COMMENTARY

The Semi-Enzymatic Origin of Metabolic Pathways: Inferring a Very Early Stage of the Evolution of Life

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Abstract

The early evolution of life is a period with many important events with a lot of big and open questions. One of them is the evolution of metabolic pathways, which means the origin and assembly of enzymes that act together. The retrograde hypothesis was the first attempt to explain the origin and evolutionary history of metabolic pathways; Norman Horowitz developed this first significant hypothesis. This idea was followed by relevant proposals developed by Sam Granick, who proposed the "forward direction hypothesis," and then the successful idea of "Patchwork" assembly proposed independently by Martynas Yčas and Roy Jensen. Since then, a few new hypotheses were proposed; one of the most influential was made by Antonio Lazcano and Stanley Miller in the Journal Molecular Evolution, the "semi-enzymatic origin" of metabolic pathways. This article was cited more than 160 times, including in most papers published about the early evolution of metabolism, placing it as influential work in the field. The ideas proposed in this work and their effects on studying the origin and early evolution of life are analyzed.

The origin of metabolic pathways is one of the most significant events in the early evolution of life, and it is also one of the most exciting and challenging questions in evolution and biology. This research field has been of interest to several researchers since the beginning of the last century. The first coherent hypothesis about this subject was proposed in 1945 by Norman Horowitz (Horowitz 1945); since then, a larger number of works have been published. However, fundamental ideas or hypotheses that have managed to set the course of research are few. These transcending ideas can be found by Sam Granick, who proposed the "forward direction hypothesis" in the 1950s, the successful idea of "Patchwork" assembly proposed independently by Martynas Yčas (Yčas 1974) and Roy Jensen (Jensen 1976), and the proposal made by Antonio Lazcano and Stanley Miller 21 years ago in the Journal Molecular Evolution (Lazcano and Miller 1999), the "semi-enzymatic origin" of metabolic pathways. This

approach proposes that the origin of simple metabolic-like routes produced crucial components required by primordial living entities. These routes were based upon the preponderance of non-enzymatic or semi-enzymatic autocatalytic processes that later became fine-tuned as ribozyme-mediated and protein-based enzymatic metabolic pathways.

The following lines review the ideas proposed in this latter work and analyze its influence on studying the origin and early evolution of life.

Metabolism First?

It is hard to find a characterization of life that does not include metabolism and replication, and these are undoubtedly two essential features of living things. However, knowing which of the two occurred first from the origin of life has led us to another chicken-egg problem, dividing the researchers of life's origin into two blocks. The problem lies in the definition of metabolism and the bias of the concept used. The very open suggestion that chemical cycles from primitive Earth led to networks of reactions, should be considered a type of metabolism and opens up the possibility of locating these events before the origin of life. Since

Yčas (Yčas 1955) suggested that these are non-organismal cycles, the metabolism-first idea has become an active and proliferating research line. That has caught the attention of most chemists and physicists interested in the origin of life. Also, autocatalytic cycles were proposed as a crucial part of the origin of life. Theoretical approaches, such as the "Chemoton" by Gánti (Gánti 2003) say that a hypothetical protocell owns three properties or systems: (1) an autocatalytic network for metabolism; (2) a lipid bilayer structure; and, (3) replicating machinery, conferring to this unit of life, the possibility to evolve by natural selection. The Chemoton model has contributed to the discussion of the origin of life, and it is well accepted in the circle of geochemists, where it is considered an important idea that opens up theoretical and philosophical debate. The autopoiesis by Maturana and Varela (Varela and Maturana 1973) is an idea that targets the living condition of a system capable of reproducing and maintaining itself. Both of the above mentioned situate metabolism at the core of life (Peretó 2012).

