

Selection and the Origin of Cells

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Cells are the smallest known pieces of biology that are capable of independent reproduction and are therefore the simplest units that can evolve by conventional natural selection. This is problematic because even the simplest self-replicating cell-like entities seem to be too complicated to arise without the guiding hand of selection. To solve this conundrum, I argue that selection began before there were bounded entities in the form of neighborhood selection, an analog of group selection without bounded groups. This, I suggest, acted on chemical consortia bound to mineral surfaces to enhance their autocatalytic abilities. Then, selection for an ability to colonize new mineral surfaces resulted in the origin of propagules, which later evolved into free-living protocells. This model implies that much of life's complexity is the product of selection rather than of chance and that cells might arise predictably and rapidly in any environment with abundant free energy and appropriate chemical building blocks.

Keywords: autocatalytic sets, neighborhood selection, origin of life, protocells, surface metabolism

The metabolism, growth, and division of cells are core to life on earth. Even viruses need to enter a cell in order to complete their life cycle. Therefore, explaining the origin of cells is a central challenge in understanding the origin of life. However, the origin of cells poses a conundrum because cells are the smallest pieces of modern biology that can evolve by conventional natural selection. Whereas cells, as replicating entities, can form populations of individuals that compete with one another for representation in future generations, there is no bounded entity smaller than a cell that is capable of independent reproduction. Therefore, if selection requires the existence of bounded replicating entities and cells are the smallest such entities, then cells *must* have arisen without selection. However, this has a troubling implication: Because selection is the only natural mechanism known that can gradually build complexity over time, saying that a cell arose before selection amounts to claiming that cellular complexity arose in one spontaneous, mutational leap. The instantaneous origin of anything as complex as a living cell by chance is impossible to imagine, famously likened to a whirlwind blowing through junkyard and assembling a Boeing 747, ready to fly (Hoyle 1981).

There are three possible resolutions of this conundrum: First, a lipid membrane-bound *protocell* (defined below) that was simpler than any living cell arose spontaneously, by chance. Second, there was the spontaneous origin of an even simpler precellular entity that was individuated by some means other than by a lipid membrane. Third, selection began on chemical consortia adsorbed onto mineral surfaces before any discrete, independently replicating entity existed, and this selection ultimately gave rise to bounded entities,

such as cells. In this article, I consider these three potential resolutions in turn, concluding that the last offers the least problematic pathway toward complex cellular life because more of the work of building complexity is done by selection.

The idea that surface-bound protoplasm gave rise to cells has been proposed previously (Wächtershäuser 1988, 2007). However, prior versions of this theory failed to explain how selection in the absence of bounded entities would result in the appearance of cells. To close this plausibility gap, I present a scenario in which selection acting on surface-associated protoplasm resulted in the formation of nondividing, lipid-bound propagules as a means of colonizing new mineral surfaces. This cells-as-propagules model suggests that selection for propagule division and the eventual loss of the surface-bound portion of the life cycle explains how protocells—and eventually cells—arose by incremental selective improvement without needing to invoke any great leaps in complexity by mutation alone.

The origin of life is a notoriously controversial topic with an immense amount of literature. Rather than fully reviewing the field, this article aims to provide a concise and relatively accessible scheme for thinking clearly about the core problems. Certainly, some claims are controversial and would benefit from a more detailed and technical treatment. However, doing so in this article would undermine its primary goal of providing a succinct entrée to the field for students and other nonexperts while also introducing the idea that cells might be descended from propagules. To aid in the possible use of this article for teaching purposes, a multiple-choice quiz has been provided as supplementary information.

Definitions

I will apply the terms *cell* and *protocell* to lipid-bound compartments containing protoplasm that have the ability to grow and divide. *Protoplasm* refers to a mixture of chemicals that can collectively use sources of energy and chemical building blocks in a suitable environment to synthesize or assimilate more of the same set of chemicals. Whereas cells have an encoded genetic inheritance system (based on nucleic acids in all cells we know of), protocells do not (Gabora 2006). I will use the term *precell* to refer to any individuated, self-replicating entity that is not a protocell or cell.

