REFERENCES

Cancer Genome Atlas Research Network. (2008). Nature *455*, 1061–1068.

Cragg, M.S., Harris, C., Strasser, A., and Scott, C.L. (2009). Nat. Rev. Cancer *9*, 321–326.

Kaelin, W.G., Jr. (2005). Nat. Rev. Cancer *5*, 689–698.

Letai, A.G. (2008). Nat. Rev. Cancer *8*, 121–132.

Luo, J., Emanuele, M.J., Li, D., Creighton, C.J., Schlabach, M.R., Westbrook, T.F., Wong, K., and Elledge, S.J. (2009). Cell, this issue.

McInnes, C., Mezna, M., and Fischer, P.M. (2005). Curr. Top. Med. Chem. *5*, 181–197.

Parsons, D.W., Jones, S., Zhang, X., Lin, J.C., Leary, R.J., Angenendt, P., Mankoo, P., Carter, H., Siu, I.M., Gallia, G.L., et al. (2008). Science *321*, 1807–1812.

Scholl, C., Fröhling, S., Dunn, I.F., Schinzel, A.C., Barbie, D.A., Kim, S.Y., Silver, S.J., Tamayo, P., Wadlow, R.C., Ramaswamy, S., et al. (2009). Cell, this issue.

Steegmaier, M., Hoffmann, M., Baum, A., Lenart, P., Petronczki, M., Krssak, M., Gurtler, U., Garin-Chesa, P., Lieb, S., Quant, J., et al. (2007). Curr. Biol. *17*, 316–322.

Yan, H., Parsons, D.W., Jin, G., McLendon, R., Rasheed, B.A., Yuan, W., Kos, I., Batinic-Haberle, I., Jones, S., Riggins, G.J., et al. (2009). N. Engl. J. Med. *360*, 765–773.

Size and Speed Go Hand in Hand in Cytokinesis

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In animal cells, cytokinesis is mediated by the constriction of a cortical ring. In this issue, Carvalho et al. (2009) show in embryos of the worm *Caenorhabditis elegans* that the rate of ring constriction during cytokinesis is proportional to the initial cell perimeter, ensuring that the duration of cytokinesis is cell-size independent.

When animal cells divide, one cell is cleaved into two by the constriction of a cortical ring (Rappaport, 1996). The ring is made of actin, myosin II, and actin-binding proteins, but the precise mechanism by which it assembles and constricts is still not understood. In the prevalent model for constriction (sometimes called "pure string contraction"), the force for constriction is generated by myosin II motors sliding actin filaments against each other parallel to the cell membrane, contracting the diameter of the ring (Schroeder, 1975). However, this view has been questioned and alternative arrangements of actin and myosin II have been proposed (Eggert et al., 2006). It has even been suggested that constriction force could be generated by actin depolymerization rather than myosin II activity (Zumdieck et al., 2007). In this issue of *Cell*, Carvalho et al. (2009) investigate the rate of ring constriction (the change of ring diameter over time) during early development of the worm *Caenorhabditis elegans*, shedding new light on the mechanism of cytokinesis and its scalability with cell size.

Cortical ring constriction rate in a dividing *C. elegans* embryonic cell is initially constant but decreases once the ring comes in proximity to the midbody, a microtubule-based structure that is formed between the separated chromosomes in the dividing cell. When formation of the midbody is inhibited, ring constriction continues at a constant rate until complete closure. This suggests that a constant rate of constriction is the default behavior that is modified by the midbody.

When early embryos undergo cell division, their cells become progressively smaller. This provides researchers with an opportunity to investigate physical scaling relationships (Wühr et al., 2008), as it is likely that the biochemistry of the embryo (such as protein levels and modifications) remains relatively constant during early embryogenesis. Carvalho et al. now measure the rate of cytokinesis constriction in *C. elegans* embryonic cells of different sizes. They find that cleavage rings constrict at a rate that is proportional to their initial diameter—a cell with twice the diameter constricts twice as fast. As a result of this proportionality, the time it takes to execute cytokinesis remains mostly constant over a wide range of cell sizes. Because the rate of ring contraction is constant once initiated, and larger cells have a faster rate of constriction, the authors interpret this data as showing that cortical rings somehow "memorize" their initial circumference and use that memory to control the rate of constriction throughout cytokinesis. As the ring is an assembly of cytoskeletal proteins, the authors further hypothesize that this memory is encoded in the structure of the initial ring.

How might such a structural memory be achieved? One explanation is that the number of myosin II molecules recruited to the cortical ring is proportional to the initial ring diameter. As the ring constricts, the motors stay bound to the ring. One

could imagine that each motor is responsible for reducing a certain portion of the ring perimeter per unit of time. Because the total number of motors would stay constant, constriction rate would also stay constant and depend on the initial ring circumference (Figure 1A). However, the authors reject this model because they could show that the amount of labeled myosin II decreases in proportion to ring perimeter as the ring constricts.

