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DOI: 10.1016/j.cub.2009.02.049

Cell Division: Breaking Up Is Easy to Do

How did cells divide before protein machines evolved? A new study shows that bacteria can reproduce without the division machinery, supporting the idea that primordial cells could have divided using physical mechanisms alone.

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Life is organized into cells that grow and divide. In addition to providing a semipermeable barrier and restricting diffusion, cellular organization would have been important during the origins of life to help prevent the rise of genetic 'parasites'. For example, a ligase ribozyme might catalyse production of a complementary copy of itself by stitching together two shorter RNAs, but it could also help produce unrelated, inactive molecules that benefit from the ribozyme's activity without contributing to the system. Compartmentalization into cells reduces this problem by keeping related molecules together, with cell division periodically purging the parasites [1,2]. Cell membranes might have formed spontaneously early on, because amphiphilic lipids readily self-assemble into liposomes in aqueous solution, and such molecules have been found in carbonaceous chondrite meteorites, whose composition is thought to resemble the early solar system [3]. In fact, organic extracts from the Murchison meteorite form cell-like boundary structures in water [4].

Primitive cells have been studied primarily through a bottom-up approach, in which minimal systems are built up from scratch, and chemical or physical forces used to achieve growth and division. For example, vesicles composed of fatty acids grow larger when given a fatty acid feedstock, such as micelles [5,6]. Although such systems are exceedingly simple compared with modern life, this approach has yielded surprising insights into prebiotic cellular dynamics. Even a simple form of competition can emerge among these model protocells, as osmotically swollen vesicles 'steal' amphiphiles from relaxed ones to relieve membrane tension, suggesting that cells that accumulate solutes would grow at the expense of less active cells [7].

The top-down approach, stripping down an existing cell to a minimal set of parts, has traditionally been less powerful for understanding the early origins of life, because life as we know it today is a complicated system of interconnected parts. Although the modern cell presumably evolved from a very simple chemical system through a series of intermediate forms, the last ~3.5 billion years of evolution have optimized the system as a whole and probably obscured most traces of early events. Conventional wisdom and experience have argued that removing genes beyond a minimal subset would kill the cell, preventing the study of less complex life forms. A recent study by Leaver *et al.* [8] begins to dispel this perception, demonstrating that disabling two fundamental processes previously thought to be essential in the bacterium *Bacillus subtilis*, cytokinesis and cell-wall synthesis, nevertheless yields a viable, reproducing organism.

Cell division in bacteria generally proceeds through the formation of a contractile ring composed of the protein FtsZ (the Z-ring), to which other components of the division machinery are recruited. This ring contracts in concert with the synthesis of a new cell wall that separates the two daughter cells. Leaver *et al.* [8] generated a mutant strain of *B. subtilis* that consistently lacked cell walls (L-form bacteria), characterized by an amorphous appearance and large cell size compared with the wild-type strain. Survival of the L-forms was not unexpected, because they can also be generated by exposure to certain antibiotics (for example, penicillin), and some bacteria, such as mycoplasma, naturally lack cell walls. Cell division of L-forms, however, was assumed to involve the Z-ring. Remarkably, when FtsZ was deleted from the L-forms, the cells were largely unaffected and continued to grow and divide, indicating that neither the contractile ring nor the cell wall are necessary for cell division [8].

How do these cells divide without a Z-ring or cell wall? As the authors suggest, it is possible that other biological mechanisms are at work, such as actin homologs that form a cytoskeleton, or chromosome segregation that actively drags the nucleoids apart [8]. But could physical mechanisms alone explain cell division? In model protocells, division can occur through simple shearing, which is routinely accomplished in the laboratory [5], and the morphology of large vesicles covers a particularly rich landscape of dynamic and often unexpected forms.