The term *selection* is used here to broadly refer to situations in which entities *multiply* (i.e., promote, directly or indirectly, the local appearance of more such entities) and the rate or efficiency of multiplication has some degree of heritability. In such circumstances, variants that have an enhanced ability to multiply themselves will tend to increase in frequency. This definition encompasses conventional natural selection, which involves a population of discrete, self-replicating entities that compete for representation in future generations. However, it also includes what I will call *neighborhood selection*, a kind of selection that can, in principle, result in improvements in collective multiplication and enhanced complexity, even though neighborhoods are not discretely bounded and do not, in any simple sense, self-replicate.

Complexity is a notoriously difficult concept to define (McShea 1991, Lloyd 2001, Adami 2002). Although it is common in biology to think of complexity in terms of the number of phenotypic parts (e.g., Valentine et al. 1994, Baum 2013), this is not the criterion of relevance here. Rather, the pertinent notion of complexity is the improbability of spontaneous appearance: A structure that is very unlikely to appear by chance has, by definition, high complexity (see Machta 2011). The key point is that high-complexity structures, such as cells and 747s, have a virtually zero chance of arising spontaneously in one mutational leap. However, high-complexity entities can arise via many small, sequential mutations that each happen to be favored by selection (inset in figure 1). It should be born in mind, however, that although selection is capable of favoring higher-complexity variants, this need not always apply: Selection, at times, can favor apparent simplification, most famously in parasites (Miconi 2008). However, the fact that selection does not *disfavor* complex entities, combined with the theory suggesting that more complex forms will tend to be better able to survive and reproduce across a diversity of possible environments (Krakauer 2011), means that selection will tend to yield sustained increases in complexity over time.

Potential resolution 1: The emergence of protocells without prior selection

Although all living cells are very complex, it is important to acknowledge that a cell-like entity capable of evolving by selection toward increasing complexity need not be as complicated as any living cell. Most importantly, it need not have

had a digital genetic code: It could have been a protocell. This follows because *analog inheritance*, best understood as the relative amounts of each metabolically active chemical moiety (Shenhav et al. 2003, Walker and Davies 2013), is, in principle, sufficient for evolution by natural selection. In a population of growing and dividing protocells, some would have a ratio of chemical moieties (i.e., stoichiometry) that results in higher survival and reproduction than those of other protocells. If we assume that chemicals are homogeneously distributed across a parental protocell, offspring will tend to inherit their parent's stoichiometry and therefore its fitness (Shenhav et al. 2003). In principle, then, once we explain the origin of growing and dividing protocells, we can envisage selection over many generations resulting in true cells and a transition to digital information encoding using nucleic acids (Szostak et al. 2001).

Nonetheless, although it is far easier to imagine a protocell than a cell arising spontaneously, it is still far from easy to see how a potentially evolving protocell could arise without any prior selection. It is not enough that its protoplasm have a viable metabolism; the protocell would also need to regulate transport through its bounding membrane, retain metabolically active chemicals, acquire chemical building blocks and energy, exclude toxins, and excrete waste. It would need a way to regulate its osmotic state and to control the rate of membrane production so as to match changes in volume. And, in order to evolve by selection, a protocell would need to divide in a somewhat predictable and reliable way. Adding these additional factors, even the simplest evolvable protocell can only be considered very complex, which is to say unlikely to arise by chance (figure 1). Deacon and Sherman (2007) tried to avoid these problems by envisaging a kind of protocell (an *autocell*) whose membrane breaks and is reformed each generation. However, they failed to explain how the cooperating molecules in the protoplasm could avoid being separated by diffusion when not enclosed by a membrane.

Taking these considerations together, I would submit that selection is needed to gradually build the key attributes of an evolvable protocell—namely, a viable protoplasm, membrane synthesis, regulation of transport, and an ability to divide. But—and this is the core problem—conventional selection could not have started until all these attributes were already in place.

