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PERSPECTIVE

Pre-Darwinian Evolution Before LUCA

Shiping Tang[1]

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Abstract
If the coming of the last universal cellular ancestor (LUCA) marks the crossing of the "Darwinian Threshold" (Woese in Proc Natl Acad Sci USA 99:8742–8747, 2002), pre-LUCA evolution must have been pre-Darwinian. But how did pre-Darwinian evolution actually operate? Bringing together and extending insights from both earlier and more recent contributions, this essay advances three principal arguments regarding the pre-Darwinian evolution. First, in the pre-Darwinian epoch, survival essentially meant persistence within the prebiotic system, and it depended mostly on chemical variation and interaction. Second, selection operated upon four different properties: chemical; chemical-physical; vesicles' capacities in absorbing, engulfing, and merging; and protocells' coupling of metabolism, replication, and division. Third, division evolved from a state without tight coupling of replication with division to a state of tight coupling. Eventually, protocells with a tight coupling of replication with division became the First Universal Cellular Ancestors (FUCAs) and then LUCA.

Keywords Darwinian Threshold · FUCAs · Horizontal biomolecule transfer (HBMT) · Horizontal gene transfer (HGT) · LUCA · Pre-Darwinian evolution

Introduction: Evolution Before the Darwinian Threshold

The central mechanism of biological evolution, variation-selection-inheritance, is one of the most universal mechanisms known. Much of our understanding of variation-selection-inheritance, however, has been dominated by the gene-centric neo-Darwinian Modern Synthesis with a rather narrow understanding of what constitutes variation, selection, and inheritance. This unduly narrow understanding of variation, selection, and inheritance may have been a key cause behind our failure to adequately explain some critical puzzles in biological evolution, including the origin of the first cell.

If the coming of the last universal cellular ancestor (LUCA) marks the crossing of the "Darwinian Threshold" (Woese 2002), it follows that pre-LUCA evolution must have been pre-Darwinian.[1] By pre-Darwinian, I mean that evolution *before* the Darwinian Threshold must have operated in a non-Darwinian way that eventually paved the way for Darwinian evolution *after* the Darwinian Threshold.

But how did pre-Darwinian evolution actually operate? And if pre-Darwinian evolution did operate (cf. Tessera 2018), how can we modify variation-selection-inheritance with a pre-Darwinian logic in order to explain the origin of the first batch of protocells (or the first universal cellular ancestors, FUCAs) before they evolved into LUCA?

I advance three principal arguments regarding the pre-Darwinian evolution, by bringing together and extending insights from earlier and more recent contributions (e.g., Oparin 1953; Woese and Fox 1977; Margulis 1991; Norris and Raine 1998; Woese 1998, 2002; Fry 2011; Bouchard 2014; Doolittle 2014; Koonin 2014a, b; O'Malley 2014; Pascal and Pross 2016; Egel 2017; Garson 2017; Lanier and Williams 2017; Toman and Flger 2017; Doolittle and Inkpen 2018).

Two statements on terms are now in order.

First, FUCAs correspond to what Woese called "progenotyes," whereas LUCA corresponds to genotes (Woese 2002). More critically, although LUCA has been conventionally understood to be the "last universal *common* ancestor," it is implicitly understood that LUCA must have been a cell. In fact, Woese's two seminal contributions (Woese 1998,

✉ Shiping Tang
twukong@fudan.edu.cn

[1] School of International Relations and Public Affairs (SIRPA), Fudan University, Shanghai, China

[1] For a discussion regarding the exact nature of LUCA, see Cornish-Bowden and Cárdenas (2017).

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Table 1 Four pre-Darwinian selection mechanisms before FUCAs

Mechanisms	Entities being selected upon	Properties being selected
Most chemical	Molecules	Availability, stability, polymerization, and interaction
Chemical and physical	Bioorganic molecules and complexes	Interactions with other bioorganic molecules, forming complexes, and generating emergent chemical and physical properties (e.g., permeable membrane)
Vesicular	Vesicles	Absorption, merger, and acquisition
Protocellular	Protocells (before FUCAs)	Persistence (as survival), absorption, growth, and division, first without and then with primitive metabolism and genetic replication

2002) were really about the origin of (proto-)cells (for similar interpretations, see Koonin 2014a, b). "The universal *cellular* ancestor" is therefore more proper than "the universal *common* ancestor" because the former eliminates any ambiguity that both FUCAs and LUCA must have been protocells (Koonin 2014a; Gogarten and Deamer 2016; Egel 2017).

