mouse model, despite normal in vitro binding of mutant MeCP2 to ATRX? Third, what is the structural basis for MeCP2 binding to 5hmC and 5mC? It is intriguing that other MBD family members showed no or much weaker binding to 5hmC, although R133 is highly conserved among the MBD family. The in vitro binding properties of MeCP2 to 5hmC also beg further confirmation of interaction in vivo. Fourth, do posttranslational modifications of MeCP2, which are known to affect MeCP2 function (Guy et al., 2011), regulate binding of MeCP2 to 5hmC and/or AT-rich DNA? Both studies, while investigating neurons only in the basal state, raise the possibility of dynamic interactions between MeCP2 and different binding partners to regulate chromatin structure, which can be corroborated with dynamic changes of 5mC and 5hmC in neurons in response to neuronal activity (Guo et al., 2011a, and 2011b). Rapidly accumulating evidence supports the contribution of diverse chromatin remodeling factors to ASD. Baker et al. and Mellén et al. highlight the importance of incorporating complex and dynamic chromatin structures into our understanding of RTT and other ASDs. By identifying molecular events triggered by MeCP2 dysfunction, we will be able not only to identify therapeutic targets for RTT and ASD patients, but also to elucidate fundamental epigenetic regulatory mechanisms in the brain.

ACKNOWLEDGMENTS

We thank the support by a Samsung Scholarship to J.S., from NIH (HD069184, NS048271), MSCRF and Dr. Miriam and Sheldon G. Adelson Medical Research Foundation to G-I.M. and from NIH (NS047344, ES021957) and SAFRI to H.S.

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Evolution of Cell Division: From Shear Mechanics to Complex Molecular Machineries

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http://dx.doi.org/10.1016/j.cell.2013.02.008

Cell division depends on sophisticated molecular machinery. However, wall-less forms of bacteria use a much simpler mechanism that mimics spontaneous division of synthetic lipid vesicles. Mercier et al. (2013) show that this "mechanical" division can be activated by increased lipid synthesis. Conceivably, the first cells divided via this route.

Cell division, even in the relatively simple bacterial and archaeal cells, is mediated by highly complex, elaborate molecular machinery. However, the cell-wall-deficient L forms to which many bacteria convert when cell wall biogenesis is inhibited, in particular by cell-wall-targeting antibiotics, bypass these mechanisms and instead divide via a much simpler mechanism that involves shape perturbations, including blebbing, tubulation, and vesiculation (Errington, 2013). In this issue of *Cell*, Mercier et al. (2013) show that the switch to this "biophysical" mode of division can be triggered by an increased lipid synthesis that results in an increased cell surface to volume ratio. The first cells, up to the stage of the last universal cellular

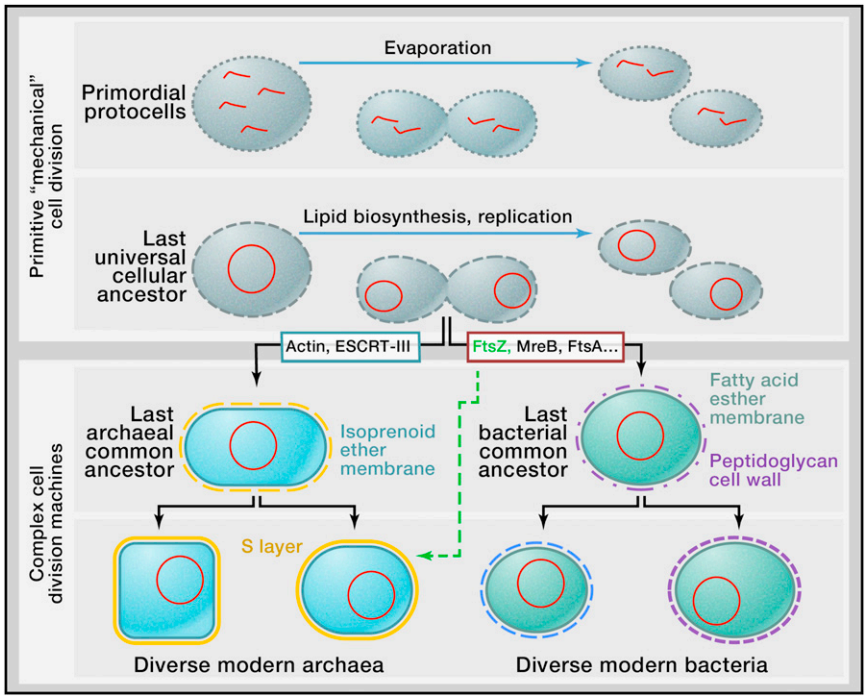

Figure 1. Evolutionary Transition from Primitive "Mechanical" Cell Division to Complex Cell Division Machineries

Under the depicted scenario, the first protocells possessed abiogenic membranes and divided via the mechanical mode. The division of these primitive cells could have been driven by environmental fluctuations such as periodic evaporation in shallow water basins. The mechanical division persisted through the stage of the last universal cellular ancestor (LUCA) that conceivably synthesized primitive and chemically simple membranes. Complex, modern-type membranes and cell division machineries evolved independently in the bacterial and archaeal lines of descent, possibly driven by the evolution of cell envelopes.