Potential resolution 2: Precellular, bounded entities as stepping-stones to protocells

If protocells did not arise spontaneously, could there have been some simpler, precellular entity that could arise spontaneously with an ability to self-replicate and that could then evolve into a cell? Many such precellular theories have been proposed. However, I am aware of no precellular theory proposed to date that satisfies the goal of offering a largely selective path toward cells. They fall short in one of three ways: (1) the entities proposed would not have been capable of evolving by selection, (2) the entities might have

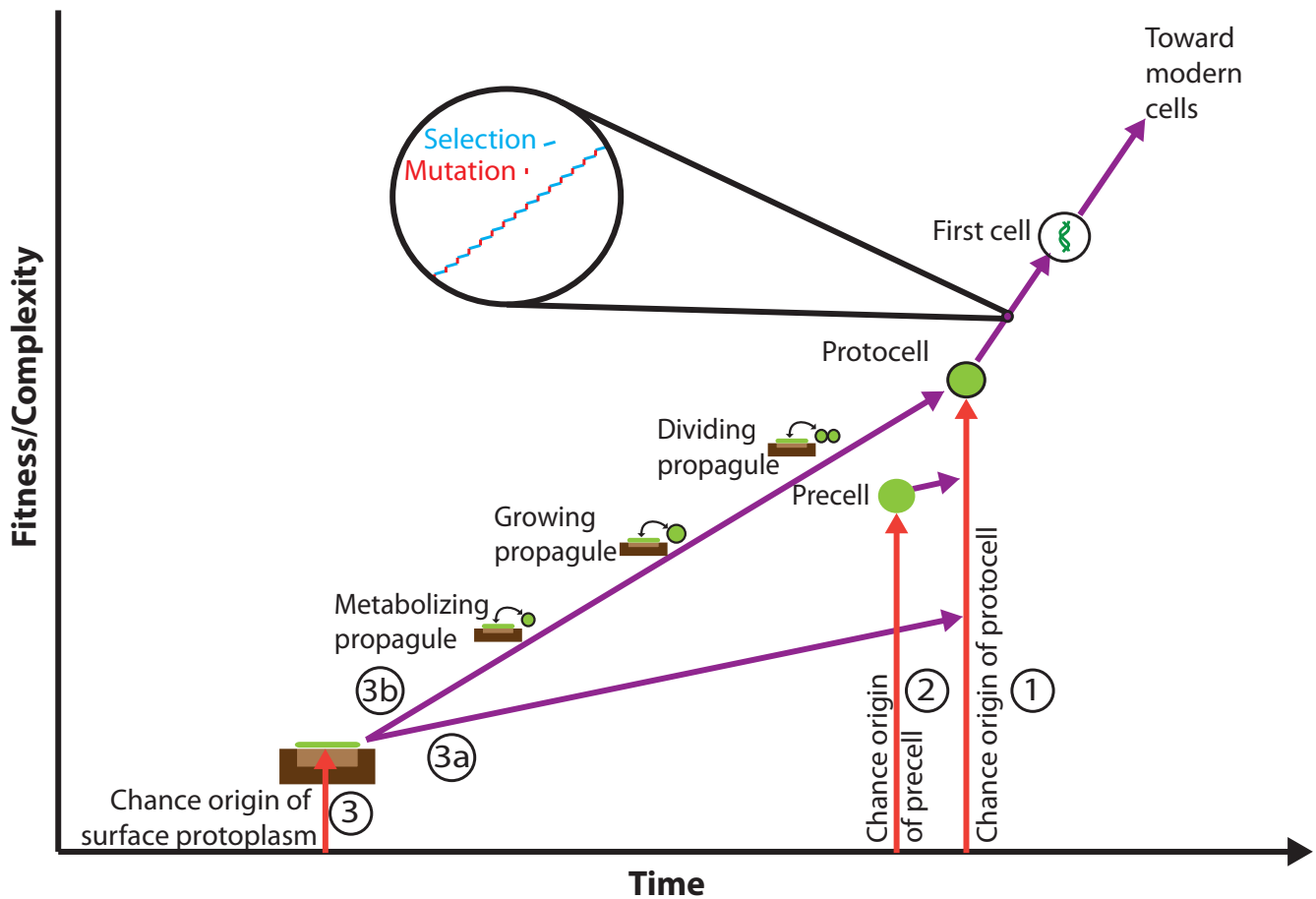


Figure 1. Alternative paths to the first cell. The vertical axis shows the capacity for faithful and efficient reproduction (which is roughly equivalent to fitness). In addition, because selection for enhanced fitness often results in greater order and, consequently, a reduced likelihood of arising spontaneously, the vertical axis is assumed to also represent complexity. The red vertical arrows represent spontaneous events (which are roughly equivalent to mutations) that increase complexity. The purple diagonal arrows represent progressive evolution by selection. The blow-up of a portion of a purple line clarifies that progressive selection should properly be seen as selective retention (blue lines) of many small beneficial mutations (the vertical red lines). If we discount the possibility that a true cell with a nucleic acid-based digital genetic system arose spontaneously, there are three possible paths to the first cell: (1) The spontaneous origin of a protocell (a membrane-bounded, individuated entity with an analog inheritance system) that later evolved into a cell; (2) the spontaneous origin of a precellular entity that could evolve by selection into a protocell (or, not shown, directly to a cell); and (3) the spontaneous origin of surface protoplasm that ultimately evolved into a protocell by either (a) spontaneously generating a protocell capable of dividing or (b) evolving progressively more complex propagules that eventually became a protocell when the surface-bound part of the life cycle was lost. As I argue in the article, option 3b is preferred, because it invokes the fewest large increases in complexity by chance alone.

been capable of evolving, but there was no plausible path from them to protocells, or (3) the entities would have been capable of evolving but were not much simpler than protocells and were therefore equally unlikely to arise by chance, without prior selection.

In the first category, I would list aerosol droplets (Dobson et al. 2000) and cavities in porous rocks (Kuhn and Waser 1981). Each defines a bounded compartment, but neither aerosol droplets nor pores in rock can, themselves, divide. We could imagine the components of protoplasm inhabiting droplets or pores diffusing to other droplets or pores,