Having demonstrated that myosin II and other known proteins at the cleavage furrow decrease in abundance during constriction, Carvalho et al. hypothesize that some other component of the ring must stay constant during ring closure. This component would define a fixed number of "constriction units" that shorten at a constant rate so that the whole ring constricts at a constant rate (Figure 1B). The larger the starting ring, the larger the number of units (which have a fixed initial size) and the faster the ring constricts. This hypothetical component is likely to be a structure, rather than a protein. The authors propose that the constant component may be the actin filament ends. They further suggest that the depolymerization of actin filament ends is the rate-limiting step for constriction and that filament ends may divide the ring into smaller constriction units. This is an interesting idea; the depolymerization of actin filaments from their ends could, in principle, govern the constriction rate. However, it is not clear that actin filaments depolymerize smoothly from their ends in the cell. Depolymerization is catalyzed by cofilin and other factors and may also occur through filament severing and rapid bursts of depolymerization (Kueh et al., 2008 and references therein).

One prediction from the structural memory model is that the cortical ring does not undergo continuous remodeling because remodeling tends to scramble structural information. This is a counterintuitive prediction given that many cytoskeletal assemblies are known to undergo continuous turnover where components are lost but always replaced. Carvalho et al. test this prediction for three components of the ring, myosin II, septin, and actin. In experiments using fluorescence recovery after photobleaching (FRAP), myosin II and septins are lost but not replaced in the ring. FRAP of actin is technically not feasible. Rather, the authors test actin turnover by adding the monomer-sequestering drug latrunculin A, which blocks actin polymerization and traps actin monomers after filament depolymerization without perturbing actin filaments directly. When latrunculin A is added after ring assembly, constriction continues to completion, suggesting that actin indeed does not turnover in the cortical ring. Thus, none of the ring components tested undergo continuous turnover. As the ring contracts, the components are progressively lost but not replaced. These data are consistent with the structural memory model. However, the lack of actin turnover in *C. elegans* embryo cortical rings is somewhat surprising, as photobleaching experiments have revealed fast actin turnover in cleavage furrows of mammalian cells and fission yeast (Murthy and Wadsworth, 2005; Pelham and Chang, 2002). It will be crucial to determine whether this is a real difference between the organisms. If actin filament turnover is rapid in comparison to the constriction rate, it would make it difficult for actin filament ends to encode structural memory.

For sake of simplicity, the authors did not take into account in their experiments forces that oppose constriction. These forces may include molecular friction in the cleavage furrow, as well as resistance forces from the cell body and cortex such as elastic, viscous, and poro-elastic (resulting from interactions between porous cellular structures and liquid cytosol) resistance. Ignoring these forces is perhaps necessary given our lack of knowledge regarding the mechanics of cytokinesis. However, we know these forces must exist, and different assumptions concerning them and their dependence on cell size might lead to very different models of cortical ring constriction. It has been observed in various systems that the rate of cortical ring constriction is initially constant, and previous studies have generated models of cytokinesis with constant constriction

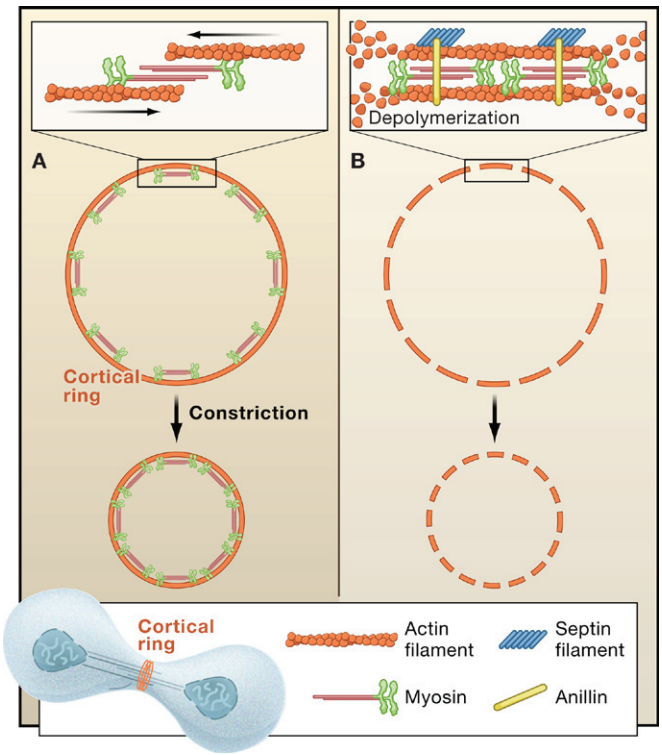

Figure 1. Connecting Cortical Ring Constriction Rate to Initial Ring Perimeter

(A) In one possible model, the amount of bound motors responsible for cortical ring constriction is proportional to the circumference of the initial ring perimeter. To generate "memory" of the initial ring circumference, the total number of myosin II motors should stay constant throughout constriction. Contrary to this model, Carvalho et al. (2009) show that the concentration of bound myosin II decreases in proportion to ring circumference.

