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Is LUCA a thermophilic progenote?

To the Editor — We wish to comment on several claims made in the paper by Weiss *et al.*[1], which describes a genomic analysis that they believe is consistent with the origin of life and emergence of a progenote-like last universal common ancestor (LUCA) in hydrothermal vent conditions. The hydrothermal vent concept was proposed by researchers in the 1980s as an ocean would have been the dominant aqueous medium on the early Earth. Most would also agree that life could not begin in the open ocean because there is no obvious source of free energy to drive energetically uphill processes, so when the vent idea was first proposed it was welcomed[2]. The vents provide an obvious source of free energy in the form of redox potentials and pH gradients, and their sponge-like mineral structures could potentially serve as compartments. Furthermore, microbial life has adapted to vent conditions, so maybe it began there. Proponents adopted the idea and published numerous papers on the subject in the form of essays (for example, refs 3,4).

The article begins by reinforcing the frequent misconception that the terms 'LUCA' and 'progenote' share the same definition. They do not. Carl Woese and George Fox put forward the hypothesis that LUCA (also known as the cenancestor or most recent common ancestor of all life) was a progenote, which they defined as an organism "still in the process of evolving the relationship between genotype and phenotype"[5]. Fourteen years ago, one of us wrote an entry for the *Encyclopedia of Molecular Biology*[6] discussing the relationship between the progenote and LUCA concepts. The conclusion reached at that time is still valid today: sequence data, including the data presented by Weiss *et al.*, support the idea that LUCA was a prokaryotic cell using nucleic acids as genetic material, 20 genetically encoded amino acids, ribosomes for template-directed protein synthesis, and membranes that allowed for chemiosmotic coupling[7,8]. To consider a cellular organism with these properties as only "half-alive"[1] reflects an uncommon definition of life.

Weiss *et al.* propose a computational scheme that provides a shortcut to identify genes that may have been present in LUCA. This approach is subject to two types of error:

- False positives. The stated criterion[1] for inclusion in the LUCA gene set is that the gene needs to be present in two archaeal and two bacterial groups. From the presented tables, it is clear that orders are considered as distinct groups. The criterion identifies a gene as present in LUCA if a single transdomain transfer occurred before the two 'groups' (that is, orders) in the receiving domain split, or if the transferred gene was subsequently transferred between the two groups. Given that gene transfer within domains occurs more frequently than transfer between domains[9,10], a large number of false positives are expected under the implemented scheme.
- False negatives, which are likely to be an even bigger problem. The authors correctly assume that gene transfer between the domains has occurred. Consequently, many genes that were present in LUCA will not be inferred as present. ATP synthases[11] and aminoacyl-transfer RNA (tRNA) synthetases[12] illustrate this point, because only one out of at least five ATP-synthase subunits was part of the inferred LUCA set[1], and only eight aminoacyl-tRNA synthetases, whereas LUCA appears to have used the full complement of today's genetically encoded amino acids, and had a functional ATPase/ATP synthase.

The consequence of these errors is that the inferred LUCA gene set is strongly biased toward genes that have a limited distribution and utility in today's organisms. An enzyme that is used by most organisms today is more likely to have been successfully transferred between archaea and bacteria than a gene with limited distribution. Consequently, a bias in favour of enzymes used only in extreme thermophiles is expected if these were transferred between the domains and, subsequently, between orders of thermophiles within the same domain. Given these caveats, the findings reported by Weiss *et al.* should be considered a preliminary and strongly biased list of genes possibly present in LUCA. We also note that a hyperthermophilic LUCA is in conflict with the analysis of nucleotide and amino acid composition of reconstructed ancestral sequences[13].

Weiss *et al.* not only propose that LUCA could have originated in hydrothermal vents, but also suggest that this represents the origin of life. To support their view, they drew a cell-sized compartment bound by a mineral membrane with an underlying lipid bilayer added to provide a permeability barrier to ions such as Na^+ and H^+. An obvious question is the source of the lipid that forms the membrane, and the process by which it would adhere to the mineral surface. There is no experimental evidence supporting the possibility that lipid bilayers can assemble in sea water and coat a mineral surface. The mineral membrane is drawn with pores to accommodate ion flux, and is shown as approximately the same thickness as the bilayer. Both the size of the compartment and the thickness of the membrane are misleading. In alkaline hydrothermal vents, the compartments have dimensions of hundreds of micrometres, much larger than typical cells, and the walls of the compartments are tens of micrometres thick[14], several thousand times thicker than a 5 nm bilayer. The drawing includes an ATP synthase and a sodium–proton exchange mechanism embedded in the bilayer. The authors propose that these generate a sodium ion gradient required to drive chemiosmotic synthesis of ATP. The claim that chemiosmosis can occur in a mineral compartment has been recently challenged[15]. Various metabolic pathways and associated enzymes are also contained in the compartment. These biochemical systems and catalysts are characteristic of an advanced form of life having ribosomes, translation, genes and a genetic code, far beyond what most would imagine as the first form of life.

The paper by Weiss *et al.* has merit as a preliminary but biased screen of genomic information related to evolution of LUCA, and for interesting speculations that might guide experimental testing. We hope that in the future, the authors will propose feasible experiments that will either support or falsify their conjecture about the origin of life in hydrothermal vents. ❐

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Johann Peter Gogarten[1] and David Deamer[2]
[1]University of Connecticut, Storrs, Connecticut 06269-3125, USA. [2]University of California, Santa Cruz, California 95064, USA.
e-mail: deamer@soe.ucsc.edu