making it conceivable that one or the other served as a physical milieu for surface protoplasm (discussed below). However, because droplets and pores cannot, themselves, divide, the idea that they could evolve into cells is not grounded in reasonable evolutionary theory.

In the second category, I would include crystal replicator models, of which the classic formulation is Cairns-Smith's (1966) clay hypothesis, presented in an especially engaging manner by Cairns-Smith (1990). This theory spun off the fact that crystal growth is a templated seeding process in which information encoded in one crystal, such as a pattern

of imperfections, can be passed on to other crystals that arise by crystal growth followed by splitting. Clays, which are composed of complex layered crystals, were highlighted, with the suggestion that these might have become populated by nucleic acid molecules that gradually took over the evolutionary process. However, although it is reasonable to suppose that clay crystals subjected to rounds of crystallization and fragmentation could evolve by selection, in the last fifty years, no plausible model has been proposed to explain how clay crystals could transition into growing, dividing protocells.

In the third category, I would include classic precellular models (Oparin 1957, Fox 1988, and others) and gene-first models. The classic models imagined that abiological synthesis generated a high concentration of organic molecules in the water column, especially proteinlike molecules. These, it is proposed, would spontaneously form aggregations having various names, of which I will use *microspheres*. Depending on the model, microspheres were either held together by internal hydrophobic interactions or had a spontaneously formed, semipermeable bounding layer generated by chemical cross-linking or by self-assembly of lipidlike molecules (the latter would arguably constitute protocells). The implicit or overt argument is that these precellular entities gradually evolved into cells. But how? In order to evolve by natural selection, it is not enough that microspheres arise; they would also need to replicate. But, as was discussed in the case of protocells, it seems extremely improbable that a microsphere that already had the ability to grow, regulate material exchange with the exterior, and divide could arise by chance. This should not be surprising: The challenge of imagining the spontaneous origin of a discrete, dividing entity is not much dependent on whether the boundary is based on lipids or not. Therefore, the probabilities of evolvable protocells and microspheres arising by chance are about equal—and very low.