Second, I use persistence for noncellular entities but survival for (proto-)cellular entities. Similarly, I use replication for genetic replication only but reproduction for vesicles and protocells that may grow and then divide, with or without genetic replication.

Persistence as Survival Via (Physical–Chemical) Variation and Interaction

Persistence (as survival) comes before replication, and certainly before division (with or without genetic replication) or reproduction: before replicators and reproducers, there must be survivors, to paraphrase Szathmáry and Maynard Smith (1997). An entity, be it a compound, a complex, or a vesicle, has to exist and then persist within the (pre-)biotic system before it can become part of life, especially when it cannot replicate (or metabolize). This law that persistence comes before replication and reproduction holds most forcefully in the pre-Darwinian epoch (e.g., Pascal and Pross 2016; Egel 2017; Toman and Flger 2017).

For biomolecules and complexes in the early stage of prebiotic evolution, their persistence was not coupled with (cellular) metabolism or replication: the coupling of persistence, metabolism, and replication was a product of pre-Darwinian evolution. In other words, persistence of biomolecules and complexes does not depend on metabolism or replication. Rather, persistence depends mostly on chemical variation and interaction. Moreover, variations were not generated by genetic mutation (which did not exist for a long time), but by two other processes: (1) abiotic synthesis and (2) polymerization and interaction which generates not only variations but also new properties, including chemical and physical stabilities.

The Making of FUCAs: Four Pre-Darwinian Selection Mechanisms

Natural selection can operate without replication or even metabolism (at least not cellular metabolism), as long as different molecules, complexes, and vesicles have different persistence rate within a system. A pre-Darwinian and hence non-Darwinian kind of natural selection must have operated during the pre-Darwinian epoch and long before the crossing of the Darwinian Threshold. In fact, Darwinian selection itself must have been a product of the pre-Darwinian epoch (Woese 1998, 2002; cf. de Duve 2005). Four major non-Darwinian selection mechanisms, which most likely had appeared in the following order, had worked together in the process leading to FUCAs (see Table 1 for a summary).

(a) The first pre-Darwinian selection mechanism is mostly chemical. It operates upon molecules and selects not only their chemical properties as monomers but also their capacities for forming polymers and complexes. Here, the key yardsticks of "fitness" include steady supply from abiotic synthesis (i.e., availability), kinetic and thermochemical stability or persistence (Meléndez-Hevia et al. 2008; Pascal and Pross 2016; Toman and Flegr 2017), solubility, polymerization, and stereochemical "mutualism" for forming larger complexes (Lanier et al. 2017; Vitas and Dobovisek 2018).

(b) The second pre-Darwinian selection mechanism is both chemical and physical. It selects the different capacities of different bioorganic molecules and complexes to interact with each other, and in turn, whether their interactions confer new (or emergent) life-facilitating properties, structural and functional. Among the various possible interactions, two were perhaps central: (1) alpha-helix forming peptides, perhaps (poly-)nucleotides too, that can not only interact with and stabilize vesicles but also make vesicles selectively permeable (e.g., Lear et al. 1988; Black et al. 2013); and (2) pep-

tides and RNAs that can not only interact with each other but also lead to new or enhanced properties (e.g., more efficient and reliable) via their interactions.

(c) The third pre-Darwinian selection mechanism selects the different capacities of different vesicles (1) to absorb biomolecules and components via simple absorption and breaking-and-re-encapsulation and (2) to engulf (or acquire) via proto-endocytosis and to merge (or fuse) via proto-endosymbiosis or similar processes. Vesicles with superior capacities in both absorption and merger/acquisition will enjoy advantages over those with less effective capacities, in terms of persistence, variation, and evolvability (Oparin 1953; Margulis 1991). For both processes, a wet-and-dry cycle might have played a key role (Damer and Deamer 2015; Higgs 2016). Notably, absorption, acquisition, and fusion entail extensive "horizontal biomolecule transfer" (HBMT) rather than merely horizontal gene transfer (HGT): HBMT thus subsumes HGT. Only with HBMT could pre-Darwinian evolution draw from "global inventions" (Woese 1998, 2002). HBMT was therefore the more pivotal and pervasive process than HGT, at least in the pre-Darwinian epoch. In fact, Woese's emphasis of HGT during the evolution from progenotes (i.e., FUCAs) to genotes (i.e., LUCA) is valid only if he meant HBMT with HGT.