In the last decades, a series of influential theories highlighting the role of metabolism in life's origin were produced. Freeman Dyson proposed a statistical model that describes the transition from disorder to order in a small population (islands) of mutually catalytic molecules. The evolution occurs initially by random genetic drift only as of the primary process in life's origin (Dyson 1982, 1999). Stuart Kauffman is recognized for proposing that biological complex systems are the result of self-organization. He also proposed a hypothesis where the emergence of self-replicating systems may be a self-organizing collective property of critically complex protein systems in prebiotic evolution. In other words, he suggests that the collective autocatalytic sets (CAS) originated first, relative to template replication of an RNA-like molecule (Kauffman 1971, 1986, 1993). Wächtershäuser proposed a protometabolism, an autocatalytic carbon fixation process, where pyrite formation was the first energy source for life. This process was mediated by transition metal complexes driven by the electrons obtained from H_2S and FeS (Wächtershäuser 1988, 1990).

Perhaps the most representative idea in the line of "metabolism first" was made by Harold J. Morowitz, who proposed the Reductive Tricarboxylic Acid Cycle (rTCA) as the primordial metabolic core. This elemental cycle develops radially, adding successive layers of complexity to the original basic version (Morowitz 1999). Similar ideas have been proposed by Robert Shapiro (Shapiro 2000) and Lindahl (Lindahl 2004). As an alternative, Martin and Russell suggest the emergence of reaction networks leading from CO or CO_2 to the production of organic molecules essential to life, where non-enzymatic synthesis of acetate from CO_2 takes place (today it is made through the Wood–Ljungdahl pathway). Their model is for systems located in primitive hydrothermal vents and raises critical energetic roles for H_2, catalysis by transition metals, and serpentinization (Martin and Russell 2003).

Despite the importance of this area, it also has raised a series of critiques and problems that are difficult to overcome to this day. As Anet mentions in his critical analysis (Anet 2004), the metabolism-first theories do not seem robust. In conjunction with the non-precise term of "metabolism" used by the proponents of this approach, the theories that suggested that metabolism precedes replication challenge the severe problem that Lazcano and Miller visualized in 1999. And that one is: "such schemes need to explain how a genetic system could arise from such metabolic systems so that Darwinian evolution could take over."

Unlike the origin of life, the early evolution of metabolic pathways has directly benefited from the development of genomics and molecular evolution. Since the publication of Lazcano's and Miller's article (Lazcano and Miller 1999), more than 40,000 genomes have been completely sequenced (Genomes onLine Databases, GOLD). Thanks to this significant increase and the development of tools to compare the complete sequences of prokaryotic and eukaryotic genomes, it is possible to study the origin and evolution of metabolism. The different hypotheses on the origin of metabolism are related to a greater or lesser degree, with gene duplication, a crucial mechanism for the generation of genomic complexity (Fani 2012; Innan and Kondrashov 2010). The study of gene evolution related to the evolution of contemporary metabolic pathways has generated a series of works that have allowed us to elucidate some aspects of its assembly processes. Even models of how cellularity and metabolism coevolve in response to early environmental conditions (Takagi et al. 2020) contributed to this dilemma, but not about its primordial origin. As Lazcano and Miller wrote: "the origin of metabolic pathways lies closer to the origin of life than to the last common ancestor" (Lazcano and Miller 1999). Hence, studying the origin and evolution of contemporary metabolic pathways gives limited knowledge about the process near the beginning of life. It is important to remember that life's origin is not discernible only by phylogenomic analysis. This is because comparative genomics cannot be extended beyond a threshold that corresponds to a period of evolution in which protein biosynthesis already evolved (Becerra et al. 2007, 2014; Lazcano 2010). This does not mean that we cannot use the crucial top-down reconstruction; it is just a reminder that we need to be careful when we extrapolate and infer from contemporary metabolism to very early life stages. As many authors have mentioned, and Goldford and Segrè (2018) explain, there is "a massive gap in knowledge regarding the transition from prebiotic geochemical processes to the biochemical complexity of LUCA."