It may be less obvious why gene-first models, as embodied most famously in the RNA-world hypothesis (Gilbert 1986), face a similar challenge. At first glance, it seems reasonable to imagine that a single RNA molecule that had the ability to catalyze its own templated replication would inevitably evolve by natural selection. Might not such selection eventually result in the production of a protective and nurturing compartment—a cell (note, there is no protocell stage in this model)? There are, however, many problems with this hypothesis. First, it is highly doubtful that any single RNA molecule could have both the catalytic and information-encoding capability to self-replicate. Second, although it is easy to say that an evolving naked gene built a compartment to protect itself, the actual steps underlying such a transformation are far harder to spell out. Finally, and most significantly, even if a self-replicating molecule could exist, it is almost inconceivable that it could copy itself with sufficient accuracy to evolve effectively by natural selection (Eigen and Schuster 1977). Because of this last factor, modern gene-first models do not invoke a single talented molecule but sets

of cooperating replicators (genes) organized in hypercycles (Eigen and Schuster 1978, Maynard Smith 1979). This poses a problem, however: If replication requires multiple cooperating genes, wouldn't they need to be enclosed in a bounded entity? And for the enclosed genes to actually replicate themselves, wouldn't that bounded entity need to be able to grow and divide? In short, I would argue that gene-first models do not avoid the problems discussed earlier: One either needs to invoke the *spontaneous* appearance of a cell or some such bounded, replicating entity to enclose the hypercycle, or one needs a model of selection that does not require boundedness.

Potential resolution 3: The evolution of cells by neighborhood selection

I have argued that the spontaneous appearance of bounded, replicating cell-like entities is phenomenally unlikely and that there is no other kind of bounded entity known that could plausibly evolve by selection into a cell. Consequently, if we want to avoid the contention that the origin of life was more or less miraculous, there is only one option: Selection began before there were bounded entities. This is impossible under a naive version of selection that assumes a population of discrete entities, each competing for representation in future generations. However, in the sophisticated evolutionary framework of multilevel selection theory, selection can occur in the absence of discrete entities. The easiest way to see this is to briefly consider the evolution of cooperation by group or neighborhood selection.

It is now well established that if a population of organisms is composed of many distinct groups (e.g., clans, tribes, kin groups), intergroup selection can favor cooperative variants (altruists) that enhance group fitness, even if the cooperators' fitness is lower than the noncooperators' within each group (for an accessible summary, see Sober and Wilson 1999). What is interesting—but less well appreciated—is that analogous selection can favor the origin of cooperation even if there are no bounded groups. Consider, for example, a two-dimensional array of individuals, some of whom are cooperators and some of whom are not: It has been shown that if each individual interacts (cooperatively or not) with its surrounding individuals, then cooperation can be favored by intergroup selection (e.g., Grim et al. 2006), even though there are no discrete, nonoverlapping groups.

The problem of how cooperation among organisms evolves has obvious parallels to the origin of life. After all, cellular life is composed of heterogeneous chemical moieties that cooperate to generate more of the same. There are differences, of course. The individual chemicals of life, unlike individual organisms, cannot reproduce at all without help from other members of the group. Furthermore, rather than there being just two types (cooperators and noncooperators), nonbounded, lifelike chemistry presumably entails very many distinct kinds of organic and inorganic chemicals, a subset of which have the ability to cooperate to achieve group-level reproduction. Nonetheless, the basic parallels

are close enough that we can infer, by analogy, that (a) group selection can occur in a two-dimensional array, in which neighborhoods differ in the extent of cooperation among their components, and (b) this will happen even if neighborhoods lack boundaries. Indeed, theoretical models show that, under certain assumptions, two-dimensional arrays are very conducive to the establishment of hypercycles of cooperating molecules (Boerlijst and Hogeweg 1995). It is also noteworthy that when catalysts act sequentially on one another's products, maintaining them in close proximity (in neighborhoods) can result in a much more efficient synthesis of certain products because of the existence of unstable intermediates (Bauler et al. 2010, Castellana et al. 2014).

Given these considerations, we can readily imagine selection beginning when organic and inorganic molecules adsorbed onto mineral surfaces spontaneously formed cooperative autocatalytic neighborhoods. This could also happen in a porous solid, which is really just a highly contorted (fractal) surface, but some solid foundation is needed to ensure that cooperating molecules remain in physical proximity. One specific hypothesis is provided by Wachtershauser's (1988, 1990, 2007) surface metabolism theory, which proposed that lifelike chemistry arose when organic molecules accumulated on the surface of iron pyrite and harnessed redox potential energy to fix carbon, thereby generating more organic molecules. Martin and Russell (2007), meanwhile, have argued for a different kind of chemistry occurring at alkaline vents that resulted in the evolution of membranes with electron transport chains before the formation of cells. Regardless of the specific chemistry, however, mineral surfaces provide the perfect milieu for the onset of boundary-free selection. If ever an autocatalytic network arose on a surface, neighborhood selection could result in increased cooperation over time, causing progressively more effective acquisition of energy (Pross 2012) and more efficient growth over the surface. Just as conventional selection tends to result in increases in fitness, so does neighborhood selection tend to yield neighborhoods composed of chemicals that show more effective collective multiplication.

