Self-replication: Spelling it out in a chemical background

ARTICLE *in* THEORY IN BIOSCIENCES · DECEMBER 2010

Impact Factor: 1.23 · DOI: 10.1007/s12064-010-0117-5 · Source: PubMed

5 AUTHORS, INCLUDING:

Wentao Ma
Wuhan University
23 PUBLICATIONS **317** CITATIONS
SEE PROFILE

yu Chunwu
9 PUBLICATIONS **77** CITATIONS
SEE PROFILE

Wentao Zhang
Harbin Institute of Technology
31 PUBLICATIONS **334** CITATIONS
SEE PROFILE

Ping Zhou
Wuhan University
15 PUBLICATIONS **140** CITATIONS
SEE PROFILE

Theory Biosci. (2011) 130:119–125
DOI 10.1007/s12064-010-0117-5

ORIGINAL PAPER

Self-replication: spelling it out in a chemical background

Wentao Ma · Chunwu Yu · Wentao Zhang · Ping Zhou · Jiming Hu

Received: 16 December 2007 / Accepted: 6 December 2010 / Published online: 21 December 2010

Abstract Self-replication, an important concept abstracted from reproduction, the key feature of life, remains vague in definition and lacking in clear interpretation in terms of its chemical mechanism. Mentioned frequently in discussions concerning the essence of life and its origin, the vague concept has caused a lot of uncertain statements, confusable references, and malposed debates, and has seriously held back efforts in this field. In this article, we try to improve the situation by a conceptual analysis in a more fundamental and clearer background. Self-replication in the substantial world could not mean anything but that "an entity favors the production of its own." The major chemical mechanism for such favoring is catalysis, which can be classified into speed- and direction-favoring types (the template-directing function is actually a type of direction-favoring catalysis). Molecular self-replication could be based on autocatalysis or self-metabolism; the self-replication of a complex entity could be based on autocatalytic and/or self-metabolic sets, and should involve a mechanism of self-division. This conceptual clarification sheds light on the dim areas concerning the essence of life and its origin.

Keywords Autocatalysis · Catalysis · Metabolism · Replication · Template-directing function

W. Ma (✉)
College of Life Sciences, Wuhan University, Wuhan 430072, People's Republic of China
e-mail: mwt@whu.edu.cn

W. Ma
State Key Laboratory of Software Engineering, Wuhan University, Wuhan 430072, People's Republic of China

C. Yu · W. Zhang
College of Computer Sciences, Wuhan University, Wuhan 430072, People's Republic of China

P. Zhou · J. Hu
College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, People's Republic of China

Introduction

Reproduction is a feature characterizing all forms of life on earth. Furthermore, it is a prerequisite for another key feature of life, Darwinian evolution (Luisi 1998). Thus, it is a necessary feature of the life phenomenon. Because sexual reproduction is usually believed to be a result of long-term evolution, people who are interested in the essence of life and its origin focus their attentions on "self-reproduction," or "self-replication," a term more frequently used in the field.

How can an entity self-replicate? And what is the earliest form of self-replication in the origin of life? To address such questions, much effort has been focused on molecular self-replication (Joyce 1987; Orgel 1992; Bag and Von Kiedrowski 1996; Wintner and Rebek 1996; Robertson et al. 2000), compartment-associated self-replication (Bachmann et al. 1992; Szostak et al. 2001; Oberholzer and Luisi 2002; Hanczyc et al. 2003; Rasmussen et al. 2004), and the role of metabolism (Shapiro 2000; Pross 2004; Anet 2004).

However, to date, knowledge regarding the principle of self-replication is limited (Paul and Joyce 2003). Even the term 'self-replication' has been used without a consistent meaning. This situation could be reflected by our blurry comprehension of the essential relationships between some important concepts, such as "catalysis and template-directing function," "autocatalysis and self-replication,"

and "metabolism and replication." Such a poor conceptual system has seriously held back efforts to understand the essence of life and its origin. In this article, we would like to address the problem through a conceptual discussion, starting from "reconstructing" the concept of self-replication, by getting to its most basic meaning, and then directing the analysis to the fundamentally chemical background that is the essence of the problem.