Horowitz, Granick and the Patchwork Hypotheses

Current proposals about the origin of metabolic pathways argue: (i) how the reaction chains were assembled; (ii) where the substrates are obtained; and (iii) how enzymes are recruited (Fani and Fondi 2009; Fani 2012; Scossa and Fernie 2020). The retrograde hypothesis was the first organized attempt to explain the origin and evolutionary history of metabolic pathways; Horowitz proposed it in 1945 and is described as retrograde evolution. That means the pathways were built up backward, step at a time, in the forward direction using intermediates present in the prebiotic conditions (Horowitz 1945). In addition to being the first hypothesis with an evolutionary perspective where natural selection is part of the explanation for the origin of metabolic pathways, in his proposal, Horowitz manages to connect the processes of prebiotic chemistry and the assembly of the first metabolisms. This idea allowed years later to open a research line, where the sequences of the proteins involved in metabolic pathways, could be analyzed to infer their evolutionary process (Falkowski 1997; Benner et al. 2002; Kacar et al. 2017). Unfortunately, very few results have been found that support this hypothesis (Díaz-Mejía et al. 2007; Light and Kraulis 2004; Wilmanns et al. 1991). Some results only show two homologous enzymes catalyzing subsequent and regressive steps (Mayans et al. 2002). For example, in histidine biosynthesis, where the prebiotic formation and accumulation of intermediates is improbable (Alifano et al. 1996). Therefore, this hypothesis in historical terms is one of the most important but not the most supported, nor the one that seems to explain this evolutionary phenomenon best.

The Granick hypothesis suggests that the expansion of biosynthetic pathways assembled in the forward direction, where the prebiotic compounds do not perform a significant role (Granick 1957). The less-known "forward pathway evolution" proposal has more important implications than can be seen at first glance, since it is not just a forward version of Horowitz's proposal. Just as Noda-Garcia and collaborators mentioned (Noda-Garcia et al. 2018), the evolution of metabolism includes not only the appearance of enzymes but the emergence of new metabolites. This idea is an essential aspect in the proposal from Granick. Some work that supports this proposal include in polyamine biosynthesis (Minguet et al. 2008), in bacteriochlorophyll biosynthesis (Bryant et al. 2012), and in isoprene lipid pathway (Ourisson and Nakatani 1994). These are examples that can be interpreted as a Granick-type assembly. However, these examples are isolated and are far from being used to generalize this process.

The patchwork assembly hypothesis is an impressive idea proposed independently by Yčas in 1974 (Yčas 1974)

and Jensen in 1976 (Jensen 1976). The biosynthetic pathways result from the serial recruitment of promiscuous enzymes endowed with broad catalytic specificity that could react in different steps and routes. Today with a large collection of genome data available, several works that have been published support this process as one of the most important in the evolution of metabolic pathways. However, as Lazcano and Miller stated, patchwork recruitment could operate only after the emergence of protein biosynthesis and enzymes' development. Therefore, although it is a successful approach to understand the assembly process of various metabolic pathways, it is clear that it cannot be applied to all routes, nor all the steps. That can also not be the process that existed in stages close to the origin of life. It can only locate it very early in the time of the Last Common Ancestor of life (LCA) (Lazcano and Miller 1999; Becerra et al. 2007).

The Semi-Enzymatic Origin of Metabolic Pathways

This idea of a semi-enzymatic origin for metabolic pathways proposes that the origin of simple metabolic-like pathways produced crucial components required by primordial living entities. These pathways were originally non-enzymatic or semi-enzymatic autocatalytic processes that later became fine-tuned as ribozyme-mediated and protein-based enzymatic metabolic routes (Lazcano and Miller 1999; Delaye and Lazcano 2005). Lazcano and Miller based their scheme on the following four postulates: (1) A collection of rather stable prebiotic compounds was available in primitive ponds; (2) Due to leakage from existing pathways within cells, several compounds were also available. These compounds need not be remarkably stable because they are produced within the cell and used rapidly; (3) Existing enzyme types are assumed to be available from gene duplication, and they were non-specific; (4) Starter-type enzymes are assumed to arise by non-enzymatic reactions followed by the acquisition of the enzyme (Lazcano and Miller 1999; Fani and Fondi 2009). The authors notice that although enzymes mediate most of the metabolic reactions, some occur spontaneously, and the chemical step can also happen by changing the reaction conditions in the enzyme's non-existence.