Cells as propagules

Even if we assume that protoplasm began evolving by selection on mineral surfaces long before it became bounded in protocells, this model only helps us explain the origin of cellular life if neighborhood selection would favor the evolution of protocells. But why should it? Wouldn't we just end up with mineral surfaces being coated in more and more complex mixes of chemicals, with newly exposed surfaces being colonized more and more quickly? Why would selection acting on surface-bound protoplasm ever result in the formation of lipid-bounded protocells?

Wachtershauser (1988) suggested that selection for protecting surface-bound protoplasm from being washed away might favor the formation of a lipid surface layer. Such a membrane might also have been beneficial because it allowed for chemiosmotic energy capture—though chemiosmosis is

perhaps more likely to have originated in cells or protocells (Sojo et al. 2014). Wachtershauser proposed that the coating membrane would commonly reorganize spontaneously to release a membrane-bound vesicle and that, on at least one occasion, such a membrane-bound vesicle trapped enough protoplasm to become a viable cell that could live free of the surface. However, this model does not explain how released membrane-bound entities acquired the ability to grow and divide in the water column, because it seems unlikely that they would have had this ability spontaneously. I will suggest that there is a logical path from surface protoplasm to protocells via selection for the ability to colonize distant mineral surfaces, which favored the production of propagules.

Surface-associated protoplasm would almost certainly have been adapted to one particular kind of mineral and therefore would have initially been limited to the contiguous area of mineral surface on which it had arisen. This would mean that each discontinuous mineral surface on the planet would represent an independent evolutionary origin of life-like chemistry (figure 2a). However, if ever one consortium happened to release globs of itself that could drift for a while before colonizing a new surface, this kind of protoplasm would have rapidly spread (figure 2b). These propagules need not have been very complicated: Consider soredia, the asexual propagules of some lichens, which are little more than a clump of fungal and algal cells that are released from the lichen surface. But even if the propagules of precellular life were not bounded initially, selection would have likely favored the evolution of an enclosing membrane, permitting longer persistence in the face of diffusion and therefore greater odds of successful colonization.

Once membrane-bound propagules had arisen, it is easy enough to imagine incremental selection for increasing metabolic activity. From metabolically dormant propagules lacking any ability to grow, regulate transport, or osmoregulate, it is easy to imagine selection for variants that could use free energy and food encountered while drifting in the water column to fight entropy, allowing them to live longer, to grow, and to be more competitive colonists. Therefore, selection for improved colonizing ability could explain the eventual evolution of bounded entities that could persist and grow en route to a new surface.

Given this model, it is not hard to imagine that an ability to divide in transit to a new surface would be advantageous by allowing multiple surfaces to be colonized (figure 2c). And, finally, it is easy to suppose that the need to ever colonize a new surface could be lost (figure 2d). This is analogous to one hypothesis for the origin of chordates, in which a motile larval stage produced by a sessile sea squirt-like ancestor eventually acquired the ability to reproduce without settling (Gee 1996). It also has some similarity to the prevailing theory for the origin of land plants, which proposes that a single-celled diploid cell acquired the ability to divide, ultimately giving rise to the diploid plant body, which dominates vascular plant life cycles (Graham 1996). Therefore, from lifelike surface protoplasm, it is easy to