(d) The fourth pre-Darwinian selection mechanism operates upon vesicles that now approach protocells. Among those now fairly stable vesicles, those that can (1) absorb, acquire/engulf via proto-endocytosis, and fuse/merge via proto-endosymbiosis, or processes similar to them, (2) produce primitive metabolism and replication, and (3) grow, divide, and stabilize will hold critical selection advantage over those that cannot. Here, the key yardstick of "fitness" was persistence, absorption, growth, and division, first without and then with primitive metabolism and genetic replication (Norris and Raine 1998; Deamer 2008; Meléndez-Hevia et al. 2008; Mansy et al. 2008; Schrum et al. 2010; Zhu et al. 2012).

The central point is that FUCAs most likely did not come to exist via de novo evolution within individual protocells: this will imply that every FUCA had to evolve almost entirely independently and such a possibility would have been a miracle.

Certainly, FUCAs did not come to exist via HGT alone: HBMT had to come first before HGT came into play. In fact, only through HBMT rather than HGT, at least not HGT alone (cf. Woese 2002; Fournier et al. 2015), could the evolution of FUCAs be drawing useful ingredients or components from "global invention." It was only through HBMT that is underpinned by absorption, engulfing/acquisition, and merger/fusion rather than HGT alone that FUCAs came to possess both a proto-machinery of survival and a proto-machinery of replication within the same protocell. Hence, the third and the fourth pre-Darwinian selection mechanisms might have been the penultimate mechanisms before the emergence of FUCAs.

During the pre-Darwinian epoch that led to LUCA and long before eukaryogenesis, this mechanism of HBMT via absorption, acquisition, and fusion or processes similar to them, had thus been a far more powerful and foundational force of variation and selection than even Lynn Margulis and many of her supporters had appreciated (e.g., Sagan 1967; Margulis 1981, 1991; Margulis and Sagan 2002; see also Woese and Fox 1977, p. 5).

From Loose Reproduction to Reproduction with Replication Via Selection

Once FUCAs came to possess both a proto-machinery of survival and a proto-machinery of replication (both machineries require some kind of metabolism machinery), survival and replication began to coevolve with each other, *within a vesicle* (Norris and Raines 1998). Along the way, FUCAs continued to absorb useful ingredients and synthesize them into more complex, versatile, and effective macromolecules, including more complex proteins and RNAs. During this phase, FUCAs may have also continued to absorb other (sub-)cellular components from other vesicles and integrate them into more tightly regulated cellular components.

For this phase, a tight coupling of survival and replication might not hold any selective advantage. Indeed, the opposite might have been true: being more promiscuous means more flexibility and provides a protocell with significant advantage for survival. It is due to this key dynamics rather than HGT alone that FUCAs did not have a genealogical history, but only a physical–chemical one (Woese 1998, 2002; Koonin 2014a, b; Fournier et al. 2015).

Within the original population of FUCAs, each FUCA protocell competed against each other. After a period during which survival and replication coevolved with each other, some of the FUCAs eventually became protocells in which survival and replication are more tightly coupled and smoothly regulated. Protocells with a tighter coupling and smoother regulation of division and replication would come to enjoy an enormous advantage over those protocells without, and these protocells eventually became the LUCA.

Along the way, many genetic elements were selected out from FUCAs and LUCA, and those genetic elements that were left out became the first batch of genetic parasites or mobile genetic elements (MGEs), and the inevitable arms race between hosts and genetic parasites was on (Koonin et al. 2017).

Due to the promiscuous origin of FUCAs and hence LUCA, more likely than not, LUCA most likely had been a "totipotent" cell that is capable of living with quite different environments (Liepe et al. 1999; Doolittle 2014; Koga 2014). Later on, when the same population of LUCA moved into two different niches, the two subpopulations of LUCA subsequently became the two primary domains of Bacteria and Archaea.[2]

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[2] The "two primary domains" thesis after LUCA is now a near consensus (e.g., Lombard et al. 2012; Koonin 2014a; López-García and Moreira 2015; Williams et al. 2015; Spang et al. 2015; Dacks et al. 2016; Eme et al. 2017).

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