One of the most important contributions from this proposition is enabling a bridge between prebiotic chemistry and early enzymatic reactions. Most known prebiotic reactions are different from current metabolic pathways, but there are some similarities between these two constructs, the abiotic processes and extant biosynthetic routes. Examples of these similarities can be seen in riboflavin synthesis, purine de novo biosynthesis, the synthesis of orotic acid from aspartic acid and urea, the reductive amination

of 2-oxoglutarate to produce glutamate, UV-light-induced cyclisation of d-aminolevulinic acid to yield pyrrole, and others (Costanzo et al. 2007; Eschenmoser and Loewenthal 1992; Lazcano 2010; Peretó 2012). The important thing in all of these examples is that they show us that some steps that are similar to those that occur today can be carried out in the absence of enzymes, as in the case of synthesis of imidazole glycerol phosphate (IGP) in bacteria, where the reaction is catalyzed by IGP synthase that is a heterodimer formed by the *hisH* and *hisF* enzymes (Fig. 1). Interestingly enough, the synthesis of IGP can also occur *in vitro* when there is a lack of the *hisH* protein under a high concentration of NH_4 (Smith and Ames 1964). Furthermore, the reaction can also take place *in vivo* in the *Klebsiella pneumoniae*, without the enzyme and high concentrations of NH_4 (Rieders et al. 1994; Vázquez-Salazar et al. 2018). All these examples support the proposal that the metabolic routes that precede the current ones could exist with a smaller number of enzymes, using semi-enzymatic activity, and by the presence of multifunctional generalist enzymes (the patchwork assembly).

These two main axes form the basis of the proposal made by Lazcano and Miller in their article in the Journal Molecular evolution in 1999. However, there are two more aspects to highlight in that, first, their proposal allows us to return to the early stages of the evolution of life, closer to the LCA time. They warn us: it is not only a direct extrapolation, where the contemporary metabolic routes are derived from prebiotic pathways and differ primarily by enzymes' assistance, as suggested by previous works (de Duve 1991; Degani and Halmann 1967; Hartman 1975; Morowitz 1992). Second, as Noda-Garcia et al. noticed, the ideas of the patchwork model proposed earlier by Jensen and Yčas,

were formalized primarily by Lazcano and Miller in this remarkable paper.

Current Status

Because of the explosion of genomic data, together with the metabolic information available and the collaboration between biologists and chemists, the field of primordial metabolism has had a new spark in recent years. This can be reflected in the large amount of research and new ideas around this research field. As an example, the computational network expansion algorithm simulates a biochemical network's increase by iteratively adding to an initial set of compounds (Goldford et al. 2017, 2019). They assert that quantitative modeling of more extensive networks can provide substantial new insights into the origin of life. Their model generates a proto-metabolic network organo-sulfur-based fueled by a thioester- and redox-driven variant of the reductive TCA cycle, capable of producing lipids and keto acids (Goldford and Segrè 2018). Rogier Braakman and Eric Smith proposed a fascinating hypothesis; based on a novel method that integrates metabolic and phylogenetic constraints; they infer a primordial metabolism where the carbon fixation pathways were at the core.