The meaning of self-replication: favoring production of its own

Self-replication is an abstract concept. Literally, it means that an entity could replicate by itself. Research on virtual self-replication, usually belonging to the field of artificial life (Sipper 1998; Reggia et al. 1998; Sipper et al. 2001), has focused on virtual rules that may lead to the action of self-replication. However, here, we are interested in self-replication in the substantial world. In the substantial world, it is impossible for an entity to replicate completely out of the void. The "offspring" of the entity must be formed from some other substance. Thus, a self-replicating entity could not be other than "an entity favoring its own formation" (i.e., the formation of entities of its own kind). It is possible that the formation of the "offspring" is simply the assembly of its components, involving no chemical process, such as the formation of liposomes (Oberholzer and Luisi 2002). However, a major and much more significant scene of self-replication in the substantial world involves chemical processes. Thus, we prefer to say that a self-replicating entity is "an entity favoring its own production," and any entity favoring its own production could be viewed as a self-replicating one.

So, how could an entity favor its own production? First, let us consider how the production of substance could be favored, pointing at once to a chemical mechanism, catalysis.

Catalysis: speeding or directing chemical processes

Catalysis can favor the production of substance in a chemical process, usually by speeding the chemical process (Coontz et al. 2003). However, though rarely explicitly stated, catalysis may also favor the production of substance by *directing* a chemical process. If we call the former speed-favoring catalysis, then the latter is direction-favoring catalysis.

Let us examine a simple model. Suppose there is a reactive system with two reactants, A and B, and the only possible product is C. If a substance M could speed the reaction, it would be a speed-favoring catalyst. Then, suppose the reactants are still A and B, but the possible products are C or D. Here, we say the reaction has two directions. If there is a substance N that favors one of the two directions, e.g., the one producing C, it would be a direction-favoring catalyst. A well-known example of direction-favoring catalysis is "asymmetric catalysis," also called "enantioselective catalysis," which may favor the production of one enantiomer versus the other (Bolm and Gladysz 2003; Trost 2004; Noyori 2002). In fact, as has long been exploited, direction-favoring catalysis is significant in reducing side-products in the chemical industry.

In the past, "speed-favoring catalysis" and "direction-favoring catalysis" have seldom been explicitly distinguished, because it has not been necessary. Here, we will see that doing so is helpful in understanding different kinds of mechanisms involved in self-replication. First, let us analyze the essence of an important function related to self-replication, the template-directing function.

Template-directing function: a type of direction-favoring catalysis

In previous reports, on the one hand, the template-directing function is usually described separately from catalysis (e.g., Green and Szostak 1992; James and Ellington 1998; Strobel 2001 and most molecular biology textbooks). On the other hand, it has been recognized by some that the template-directing function is actually a special kind of catalysis (Inoue and Orgel 1983; Bag and Von Kiedrowski 1996; Wintner and Rebek 1996; Robertson et al. 2000), though there was little discussion as to where the specialty lies. This may cause confusion. In fact, according to the classification of speed- and direction-favoring catalysis, mentioned above, the template-directing function is simply a type of direction-favoring catalysis.

Suppose that a reactive system comprises four kinds of nucleotides, namely, A, T (U), C, G; there may be an almost infinite number of products, namely, DNA (RNA), of various lengths and sequences. When a template is added into the system, products may become much more uniform; that is, the template-directing function causes selection among the various reactive directions, resulting in the production of a sequence complementary to the template. The template-directing function can work alone, without other catalysis, such as in the non-enzymatic, template-directed formation of polynucleotides (Inoue and Orgel 1983; Joyce 1987; Kozlov and Orgel 2000). Such a template-directing function could also be implemented by analogs of polynucleotides (Joyce 2002; Orgel 2004) and even by molecules without any relation to the biopolymers (Tjivikua et al. 1990; Wintner and Rebek 1996). It is a type of chemical mechanism, direction-favoring catalysis.