(B) In the model proposed by Carvalho et al., constriction units consisting of actin, myosin II, septin, and anillin bind to the constriction ring before cytokinesis. The number of units is proportional to the initial perimeter. During cytokinesis, the actin ends of the units depolymerize, leading to shrinkage of the unit and a size-dependent rate of constriction. Consistent with this model, the authors show that total amounts of the cleavage furrow proteins that they examined (septin and myosin II) decrease proportionally with the size of the perimeter and that these proteins and actin do not exchange with cytoplasmic pools.

rates using different assumptions (He and Dembo, 1997; Pelham and Chang, 2002; Zumdieck et al., 2007). However, these previous models failed to predict the scaling relationship between cell size and constriction rate.

More than anything, this elegant study highlights our ignorance concerning the mechanics and dynamics of cytokinesis. We do not know how much force is generated by the cortical ring in most organisms, nor do we know how much force it takes to deform a cell of a given size. Further, it is unclear what sets how much actin or myosin II is recruited to the ring, or what determines the length of the actin filaments. If the model proposed by Carvalho et al. is correct, the most interesting questions are identifying the contractile units and learning how their initial lengths and numbers are set. Whether or not the contraction unit model turns out to be true, the observed independence of cytokinesis duration on cell size is an important finding that helps explain how embryos can engage in cell cleavage at regular intervals. How different aspects of cell biology scale with cell size is a fascinating and still relatively unexplored question. This paper may inspire future investigations of scaling in other cell properties and behaviors.

REFERENCES

Carvalho, A., Desai, A., and Oegema, K. (2009). Cell, this issue.

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

He, X., and Dembo, M. (1997). Exp. Cell Res. *233*, 252–273.

Kueh, H.Y., Brieher, W.M., and Mitchison, T.J. (2008). Proc. Natl. Acad. Sci. USA *105*, 16531–16536.

Murthy, K., and Wadsworth, P. (2005). Curr. Biol. *15*, 724–731.

Pelham, R.J., and Chang, F. (2002). Nature *419*, 82–86.

Rappaport, R. (1996).Dev. Cell Biol. Series *32*, i-xii, 1–386.

Schroeder, T.E. (1975). Soc. Gen. Physiol. Ser. *30*, 305–334.

Wühr, M., Chen, Y., Dumont, S., Groen, A.C., Needleman, D.J., Salic, A., and Mitchison, T.J. (2008). Curr. Biol. *18*, 1256–1261.

Zumdieck, A., Kruse, K., Bringmann, H., Hyman, A.A., and Julicher, F. (2007). PLoS ONE *2*, e696. 10.1371/journal.pone.0000696

FOXP2 and Human Cognition

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Using a mouse model, Enard et al. (2009) show that the human form of the *FOXP2* gene increases synaptic plasticity and dendrite connectivity in the basal ganglia. These results partly explain the enhanced capability of cortico-basal ganglia circuits in the human brain that regulate critical aspects of language, cognition, and motor control.

Our restless species strives ceaselessly to invent ever more useful devices, improve our social systems, and create new works of art. Our creative ability derives from motor and cognitive flexibility that allows us to form a potentially unbounded number of new words and sentences as well as tools, art, dance forms, and music; it is a fundamental defining attribute of *Homo sapiens* that presumably derives from a suite of neural capabilities absent or greatly reduced in other species. The archaeological record, however, reveals few signs of creativity earlier than ~200,000 years ago in Africa, with a burst of creativity appearing in *Homo sapiens* during the Upper Paleolithic, ~50,000 years ago (Klein, 1999; McBrearty and Brooks, 2000). Something must have modified the brains of our ancestors in that distant time, the period associated with both the appearance of the immediate ancestors of modern humans and the amino acid substitutions that differentiate the human form of the *FOXP2* gene from that of chimpanzees. Now, Enard, Paabo and their colleagues shed new light on the role of the *FOXP2* gene on the evolution of human language and cognition (Enard et al., 2009).

They report, in this issue, the results of introducing into mice the human version of the *Foxp2* gene. The mice exhibited alterations in ultrasonic vocalizations and exploratory behavior as well as changes in brain dopamine concentrations. The neurological consequences provide an explanation for why human speech, language, and cognitive capacity transcend those of living apes, as well as the cognitive abilities of our distant hominid ancestors that can be inferred from the archaeological record. In mice with a "humanized" *Foxp2* gene, the medium spiny neurons of the basal ganglia show increased synaptic plasticity and dendrite length. Such changes enhance the efficiency of neural cortico-basal ganglia circuits, the brain mechanisms that in humans are known to regulate motor control including speech, word recognition, sentence comprehension, recognition of visual forms, mental arithmetic, and other aspects of cognition (Figure 1).

Traditional "maps" of the human brain, in which one region of the cortex serves as, for example, the "language organ,"