Primitive and chemically simple membranes are shown with dashed lines, and advanced modern type membranes are shown with solid lines. The red lines within the "cells" show the genome: primitive protocells are shown with multiple segments (possibly RNA molecules), whereas the LUCA and the ancestral archaeon and bacterium are shown with a typical single circular chromosome.

ancestor (LUCA), could have divided via this type of generic mechanical process.

In the majority of the bacteria and archaea, the key structure involved in division is the Z ring that consists of the FtsZ GTPase, the prokaryotic homolog of tubulins (Adams and Errington, 2009). The Z ring assembles in the mid plane of a dividing bacterial or archaeal cell. The constriction of the Z ring, facilitated by cytoskeleton typically comprised of the actin homolog MreB and a variety of regulatory protein and accompanied by peptidoglycan septum formation, leads to segregation of the daughter cells (Adams and Errington, 2009). Although the FtsZ-centered system operates in the majority of bacteria and archaea, it is by no means the universal cell division mechanism in prokaryotes. The *Crenarchaeota*, one of the major archaeal phyla, lack FtsZ and instead possess one of the two distinct alternative actin-based and ESCRT-III-based cell division systems (Makarova et al., 2010). The FtsZ protein is also missing in some *Euryarchaeota* (Makarova et al., 2010) and bacteria, especially those of the *Verrucomicrobia-Planctomycetes-Chlamydia* superphylum (Bernander and Ettema, 2010). Moreover, many archaea encode more than one division system, suggestive of a complex scenario for the evolution of cell division in prokaryotes (Makarova et al., 2010).

Strikingly, the wall-less L forms bypass the entire FtsZ-centered division machinery and instead divide via the simple "mechanical" route (Errington, 2013). Mercier et al. (2013) identify a trigger of the division of *Bacillus subtilis* L forms. The key observation is that regulatory mutations that result in an increased fatty acid production and the consequent excess membrane formation induce the division of the L forms. According to the model proposed by Mercier et al., the resulting increase in the surface to volume ratio leads to cell deformation accompanied by torsional stress that is released by scission into daughter cells (Mercier et al., 2013).

Mercier et al. propose that the remarkably simple "biophysical" mode of cell division is a backup process that is induced when cell wall synthesis is compromised. There is a striking parallel between this mechanism of L-form division and the previous observations that simple fatty acid vesicles, studied as possible models of primordial protocells, undergo shear-induced division when their surface to volume ratio is artificially increased by addition of fatty acids (Zhu and Szostak, 2009). Recently, Budin et al. have shown that addition of fatty acids, hardly plausible under primordial conditions, could be replaced by evaporating the sample, which increased the efficient concentration of amphiphlic molecules in the solution (Budin et al., 2012).

Mercier et al. argue that the biophysical cell division process is not only simple, but actually primitive, so that the division of L forms might mimic the mode of cell division at the early stages of the evolution of life. A tentative scenario of the evolution of cell division following this hypothesis is depicted in Figure 1.

The first cell-like organisms (Figure 1) that could have existed already in the RNA world would have been fully dependent on abiotically produced amphiphilic molecules, such as fatty acids and phosphorylated branched hydrocarbons (Budin et al., 2012; Dibrova et al., 2012). In shallow water basins, the evaporation, driven by solar or geothermal heat and wind, would lead to concentration of solutes and hence to the growth of membrane vesicles ultimately leading to their division (Budin et al., 2012). Thus, the cell division cycles could follow daily environmental changes; such fluctuations (Budin et al., 2012) would have been particularly pronounced at arid, vapor-dominated geothermal fields that have been identified as plausible hatcheries for the emergence of cells (Mulkidjanian et al., 2012).

The transition to the complex mechanisms of cell division might have been

driven by the evolution of cell walls, which although energetically costly, made cells independent of the osmolarity of their habitats (Mercier et al., 2013). The structures and chemical compositions of the cell walls in bacteria and archaea are drastically different (typically, peptidoglycan cell envelopes and paracrystalline proteinaceous S layers, respectively) (Albers and Meyer, 2011). Thus, this evolutionary scenario seems to imply that the early cells, from the first hypothetical cell-like entities to the LUCA, all divided via the primitive mechanical route. Given that the chemical structures of bacterial and archaeal membrane lipids are different as well (Albers and Meyer, 2011), it seems likely that the LUCA also possessed chemically simple membranes (Dibrova et al., 2012) that were conducive to the mechanical division. The scenario further implies that evolution of cell walls could trigger the independent emergence of distinct cell division machineries at the early stages of the evolution of bacteria and archaea (Figure 1). Accordingly, the FtsZ-centered cell division system is likely to be ancestral in bacteria, whereas the common ancestor of the extant archaea would employ one (or both) of the alternative, actin-based or ESCRT-III-based cell division systems (Makarova et al., 2010) (Figure 1). Under this scenario, the FtsZ-centered system, despite its current broad representation in archaea (Makarova et al., 2010), was acquired from bacteria via horizontal gene transfer.

Regardless of the details of evolution of the cell division machineries, the findings of Mercier et al. (2013) provide at least one piece of the solution to the classical Darwinian challenge of the origin of this seemingly "irreducibly" complex system. Furthermore, these results should stimulate further experimentation aimed at modeling of primitive protocells.

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