In fact, in enzymatic template-directed reactions, such as the in vivo replication of genetic materials (DNA/RNA), their transcription (to mRNA), and even their subsequent translation (to proteins, where some intermediates like tRNA are involved), both the templates and the enzymes are essentially catalysts. The templates perform direction-favoring catalysis, while the enzymes perform speed-favoring catalysis.

Molecular self-replication: autocatalysis (speed-favoring/direction-favoring) or self-metabolism

Now, we return to the question: how can an entity favor its own production? First, let us consider the situation where the self-replicating entity is just a molecule, which is usually called "molecular self-replication." That is, how can a molecule favor its own production (i.e., the production of the molecules of its own kind)?

In nature, a molecule might catalyze its own production, commonly referred to as an "autocatalyst." It is obviously a self-replicating molecule. Meanwhile, it seems that any self-replicating molecule, which could favor its own production by definition above, "should" be able to catalyze its own production, thus being an autocatalyst. Actually, "self-replication" and "autocatalysis" are often used as alternative terms (Orgel 1992; Bag and Von Kiedrowski 1996; Wintner and Rebek 1996; Burmeister 1998; Cousins et al. 2000; Robertson et al. 2000). However, a fundamental consideration based on the mechanism of the chemical reaction may reveal that if a molecule could catalyze the formation of the reactants to produce itself, such as the building blocks of itself or energy carriers to render the production thermodynamically possible, its own production is also favored, then it should also be viewed as a self-replicating molecule. This mechanism, which we would like to term "self-metabolism" here, is in fact a prototype of so-called metabolism in biology. That is to say, molecular self-replication is not equal to autocatalysis; instead, autocatalysis is only a mechanism for molecular self-replication, while self-metabolism is another (though both are based on catalysis).

According to the character of the catalysis involved in, autocatalysis could also be classified as speed-favoring, meaning that the catalyst favors the production of itself by reactive speed (self-speeding). Direction-favoring catalysis, meaning that the catalyst favors the production of itself in the reactive direction, could thus be termed "self-directing." Speed-favoring autocatalysis can be commonly found in chemical research and need not to be exemplified. For an example of the direction-favoring autocatalysis, there is asymmetric autocatalysis (Todd 2002; Mikami and Yamanaka 2003), which leads to the auto-amplification of one of the enantiomers, and may have been responsible for the origin of homochirality in the course of the origin of life (Blackmond 2004). For other examples, the self-replication of polynucleotides through non-enzymatic, template-directed copying (Joyce 1987; Orgel 1992; Kozlov and Orgel 2000), is a direction-favoring autocatalysis, while the self-replication of a replicase ribozyme, supposed to emerge early in the RNA world (Cech 1989; Joyce and Orgel 1999; Bartel 1999; Ma and Yu 2006), which could both serve as a template for its own production and as an enzyme to speed template-directed production, is a combination of direction- *and* speed-favoring autocatalysis. Here, we see that the examples are all related to the origin of life, which further illustrates the necessary and significance of making explicit distinction between direction- and speed-favoring catalysis in this field.

Self-replication of a complex entity: autocatalytic/self-metabolic sets and self-division