Moreover, Braakman and Smith suggest coevolution of cofactor functions with an increasingly complex universal metabolic pathway, proposing an important role of cofactors in the first ability to synthesize RNA (Braakman and Smith 2012, 2014). Joseph Moran and collaborators infer from their results that some catalyzed biological reactions and, sometimes, entire biochemical pathways may have had fully prebiotic precursors relying on non-enzymatic catalysts (Muchowska et al. 2017, 2019). As an argument that this
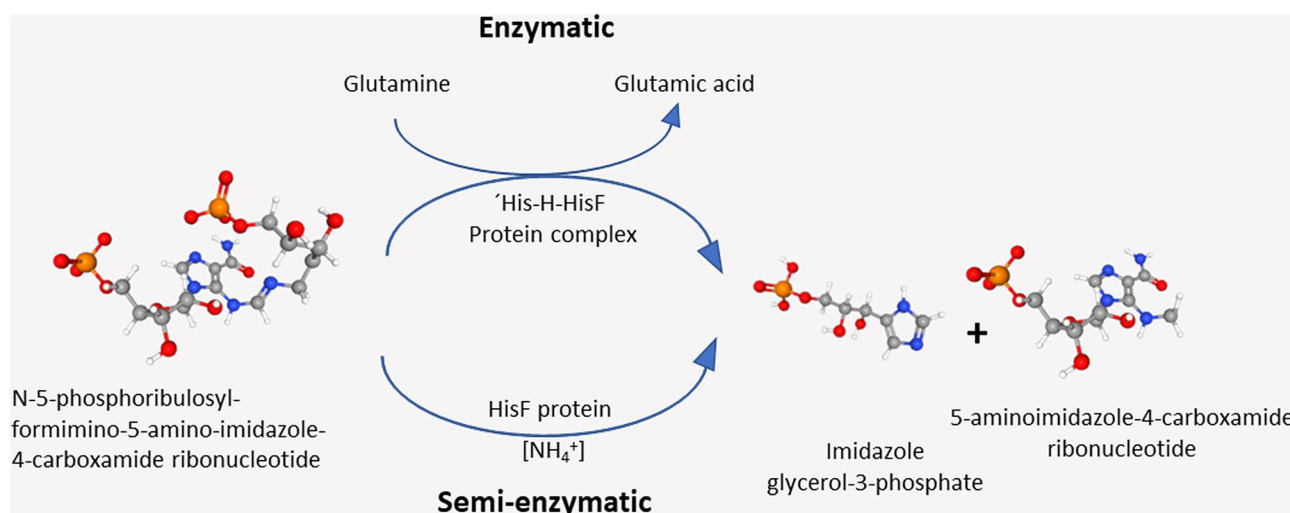

Fig. 1 Enzymatic and non-enzymatic incorporation of nitrogen to N^1-5′-phospho-ribulosylformimino-5-aminoimidazole-4-carboaxamide ribotide to produce IGP. (modified from Lazcano and Miller 1999)

option is plausible, the same group remarkably shows that a large part of the steps that make up the reverse tricarboxylic acid (rTCA) cycle, or the reverse Krebs cycle, can be catalyzed without enzymes, where the reaction occurs with metals as Zn^{2+}, Cr^{3+} and Fe^0 in an acidic aqueous solution (Muchowska et al. 2017). Some models approach very early stages of evolution. They propose moments of chemical evolution or even earlier stages, when polymer sequence diversity was generated and selected by the function in hydration-dehydration cycles (Walker et al. 2012). This list of research is incomplete and superficial, but it is only intended to demonstrate that this research area is extraordinarily vigorous and expanding. For instance, this year and during the time this paper was written, exciting publications in the field appeared in the literature. A very dynamic team from ELSI and other research centers present a continuous reaction network that generates compounds that can lead to RNA synthesis (Yi et al. 2020). Also, an approach of computational systems chemistry was used by Andersen and collaborators to explore large chemical reaction networks on the vast space of plausible prebiotic scenarios (Andersen et al. 2017). Moreover, Moran and collaborators published an important review of non-enzymatic metabolic reactions related to the origin of life (Muchowska et al. 2020). This significant development is partly due to biological (genomic and biochemical) development, geochemical data, and computer tools in combination. However, above all, it is in the legacy of work that laid the theoretical foundations for the field, where the article written by Antonio Lazcano and Stanley Miller in this journal occupies a prominent place.

Compliance with Ethical Standards

Conflict of interest The author declares that there is no conflict of interest.

