enzymatic activity, to block caspase-1 activation in the presence of microbial products (*8*). This suggests the existence of multiple layers of regulation for these inflammatory caspases during infection.

In contrast to oxPAPC binding, the function of the caspase-11 catalytic domain is required for cleavage of Gsdmd, which is potentially the executioner protein in caspase-11– and caspase-1–dependent cell death. Zanoni *et al.* show that there is no cell death correlated with activation of caspase-11; thus, perhaps oxPAPC binding to the caspase-11 catalytic domain blocks cell death by inhibiting Gsdmd cleavage in dendritic cells. Future studies should reveal the physiological importance of oxPAPC and Gsdmd, and their interactions, in caspase-11 activation and cell death.

Zanoni *et al.* uncover a role for host lipids in controlling caspase-11 activation and cell death. Such knowledge is important for understanding the involvement of caspase-11 in disease models where LPS is scarce. For example, caspase-11–dependent cell death plays an important role in neuronal necrosis in models of stroke, multiple sclerosis, Parkinson's disease, and methamphetamine-induced inflammation (*9*–*12*). Additionally, it is currently unknown whether caspase-11 plays a role during viral infection. Thus, studies to identify the role of endogenous ligands, such as oxPAPC, and their regulation of caspase-11–induced inflammation during neuronal injury and viral infection will be of great importance.

Many gaps remain in our knowledge of caspase-11—specifically, how activation and its resolution are regulated, and how this regulation differs by cell type and can affect the adaptive immune response. Zanoni *et al.* reveal previously unsuspected functions of host lipids in regulating caspase-11 activation and cell death. In addition, their findings demonstrate how the innate immune system has evolved to decode the complexity of microbial- and host-derived signals to harness an appropriate adaptive immune response to infection. ■


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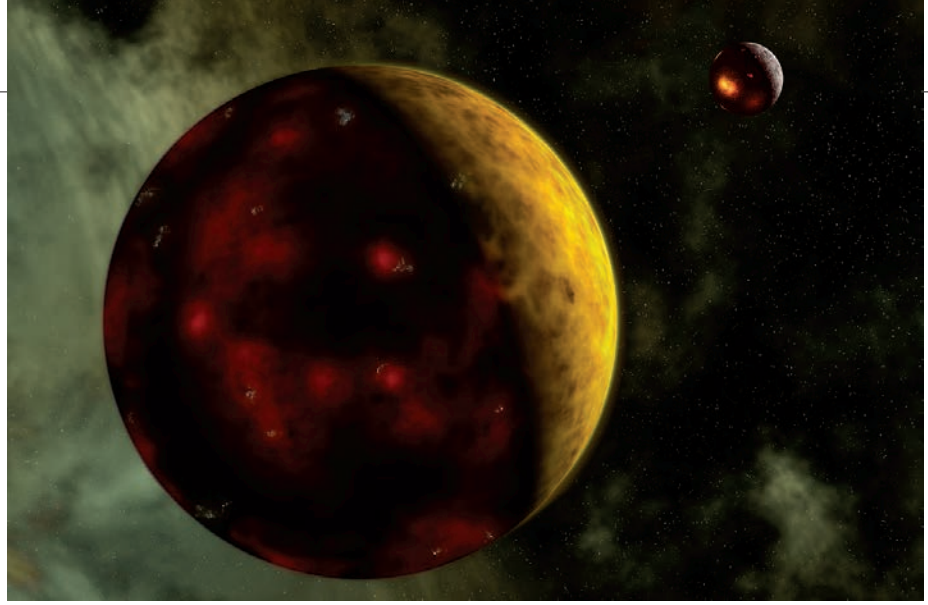

IMAGE: WALTER MYERS/SCIENCE SOURCE

ORIGIN OF LIFE

# Beyond prebiotic chemistry

## What dynamic network properties allow the emergence of life?


*By* **Leroy Cronin**[1] *and* **Sara Imari Walker**[2,3]


How can matter transition from the nonliving to the living state? The answer is essential for understanding the origin of life on Earth and for identifying promising targets in the search for life on other planets. Most studies have focused on the likely chemistry of RNA (*1*), protein (*2*), lipid, or metabolic "worlds" (*3*) and autocatalytic sets (*4*), including attempts to make life in the lab. But these efforts may be too narrowly focused on the biochemistry of life as we know it today. A radical rethink is necessary, one that explores not just plausible chemical scenarios but also new physical processes and driving forces. Such investigations could lead to a physical understanding not only of the origin of life but also of life itself, as well as to new tools for designing artificial biology.

A transition from the limited function and memory possible in a soup of weakly interacting molecules to more strongly interacting networks was essential for the emergence of life on Earth (see the figure). Left unattended, sophisticated chemistry becomes more dilute and disordered. A quick route to complexity and enrichment that could lead to the development of evolvable units seems to be required to avoid this serious issue. Yet, most research efforts have focused on detailing precise chemical mechanisms for producing high yields of individual bio-inspired products, without addressing the processes necessary to form increasingly complex molecules and networks.

What happens to our traditional perspectives if we do not restrict attention to the chemical substrates of known life? The development of networks over time may be more important than the specific chemical nature of their molecular components: Even RNA can form cooperative networks, diversifying its potential role in the earliest evolving chemistries (*5*); autocatalytic networks can evolve in the absence of genes (*4*). The first networks would have had to be simple, challenging the notion that highly complex and improbable molecules are needed to jump-start life. The molecular constituents of simple networks are more likely to arise by chance than the highly evolved molecules of extant life. Starting from networks composed of simple molecules could therefore dramatically reduce the time necessary for the emergence of life and potentially increase the probability of an origins event.