Let us consider self-replication of an entity comprising more than one component. First, the production of the components of the entity should be favored by the components also belonging to the entity. Such self-favoring production may be based on "autocatalytic sets," which may include different catalysts catalyzing the production of each other (Eigen and Schuster 1979; Lee et al. 1997; Segre et al. 1998; Kauffman 2000). The result of such "inter-catalysis" is speed- and/or direction-favoring production of every component of the entity. Though seldom described, theoretically, the self-favoring production of components may also be based on "self-metabolic sets," which may include different catalysts catalyzing the formation of reactants (such as building blocks or energy carriers) to produce each other. Life forms on earth, the best examples of complex self-replication, use combinations of the two mechanisms. In an organism, any macromolecule, DNA, RNA, or protein, is synthesized in speed- (enzymatic) and direction-favoring (template-directed) reactions, and the synthesized macromolecule, in turn, serves as a catalyst (enzyme or template) to produce others, resulting in the "autocatalysis" of the whole organism. Meanwhile, the building blocks of the catalysts, such as amino acids and nucleotides, and energy carriers, such as glucose and ATP, are synthesized in catalytic reactions, resulting in the "self-metabolism" of the whole organism.

Second, there should be a mechanism to divide the entity and distribute the over-produced components to form "offspring" entities. Though there may be a transitional form in which division is not relied on by the entity itself, a self-replicating complex entity in the full sense should take care of the division by itself (i.e., self-division, like a cell).

Here an important problem should be mentioned: should a complex self-replicating entity have a boundary, like a cell membrane? First, catalysts in an autocatalytic/self-metabolic set may diffuse away from each other, which may cause the "dilution problem" preventing their cooperation. Second, speed-favoring catalysts in the set and "nutrients" synthesized by metabolic catalysts in the set may be "occupied" or "exploited" by other "species," which may cause the "parasite problem." Thus, a boundary to keep components together and to keep non-components away seems an efficient, if not the only, solution to these problems. Further, with a membranous boundary, the division of the entity becomes easy; it is the result of the division of the membranous vesicle, which is a natural event, especially for the membrane composed of amphiphilic molecules. This provides fundamental conceptual support for research emphasizing the importance of membranous compartmentalization for self-replication (Bachmann et al. 1992; Szostak et al. 2001; Oberholzer and Luisi 2002; Hanczyc et al. 2003; Rasmussen et al. 2004).

Additionally, a complex self-replicating entity may incorporate functional components favoring the production of the entity other than catalysts. For example, construction of a structure to harvest energy (e.g., sunlight) may favor the thermodynamic aspects of the entity's production, and construction of "moving motor" may favor the seeking of raw materials (initial reactants) for the production of the entity.

In a complex self-replicating entity, every component should function to favor self-replication of the entity, or it should be viewed as only a byproduct of the entity. On the other hand, every component's production should be favored by other components, or else it should be viewed only as an environmental factor for the entity.

Conclusions and comments

From the conceptual clarifications presented here, we see that, first, in the substantial world, self-replication must mean a process in which an entity favors the production of its own kind. Second, the major chemical mechanism for such favoring is catalysis, which can be classified into speed- and direction-favoring. Third, the template-directing function, which is often mentioned separately from catalysis, actually belongs to catalysis; it is a type of direction-favoring catalysis. Fourth, the mechanisms of molecular self-replication include autocatalysis, which can also be classified into speed- and direction-favoring, and self-metabolism. Finally, the self-replication of a complex entity can be based on autocatalytic and/or self-metabolic sets, and should involve a mechanism for self-division.

By such clarifications, we reach a clearer understanding of the principle of self-replication. Such an understanding may be helpful in efforts to understand the essence of life and its origin. As a significant example, let us turn to an ongoing debate, "which came first, 'replication' or 'metabolism' in the course of the origin of life?" (Shapiro 2000; Pross 2004; Anet 2004). The debate is a rather blurry one. Even the terms "replication" and "metabolism" have seldom been clearly defined. The situation results largely from our poor comprehension of the underlying concepts and mechanisms, especially those associated with self-replication.

In view of the conceptual clarification above, an inspection of the terms used in the debate (Shapiro 2000; Pross 2004; Anet 2004) reveals that so-called replication actually corresponds to "direction-favoring autocatalysis, based on a template-directing function," which is characterized by direction-favoring catalysis, while so-called metabolism actually corresponds to "speed-favoring autocatalysis and/or self-metabolism," primarily characterized by speed-favoring catalysis.