References

Alifano P, Fani R, Lio P, Lio L, Lazcano A, Bazzicalupo M, Carlomagno MS, Bruni CB (1996) Histidine biosynthetic pathway and genes: structure, regulation, and evolution. Microbiol Rev 60(1):44–69

Andersen JL, Flamm C, Merkle D, Stadler PF (2017) An intermediate level of abstraction for computational systems chemistry. Phil Trans R Soc A 375:20160354. https://doi.org/10.1098/rsta.2016.0354

Anet FAL (2004) The place of metabolism in the origin of life. Curr Opin Chem Biol 8:654–659. https://doi.org/10.1016/j.cbpa.2004.10.005

Becerra A, Delaye L, Islas S, Lazcano A (2007) the very early stages of biological evolution and the nature of the last common ancestor of the three major cell domains. Ann Rev Ecol Evol Syst 38(1):361–379. https://doi.org/10.1146/annurev.ecolsys.38.091206.095825

Becerra A, Rivas M, García-Ferris C, Lazcano A, Peretó J (2014) A phylogenetic approach to the early evolution of autotrophy: the case of the reverse TCA and the reductive acetyl-CoA pathways. Int Microbiol. https://doi.org/10.2436/20.1501.01.211

Braakman R, Smith E (2012) The compositional and evolutionary logic of metabolism. Phys Biol 10(1):011001

Benner SA, Caraco MD, Thomson JM, Gaucher EA (2002) Evolution: planetary biology – Paleontological, geological, and molecular histories of life. Science 296:864. https://doi.org/10.1126/science.1069863

Braakman R, Smith E (2014) Metabolic evolution of a deep-branching hyperthermophilic chemoautotrophic bacterium. PLoS One 9(2):e87950. https://doi.org/10.1371/journal.pone.0087950

Bryant DA, Liu Z, Li T, et al. (2012) Comparative and functional genomics of anoxygenic green bacteria from the taxa chlorobi, chloroflexi, and acidobacteria. In: Burnap R, Vermaas W (eds) functional genomics and evolution of photosynthetic systems. Advances in Photosynthesis and Respiration. Springer, Dordrecht. https://doi.org/https://doi.org/10.1007/978-94-007-1533-2_3

Costanzo G, Saladino R, Crestini C, Ciciriello F, Di Mauro (2007) Formamide as the main building block in the origin of nucleic acids. BMC Evol Biol. https://doi.org/10.1186/1471-2148-7-S2-S1

Delaye L, Lazcano A (2005) Prebiological evolution and the physics of the origin of life. Phys Life Rev 2(1):47–64. https://doi.org/10.1016/j.plrev.2004.12.002

de Duve C (1991) The nature and origin of life. In: Patterson N (ed) Blueprint for a cell. Burlington, NC.

Degani C, Halmann M (1967) Chemical evolution of carbohydrate metabolism. Nature 216:1207. https://doi.org/10.1038/2161207a0

Díaz-Mejía J, Pérez-Rueda E, Segovia L (2007) A network perspective on the evolution of metabolism by gene duplication. Genome Biol 8:R26. https://doi.org/10.1186/gb-2007-8-2-r26

Dyson F (1982) A model for the origin of life. J Mol Evol 18:344–350

Dyson F (1999) Origins of life, revised. New York, Cambridge University Press

Eschenmoser A, Loewenthal E (1992) Chemistry of potentially prebiological natural products. Chem Soc Rev 21(1):1–16. https://doi.org/10.1039/CS9922100001

Falkowski P (1997) Evolution of the nitrogen cycle and its influence on the biological sequestration of CO2 in the ocean. Nature 387:272–275. https://doi.org/10.1038/387272a0

Fani R, Fondi M (2009) Origin and evolution of metabolic pathways. Phys Life Rev 6:23

Fani R (2012) The origin and evolution of metabolic pathways: why and how did primordial cells construct metabolic routes? Evo Edu Outreach 5:367–381. https://doi.org/10.1007/s12052-012-0439-5

Gánti T (2003) The principles of life. Oxford University Press.