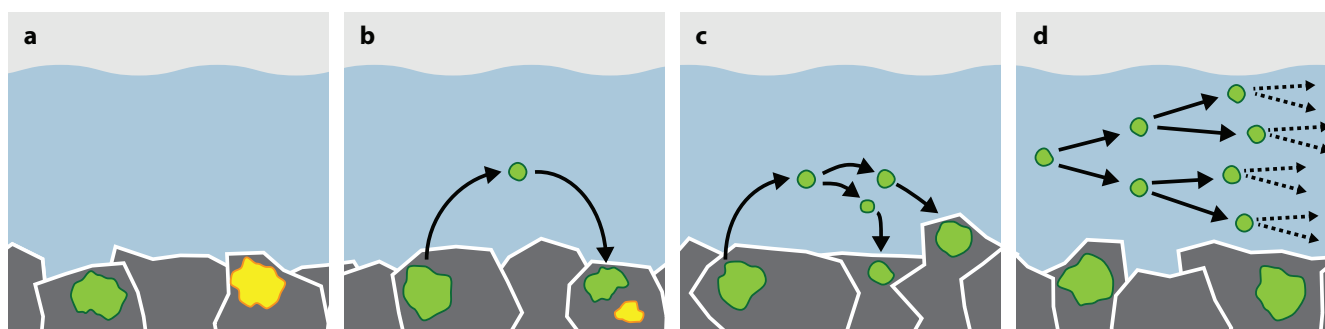


Figure 2. The evolution of cells from the propagules of surface-bound protoplasm. (a) Surface-bound lifelike chemical systems (surface protoplasm) arise spontaneously on certain mineral surfaces. Because the dispersal ability of surface protoplasm would initially be limited, discontinuous mineral surfaces would tend to be colonized by independently originating surface protoplasm (represented by the different colors). (b) A kind of surface protoplasm that released small packets of protoplasm that could float for a time and disperse to another mineral surface, a propagule, would have a competitive advantage: It would be able to more quickly colonize newly exposed mineral surfaces. (c) Over time, propagules that gained the ability to grow and divide in the water column would be favored because they could colonize more surfaces. (d) Eventually, dividing propagules would cease needing to ever colonize a mineral surface; they would become free-living protocells.

imagine that selection for improving colonizing ability could ultimately lead to bounded, growing, and dividing protocells and, from those protocells, cells.

Conclusions

In this article, I have argued that life's order and complexity began to be built up before there were any bounded, replicating entities. The answer to the question of which came first, cell or selection, is *selection*. This was possible because of neighborhood selection acting on protoplasm associated with mineral surfaces. Furthermore, I have proposed the cells-as-propagules hypothesis, which smoothes out the selective path toward cells by suggesting that neighborhood selection would favor protoplasm that released propagules to colonize new surfaces and that subsequent evolution would more or less inevitably lead to the evolution of metabolically active, growing, and dividing protocells. Such protocells—and their cellular descendants—would have spread over the earth and consumed much of the available organic matter, making it much harder for any future life-form to follow the same evolutionary path. Taking these considerations together, I would suggest that there is a plausible monotonic pathway, entirely driven by the power of selection, from weakly autocatalytic chemical assemblages on mineral surfaces to cells as we know them today (figure 1). Such a viewpoint suggests no sharp dividing line between nonlife and life but rather a gradual increase in complexity driven by incremental selection (Shenhav et al. 2003, Pross 2012).

If the perspective presented in this article is correct, then the origin of cellular life was driven largely by selection and did not depend on the highly improbable spontaneous appearance of individuated, replicating entities. Given the directionality and power of selection, this suggests that the appearance of cells might be inevitable in any planet similar

to earth, with oceans and tectonic activity generating a constant flux of solutions out of redox equilibrium, organic building blocks, and a repeated turnover of mineral surfaces.

This viewpoint also has profound implications for empirical research into the origin of life. A cell-before-selection view would imply that the origin of life required very specific and remarkable conditions, making it unthinkable that we could actually generate new lifelike entities in the laboratory. In contrast, a selection-before-cell perspective implies that most of life's order is due to selection. If, as models suggest (Kaufmann 1986, Mossel and Steel 2005), weakly autocatalytic chemical consortia spontaneously arise quite easily, we can entertain the possibility of imposing artificial selection for the ability to colonize new surfaces in the laboratory and observing the appearance of newly evolved protocells. Of course, it is very unlikely that scientists will generate new cellular life anytime soon. Nonetheless, a selection-before-cell perspective supports a more optimistic attitude toward origin of life research and may therefore stimulate new and exciting research programs that will shed new light on the origins of cellular life.

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Supplemental material

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