Let us review the possible ways leading to the emergence of a "proto-cell," with both the features of "replication" and "metabolism" (Fig. 1). Obviously, the final introduction of the template (genome) into the entity is impossible (Fig. 1a), because speed-favoring catalysts seem unlikely to form a closed autocatalytic/self-metabolic set without a template, and even if "they manage to do so," the newly introduced template is rather unlikely to "happen to" choose the reactive directions leading to the production of those speed-favoring catalysts. Thus, this kind of "metabolism first" does not seem possible.

The majority of the "replication first" school believes that the template (genome) emerged in the very beginning and the speed-favoring catalysts were subsequently incorporated stepwise (Fig. 1b). One problem is that no evidence exists for the abundance of building blocks and energy carriers for the synthesis of template molecules (e.g., a prebiotic pool of active nucleotides for the synthesis of primary RNA tends to be assumed rather than supported by evidence (Joyce and Orgel 1999; Orgel 2004)). Another problem is that the efficiency of non-enzymatic template-directed copying of a template (e.g., RNA) (Joyce 1987; Orgel 1992; Kozlov and Orgel 2000) seems to be too low to support the synthesis of a molecule long enough to be able to serve as a speed-favoring catalyst (e.g., ribozyme). The introduction of a replicase ribozyme at a very early stage may be a solution (Cech 1989; Joyce and Orgel 1999; Bartel 1999; Ma and Yu 2006). However, the existence of a replicase ribozyme efficient enough to support the synthesis of an RNA molecule approaching its own length is still problematic.