Goldford JE, Hartman H, Smith TF, Segrè D (2017) Remnants of an ancient metabolism without phosphate. Cell 168:1126–1134

Goldford JE, Segrè D (2018) Modern views of ancient metabolic networks. Curr Opin Syst Biol. https://doi.org/10.1016/j.coisb.2018.01.004

Goldford JE, Hartman H, Marsland R, Segrè D (2019) Environmental boundary conditions for the origin of life converge to an organosulfur metabolism. Nat Ecol Evol 12:1715–1724. https://doi.org/10.1038/s41559-019-1018-8

Granick S (1957) Speculations on the origins and evolution of photosynthesis. Ann New York Acad Sci 69(2):292–308. https://doi.org/10.1111/j.1749-6632.1957.tb49665.x

Hartman H (1975) Speculations on the origin and evolution of metabolism. J Mol Evol 4(4):359–370

Horowitz NH (1945) On the evolution of biochemical syntheses. PNAS 31(6):153–157. https://doi.org/10.1073/pnas.31.6.153

Innan H, Kondrashov F (2010) The evolution of gene duplications: classifying and distinguishing between models. Nat Rev Genet 11(2):97–108. https://doi.org/10.1038/nrg2689

Jensen RA (1976) Enzyme recruitment in evolution of new function. Annu Rev Microbiol 30:409–425. https://doi.org/10.1146/annurev.mi.30.100176.002205

Kacar B, Guy L, Smith E, Baross J (2017) Resurrecting ancestral genes in bacteria to interpret ancient biosignatures. Phil Trans R Soc A 375:20160352

Kauffman S (1971) Cellular homeostasis, epigenesis and replication in randomly aggregated macromolecular systems. J Cybern 1:71–96

Kauffman S (1986) Autocatalytic sets of proteins. J Theor Biol 119:1–24

Kauffman SA (1993) The origins of order: self-organization and selection in evolution. Oxford University Press, New York

Lazcano A (2010) Which way to life? Orig Life Evol Biosph 40(2):161–167. https://doi.org/10.1007/s11084-010-9195-0

Lazcano A, Miller SL (1999) On the origin of metabolic pathways. J Mol Evol 49(4):424–431. https://doi.org/10.1007/PL00006565

Light S, Kraulis P (2004) Network analysis of metabolic enzyme evolution in Escherichia coli. BMC Bioinfo 5:15. https://doi.org/10.1186/1471-2105-5-15

Lindahl PA (2004) Stepwise evolution of nonliving to living chemical systems. Orig Life Evol Biosph 34(4):371–389. https://doi.org/10.1023/B:ORIG.0000029880.76881.f5

Martin W, Russell MJ (2003) On the origins of cells: a hypothesis for the evolutionary transitions from abiotic geochemistry to chemoautotrophic prokaryotes, and from prokaryotes to nucleated cells. Phil Trans R Soc B 358:59–83. https://doi.org/10.1098/rstb.2002.1183

Mayans O, Ivens A, Nissen LJ, Kirschner K, Wilmanns M (2002) Structural analysis of two enzymes catalysing reverse metabolic reactions implies common ancestry. EMBO J 21:3245–3254. https://doi.org/10.1093/emboj/cdf298

Minguet EG, Vera-Sirera F, Marina A, Carbonell J, Blázquez MA (2008) Evolutionary diversification in polyamine biosynthesis. Mol Biol Evol 25:2119–2128. https://doi.org/10.1093/molbev/msn161

Morowitz H (1992) Beginnings of Life. Yale University Press, New Haven

Morowitz H (1999) A theory of biochemical organization, metabolic pathways, and evolution. Complex 4:39–53. https://doi.org/10.1002/(SICI)1099-0526(199907/08)4:6

Muchowska KB, Varma SJ, Chevallot-Beroux E et al (2017) Metals promote sequences of the reverse Krebs cycle. Nat Ecol Evol 1:1716–1721. https://doi.org/10.1038/s41559-017-0311-7

