

Geldmacher-Voss, B., Reugels, A.M., Pauls, S., and Campos-Ortega, J.A. (2003). Development *130*, 3767–3780.

Götz, M., and Huttner, W.B. (2005). Nat. Rev. Mol. Cell Biol. *6*, 777–788.

Kimmel, C.B., Ballard, W.W., Kimmel, S.R., Ullmann, B., and Schilling, T.F. (1995). Dev. Dyn. *203*, 253–310.

Macara, I.G. (2004). Curr. Biol. *14*, R160–R162.

Ng, M.M., Chang, F., and Burgess, D.R. (2005). Dev. Cell *9*, 781–790.

Schuck, S., and Simons, K. (2004). J. Cell Sci. *117*, 5955–5964.

Tawk, M., Araya, C., Lyons, D.A., Reugels, A.M., Girdler, G.C., Bayley, P.R., Hyde, D.R., Tada, M., and Clarke, J.D. (2007). Nature *446*, 797–800.