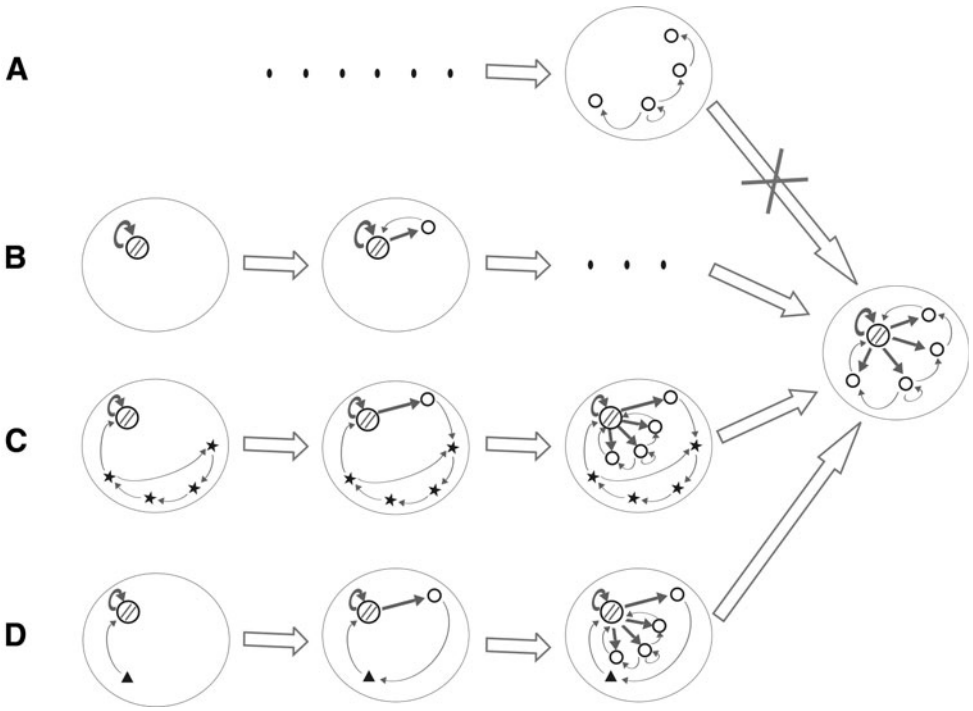

Fig. 1 Potential ways leading to the emergence of a proto-cell with the features of both "replication" and "metabolism." **a** Final introduction of the template is impossible. *Circles* represent catalysts, while the *circle with two parallel lines* represents the template (genome). *Thick arrows* mean direction-favoring catalysis, while *thin arrows* mean speed-favoring catalysis (either direct or by favoring the synthesis of the reactants to produce the component at the head of the arrow). **b** De novo emergence of the template and the subsequent stepwise incorporation of the speed-favoring catalysts to develop metabolism. **c** The primordial metabolism-assisted emergence of the template and the subsequent "metabolic takeover." *Stars* represent components of the primordial "metabolic" set. **d** The primordial independent catalyst-assisted emergence of the template and the subsequent substitution of the primordial catalyst. *Triangles* represent the primordial catalyst

The emergence of the template (genome) may be assisted by a primordial "metabolic" set (Fig. 1c), which is another potential way close to the idea of "metabolism first." A primordial "metabolic" (speed-favoring autocatalytic/self-metabolic) self-replicating entity may emerge first. One (or more) of its components may be a speed-favoring catalyst for the template-directed copying of the template, or may catalyze the production of the precursors (building blocks or energy carriers) of the template as byproducts. Then, the entity with a special template that could direct the synthesis of a speed-favoring catalyst capable of favoring the synthesis of one of the entity's components may win the competition against other entities, leading to the incorporation of the template into the primordial "metabolic" set. Subsequently, via lengthening and mutation of the template, more speed-favoring catalysts directed by the template may be incorporated, which may form a secondary "metabolic" set more efficient than the primordial one to favor the self-replication of the entity. The primordial "metabolic" set may then disappear, due to its low efficiency, which may be called a "metabolic takeover." The problem is that the existence of the primordial "metabolic" set seems to be problematic (Orgel 2000; Anet 2004).

In fact, the emergence of the template (genome) may also be assisted by one (or more) independent primordial catalysts (Fig. 1d), if the catalyst is sufficiently abundant in the prebiotic environment. Subsequently, the production of the primordial catalyst may be favored by a speed-favoring catalyst directed by the template. Finally, the function of the primordial catalyst may be substituted (or partially substituted) by that of other more efficient catalysts directed by the template. Recently, there have been reports supporting that the synthesis of building blocks of polynucleotides (Versees et al. 2004) and the template-directed synthesis of the polynucleotide itself (Jain et al. 2004) may be favored by non-enzymatic catalysts, which may be possible candidates for such primordial catalysts. This way, satisfying the idea of "replication first," but involving one (or more) independent primordial catalysts, seems to be the most likely way eventually leading to a proto-cell, with the features of both "replication" and "metabolism."

As mentioned in the beginning of this article, reproduction is a prerequisite for Darwinian evolution. Now that

we have illustrated explicitly the principle of self-replication in a chemical background, a subsequent question of interest is related to the principle of Darwinian evolution; what kind of self-replicating entity could undergo Darwinian evolution in the context of its explicit chemical mechanisms? The question is of great significance and represents a further step towards the core of the essence of life and its origin, especially when we note those efforts to define life as a chemical system capable of undergoing Darwinian evolution (Luisi 1998; Ruiz-Mirazo et al. 2004). Discussion on the question may be included in another article.

Szathmary and Smith proposed that replication and reproduction should be distinguished, and that the origin of life is a process of transition from replicators to reproducers (Szathmary and Smith 1997; Szathmary 2006). The replicators correspond to self-replicating molecules, and the reproducers correspond to complex, self-replicating entities. Further, they classified replicators based on their variational properties, and pointed out only replicators with "unlimited heredity" could undergo real Darwinian evolution (Szathmary and Smith 1997; Szathmary 2000). The replicators with "unlimited heredity" correspond here to self-replicating molecules involving template-directing functions. Such concept-creation is helpful in analyzing the essence of life and its origin. However, efforts to understand in depth the principle of the core concept, "self-replication" are at least as important, as in this article.