Muchowska KB, Chevallot-Beroux E, Moran J (2019) Recreating ancient metabolic pathways before enzymes. Bio Med Chem 27:2292–2297. https://doi.org/10.1016/j.bmc.2019.03.012

Muchowska KB, Varma SJ, Moran J (2020) Nonenzymatic metabolic reactions and life's origins. Chem Rev 120(15):7708–7744. https://doi.org/10.1021/acs.chemrev.0c00191

Noda-Garcia L, Liebermeister W, Tawfik DS (2018) Metabolite-enzyme coevolution: from single enzymes to metabolic pathways and networks. Annu Rev Biochem 87:187–216. https://doi.org/10.1146/annurev-biochem-062917-012023

Ourisson G, Nakatani Y (1994) The terpenoid theory of the origin of cellular life: the evolution of terpenoids to cholesterol. Chem Biol 1:11–2. https://doi.org/10.1016/1074-5521(94)90036-1

Peretó J (2012) Out of fuzzy chemistry: from prebiotic chemistry to metabolic networks. Chem Soc Rev 41(16):5394–5403. https://doi.org/10.1039/c2cs35054h

Rieders G, Merricko MJ, Castorphs H, Kleinersn D (1994) Function of hisF and hisH gene products in histidine biosynthesis. J Biol Chem 269:14384–14392

Shapiro R (2000) A replicator was not involved in the origin of life. IUBMB Life 49:173–176. https://doi.org/10.1080/713803621

Smith D, Ames BN (1964) Intermediates in the early steps of histidine biosynthesis. J Biol Chem 239:1848–1855

Scossa F, Fernie AR (2020) The evolution of metabolism: how to test evolutionary hypotheses at the genomic level. Comput Struct Biotechnol J 18:482–500. https://doi.org/10.1016/j.csbj.2020.02.009

Takagi YA, Diep NH, Wexler TB, Goldman AD (2020) The coevolution of cellularity and metabolism following the origin of life. J Mol Evol 88:598–617. https://doi.org/10.1007/s00239-020-09961-1

Vázquez-Salazar A, Becerra A, Lazcano A (2018) Evolutionary convergence in the biosyntheses of the imidazole moieties of histidine and purines. PloS one. https://doi.org/10.1371/journal.pone.0196349

Varela F, Maturana HR (1973) De Máquinas y Seres Vivos: Una teoría sobre la organización biológica. Editorial Universitaria, Chile

Wächtershäuser G (1988) Before enzymes and templates: a theory of surface metabolism. Microbiol Rev 52:452–484

Wächtershäuser G (1990) Evolution of the first metabolic cycles. PNAS 87:200–204. https://doi.org/10.1073/pnas.87.1.200

Walker SI, Grover MA, Hud NV (2012) Universal sequence replication, reversible polymerization and early functional biopolymers: a model for the initiation of prebiotic sequence evolution. PLoS One 7(4):e34166. https://doi.org/10.1371/journal.pone.0034166

Wilmanns M, Jansonius JN, Hyde CC, Davies DR, Kirschner K (1991) structural conservation in parallel β/α-barrel enzymes that catalyze three sequential reactions in the pathway of tryptophan biosynthesis. Biochem 30:9161–9169. https://doi.org/10.1021/bi00102a006

Yčas M (1955) A note on the origin of life. PNAS 1:714–716. https://doi.org/10.1073/pnas.41.10.714

Yčas M (1974) On earlier states of the biochemical system. J Theor Biol 44:145–160. https://doi.org/10.1016/S0022-5193(74)80035-4

Yi R, Tran QP, Ali S, Yoda I, Adam ZR, Cleaves HJ, Fahrenbach AC (2020) A continuous reaction network that produces RNA precursors. Proc Natl Acad Sci USA 16/117:13267–13274. https://doi.org/10.1073/pnas.1922139117