A concept of information relevant to biological organization may be essential to identifying these networked processes. Adami and LaBar have described life at a basic level as "information that copies itself" (*6*). Given that life not only copies information but also uses information to construct itself, we might instead describe the start of life as "simple machines that can construct slightly more complicated machines." Focusing on information in this way moves the narrative


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**Artist's impression of the young Earth.** Life evolved shortly after Earth's surface cooled enough for a solid crust to form.

even further from a chemistry-specific mode than focusing on networks alone but may perhaps provide our best shot at uncovering universal laws of life that work not just for biological systems with known chemistry but also for putative artificial and alien life. For example, Walker *et al.* have recently shown that information-theoretic measures distinguish biological networks from random ones, even in cases where the biological networks share important network properties (such as topological features) with random networks (*7*). Life requires chemistry, but the properties of the living state emerge from the dynamical properties of that chemistry, including the temporal and spatial organization of molecular networks and their information management.

Another way to reconceptualize the problem is to consider life's emergence as a phase transition that manifests as a sudden change in how chemistry can process and use information and free energy. Understanding this phase transition requires new approaches to nonequilibrium physics that hold promise for explaining the origin of structure at multiple hierarchical scales (*8*). Heterogeneity in the early Earth environment played a central role in facilitating the emergence of life by helping to sustain, select, and drive the emergence of organized systems that could persist over time. For example, pores in rocks may have influenced chemical selection, leading to increasingly lifelike chemistries over time (*9*).

One important order parameter in characterizing life's origin as a phase transition is the homochirality. Jafarpour *et al.* have shown that homochirality emerges spontaneously as a symmetry-breaking process in models of noisy autocatalytic systems, a result that could be experimentally tested (*10*). Insights may also come from studying other transitions in the biosphere where organization has emerged from messy dynamical systems, including the origins of social systems (*11*). Such comparisons could yield insights into universal properties of dynamic networks.

However, speculation should be restricted to the development of experimentally testable hypotheses that address key questions and provide a focus for progress. First, how did evolution begin if the complex machinery for evolution was not in place? Experimental studies addressing this question could evaluate the evolvability and robustness of molecular networks or systems with a lower molecular complexity than a full-blown ribosome. Second, can the emergence of life be substrate-independent? Answers may come from investigation of evolvable chemical pathways in the laboratory that are based on alternative polymers. This includes demonstrating how function can be transferred between molecules with different chemical make-up while preserving the overall network structure. Third, at what point in the historical origins of life did the current chemistry of life get selected? Could more than one version of biology exist on the planet today or in the past? This could in principle be tested in one-pot experiments and simulations that include in vitro competition between alternative chemical scenarios for early life.

***"Focusing on information... may perhaps provide our best shot at uncovering universal laws of life that work not just for biological systems with known chemistry but also for putative artificial and alien life."***

In more abstract terms, it remains unclear whether the problems of life's origin, evolution, and understanding the living state will be understood within a single unified theory or will be shown to involve different processes (*12*, *13*). In connecting these areas, understanding common features such as the emergence of complexity becomes important. For example, how complex must a chemical signature need to be before it can be considered a biosignature? Looking for complex objects that could not form randomly in an environment, but arise only as a result of lifelike machinery, might help in classifying potential biosignatures and the processes that generate them. Earth's complex inorganic and organic worlds are certainly highly connected in this respect, with even Earth's mineral diversity in part dictated by life (*14*).

Progress will be made by challenging all historical prerequisites assumed to be important in the origin of life. We should aim to develop measurable and collaborative routes to explore the physics and chemistry of life's origins and the living state. Not only is a comprehensive understanding of what it means for a physical system to be alive required but also a new multidisciplinary, multinational project to generate new life in the lab or in silico, to search for life on Earth that uses an alternative chemistry to that found in biology (*15*), and to explore the potential for life on other worlds. For this to be possible, researchers must challenge the current models and historical approach and be willing to work together across disciplinary boundaries to see if a process-based model can be used to understand and control the transition from inorganic matter to biology. ■

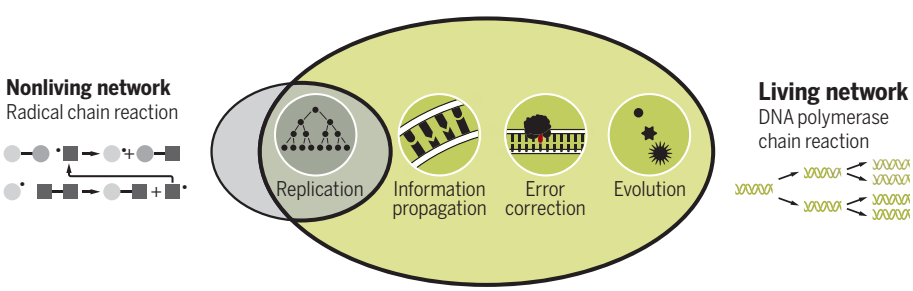


ILLUSTRATION: V. ALTOUNIAN/*SCIENCE*

**Comparison of nonliving and living networks.** Nonliving and living systems both replicate or copy, but the DNA-based living network allows information propagation, evolution, and error correction. Progress in understanding the origin of life may come from studying how simple chemical networks can transform into living networks.


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