Overall, concepts in the field concerning the essence of life and its origin seem to be more blurred in meaning and confusedly used than in other areas. Clarifying these concepts is an arduous job, but is significant. We believe a clear conceptual context is important in scientific research, especially helpful in clarifying those debates seeming intractable and in illustrating rules underlying those phenomena appearing intricate.

Acknowledgments Financial support from the National Natural Science Foundation of China (No. 30870660), the National 973 Fundamental Research Program (No. 2010CB530500, No. 2010CB530503), Hubei Natural Science Foundation of China (No. 2003S2113), and the State Key Laboratory of Software Engineering in Wuhan University (No. SKLSE01) is gratefully acknowledged.

References

Anet FA (2004) The place of metabolism in the origin of life. Curr Opin Chem Biol 8:654–659

Bachmann PA, Luisi PL, Lang J (1992) Autocatalytic self-replicating micelles as models for prebiotic structures. Nature 357:57–59

Bag BG, Von Kiedrowski G (1996) Templates, autocatalysis and molecular replication. Pure Appl Chem 68:2145–2152

Bartel DP (1999) Re-creating an RNA replicase. In: Gesteland RF, Cech TR, Atkins JF (eds) The RNA world. Cold Spring Harbor Laboratory Press, New York, pp 143–162

Blackmond DG (2004) Asymmetric autocatalysis and its implications for the origin of homochirality. Proc Natl Acad Sci USA 101:5732–5736

Bolm C, Gladysz JA (2003) Introduction: enantioselective catalysis. Chem Rev 103:2761–2762

Burmeister J (1998) Self-replication and autocatalysis. In: Brack A (ed) The molecular origins of life: assembling pieces of the puzzle. Cambridge University Press, Cambridge, pp 295–311

Cech TR (1989) RNA chemistry—ribozyme self-replication. Nature 339:507–508

Coontz R, Fahrenkamp-Uppenbrink J, Szuromi P (2003) Speeding chemistry along—introduction. Science 299:1683–1706

Cousins GRL, Poulsen SA, Sanders JKM (2000) Molecular evolution: dynamic combinatorial libraries, autocatalytic networks and the quest for molecular function. Curr Opin Chem Biol 4: 270–279

Eigen M, Schuster P (1979) The hypercycle: a principle of natural self-organization. Springer, Berlin

Green R, Szostak JW (1992) Selection of a ribozyme that functions as a superior template in a self-copying reaction. Science 258: 1910–1915

Hanczyc MM, Fujikawa SM, Szostak JW (2003) Experimental models of primitive cellular compartments: encapsulation, growth, and division. Science 302:618–622

Inoue T, Orgel LE (1983) A non-enzymatic RNA-polymerase model. Science 219:859–862

Jain SS, Anet FAL, Stahle CJ, Hud NV (2004) Enzymatic behavior by intercalating molecules in a template-directed ligation reaction. Angew Chem Int Ed 43:2004–2008

James KD, Ellington AD (1998) The endogenous synthesis of organic Compound. In: Brack A (ed) The molecular origins of life: assembling pieces of the puzzle. Cambridge University Press, Cambridge, pp 269–294

Joyce GF (1987) Non-enzymatic template-directed synthesis of informational macromolecules. Cold Spring Harbor Symp Quant Biol 52:41–51

Joyce GF (2002) The antiquity of RNA-based evolution. Nature 418: 214–221

Joyce GF, Orgel LE (1999) Prospects for understanding the origin of the RNA World. In: Gesteland RF, Cech TR, Atkins JF (eds) The RNA world. Cold Spring Harbor Laboratory Press, New York, pp 49–77

Kauffman S (2000) Investigations. Oxford University Press, Oxford

Kozlov IA, Orgel LE (2000) Nonenzymatic template-directed synthesis of RNA from monomers. Mol Biol 34:781–789