One of the common modes of cell division observed by Leaver *et al.* [8] was the gradual appearance of a long protrusion from the main body of the cell, which then resolved rapidly into several round progeny cells. This pattern is strikingly similar to the 'pearling instability' seen in lipid vesicles, an analog of the well-known Rayleigh instability of fluid cylinders, in which a thin stream separates into droplets to reduce surface area while conserving volume (a dripping faucet, for example). Pearling in tubular membranes can result from a number of different stimuli that create tension

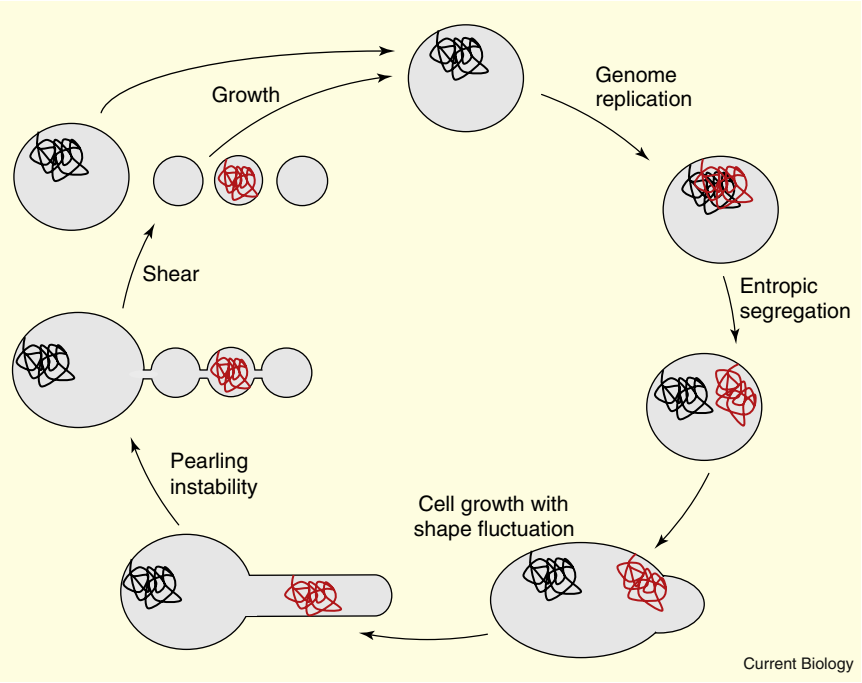

Figure 1. A theoretical scheme for cell division by physical forces.

or cause bending in the membrane [9]. For example, small asymmetries between the areas of the inner and outer leaflets of the bilayer can induce local curvature and cause pearling, as during the spontaneous uptake of a dextran-decorated lipid into the outer leaflet of phospholipid vesicles [10]. Alternatively, membrane tension can drive a reduction in surface area that induces pearling. For example, tension can be applied simply by an optical tweezer, which pulls membrane into the trap [11]. Indeed, a related phenomenon has been observed in eukaryotic cells, whose shape is believed to result from a combination of rigidity supplied by the actin cytoskeleton and tension created by adhesion points. Disruption of the actin cytoskeleton by a drug (latrunculin A) induces pearling of tubular protrusions from the cell as tension dominates the balance of forces [12]. Perhaps changes in the balance of physico-chemical forces resulting from cell growth might similarly induce pearling in the L-forms.

Once a pearling instability develops, division can follow as a result of thermal fluctuations or small mechanical or chemical perturbations [13,14]. Budding and blebbing, which Leaver *et al.* [8] also observed, have been seen in phospholipid vesicles as a sudden transition during gradual heating, where curvature changes presumably result from a small difference in the thermal expansivity of the inner and outer leaflets of the membrane [15]. Another important feature of cell division is the segregation of daughter chromosomes, which is required for producing viable progeny. Even this process may not require any biological machinery, as two intermingled polymers confined to the same space spontaneously segregate in order to maximize conformational entropy [16]. While unknown biological mechanisms may be at play in the L-forms, they need not be invoked yet; physical mechanisms alone might also suffice to explain both cell division and chromosome segregation (Figure 1).

Researchers in the origins of life community have presented several exciting advances recently, including the demonstration of a self-replicating, evolvable system of ribozymes and the development of a plausible working model for heterotrophic protocells [16,17]. Now the close resemblance of cell division in the L-forms to phenomena in membrane physics suggests that early cells may have divided through simple physical processes, and that we can expose this atavistic behavior by stripping away 'essential' genes. Maybe evolving a protocell is like drawing a fractal: easier than it looks.

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DOI: 10.1016/j.cub.2009.03.002