Lee DH, Severin K, Ghadiri MR (1997) Autocatalytic networks: the transition from molecular self-replication to molecular ecosystems. Curr Opin Chem Biol 1:491–496

Luisi PL (1998) About various definitions of life. Orig Life Evol Biosph 28:613–622

Ma WT, Yu CW (2006) Intramolecular RNA replicase: possibly the first self-replicating molecule in the RNA world. Orig Life Evol Biosph 36:413–420

Mikami K, Yamanaka M (2003) Symmetry breaking in asymmetric catalysis: racemic catalysis to autocatalysis. Chem Rev 103: 3369–3400

Noyori R (2002) Asymmetric catalysis: science and opportunities (Nobel lecture). Angew Chem Int Ed 41:2008–2022

Oberholzer T, Luisi PL (2002) The use of liposomes for constructing cell models. J Biol Phys 28:733–744

Orgel LE (1992) Molecular replication. Nature 358:203–209

Orgel LE (2000) Self-organizing biochemical cycles. Proc Natl Acad Sci USA 97:12503–12507

Orgel LE (2004) Prebiotic chemistry and the origin of the RNA World. Crit Rev Biochem Mol Biol 39:99–123

Paul N, Joyce GF (2003) Self-replication. Curr Biol 13:R46

Pross A (2004) Causation and the origin of Life. Metabolism or replication First? Orig Life Evol Biosph 34:307–321
Rasmussen S, Chen LH, Stadler BMR, Stadler PF (2004) Proto-organism kinetics: evolutionary dynamics of lipid aggregates with genes and metabolism. Orig Life Evol Biosph 34:171–180
Reggia JA, Lohn JD, Chou HH (1998) Self-replicating structures: evolution, emergence, and computation. Artif Life 4:283–302
Robertson A, Sinclair AJ, Philp D (2000) Minimal self-replicating systems. Chem Soc Rev 29:141–152
Ruiz-Mirazo K, Pereto J, Moreno A (2004) A universal definition of life: autonomy and open-ended evolution. Orig Life Evol Biosph 34:323–346
Segre D, Lancet D, Kedem O, Pilpel Y (1998) Graded autocatalysis replication domain (GARD): kinetic analysis of self-replication in mutually catalytic sets. Orig Life Evol Biosph 28:501–514
Shapiro R (2000) A replicator was not involved in the origin of life. IUBMB Life 49:173–176
Sipper M (1998) Fifty years of research on self-replication: an overview. Artif Life 4:237–257
Sipper M, Reggia JA, Emmite D (2001) Go forth and replicate. Sci Am 285:35–43
Strobel SA (2001) Biological catalysis—repopulating the RNA world. Nature 411:1003–1006
Szathmary E (2000) The evolution of replicators. Philos Trans R Soc B Biol Sci 355:1669–1676
Szathmary E (2006) The origin of replicators and reproducers. Philos Trans R Soc B Biol Sci 361:1761–1776
Szathmary E, Smith JM (1997) From replicators to reproducers: the first major transitions leading to life. J Theor Biol 187:555–571
Szostak JW, Bartel DP, Luisi PL (2001) Synthesizing life. Nature 409:387–390
Tjivikua T, Ballester P, Rebek J Jr (1990) A self-replicating system. J Am Chem Soc 112:1249–1250
Todd MH (2002) Asymmetric autocatalysis: product recruitment for the increase in the chiral environment (PRICE). Chem Soc Rev 31:211–222
Trost BM (2004) Asymmetric catalysis: an enabling science. Proc Natl Acad Sci USA 101:5348–5355
Versees W, Loverix S, Vandemeulebroucke A, Geerlings P, Steyaert J (2004) Leaving group activation by aromatic stacking: an alternative to general acid catalysis. J Mol Biol 338:1–6
Wintner EA, Rebek J (1996) Autocatalysis and the generation of self-replicating systems. Acta Chem Scand 50:469–485