



## Introduction

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# Energy, genes and evolution: introduction to an evolutionary synthesis

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Life is the harnessing of chemical energy in such a way that the energy-harnessing device makes a copy of itself. No energy, no evolution. The 'modern synthesis' of the past century explained evolution in terms of genes, but this is only part of the story. While the mechanisms of natural selection are correct, and increasingly well understood, they do little to explain the actual trajectories taken by life on Earth. From a cosmic perspective—what is the probability of life elsewhere in the Universe, and what are its probable traits?—a gene-based view of evolution says almost nothing. Irresistible geological and environmental changes affected eukaryotes and prokaryotes in very different ways, ones that do not relate to specific genes or niches. Questions such as the early emergence of life, the morphological and genomic constraints on prokaryotes, the singular origin of eukaryotes, and the unique and perplexing traits shared by all eukaryotes but not found in any prokaryote, are instead illuminated by bioenergetics. If nothing in biology makes sense except in the light of evolution, nothing in evolution makes sense except in the light of energetics. This Special Issue of *Philosophical Transactions* examines the interplay between energy transduction and genome function in the major transitions of evolution, with implications ranging from planetary habitability to human health. We hope that these papers will contribute to a new evolutionary synthesis of energetics and genetics.

Peter Mitchell first proposed the chemiosmotic hypothesis in 1961 [1]. His revolutionary conception of energy conservation in terms of vectorial chemistry—electrochemical proton gradients across membranes—was recognized in the Nobel Prize for Chemistry in 1978. The intervening years were turbulent, and came to be known as the 'ox phos' wars, in which the mechanism of oxidative phosphorylation (the coupling of electron transfer to ATP synthesis) was resolved over two decades [2]. Today, the impressive achievements of structural biology have provided functional resolution at an atomic scale for all of the respiratory chain complexes, the list being complete with the remarkable structure of the entire complex I from *Thermus thermophilus* [3]. One might then think that the major problems of biological energy transduction are now solved, and hence can be safely ignored. Indeed, many genome-wide association studies have neglected the mitochondrial genome to the point that it has been dubbed the 'neglectome' [4].

Yet how chemiosmotic coupling first arose, and its significance in evolutionary terms, is far from solved. With a few exceptions [5–7] these evolutionary aspects of chemiosmotic coupling received little attention, despite Mitchell himself having published a fine paper on vectorial chemistry in relation to the origin of life in 1957 [8]. The tide began to turn only in the late 1990s, with surprising developments in three apparently unrelated fields. The first, probably most familiar to a broad scientific audience, was the discovery that mitochondria play an important role in apoptosis, and in programmed cell death more generally. A new generation of molecular biologists with little interest in classical bioenergetics demonstrated that ROS (reactive oxygen species) leak from respiratory complexes into the mitochondria, whereupon cytochrome *c* release and declining ATP synthesis combine to induce apoptosis [9]. Since then, a

whole zoo of proteins in the mitochondrial outer membrane has been shown to induce or inhibit apoptosis, making mitochondria the hub of cellular life and death [10]. It is no longer eccentric to view mitochondrial bioenergetics as central to apoptosis, autophagy, epigenetics and genomic stability, potentially driving cancer, neurodegenerative disease and ageing [11].

The second discovery was seen as more abstruse, and is still not wholly assimilated. This was the role of mitochondria in the origin of the eukaryotic cell. Both the serial endosymbiosis hypothesis, as expounded by Lynn Margulis and others [12,13], and autogenous models of eukaryotic origins (in which basal eukaryotic traits such as the nucleus evolved before the acquisition of mitochondria [14]), predict the existence of eukaryotic evolutionary precursors that lack mitochondria. In stark contrast, the hydrogen hypothesis of Martin and Müller posits that the eukaryotic cell originated as a genomic chimera, in which a prokaryotic (archaeabacterial) host cell acquired a eubacterial endosymbiont [15]. This makes the bold prediction that all apparently ‘amitochondriate’ eukaryotes are in fact derived from more complex ancestors that once had mitochondria. Thus, every eukaryote either has, or had, mitochondria. The mitochondrion may be a defining feature of eukaryotic cells. The genomic era has so far borne out this prediction in full—hydrogenosomes and mitosomes (one or the other of which have invariably been identified in amitochondriate cells) are now recognized as highly reduced mitochondria [16]. This discovery is fomenting the beginnings of another revolution. Perplexing eukaryotic traits, including sex [17], two sexes [18–20], the nucleus [21] and apoptosis [22] are now being re-examined in light of chimeric origins.

The third development relates to the origin of life. This development is even less assimilated, at least in the origin-of-life field itself, although it is becoming more widely embraced by microbiologists [23]. This paradigm shift is supported by the discovery of submarine hydrothermal vents, by the appreciation of their significance for the origin of life [24], and later by the discovery of alkaline hydrothermal vents [25]. Even before their discovery, the latter were predicted by Michael Russell and colleagues, in the early 1990s, as the required natural far-from-equilibrium electrochemical reactors, topologically analogous to autotrophic cells, right down to natural electrochemical proton gradients across inorganic barriers [26,27]. These ideas were somewhat marginal until the discovery in 2000 [25] of a deep sea hydrothermal system—Lost City—of the type predicted by Russell. Since then, the striking congruence of alkaline vent geochemistry with the biochemistry of anaerobic microbes has attracted increasing attention [28,29]. Comparative studies point to possible biosynthetic pathways, to specific proteins and mineral cofactors, which may have been central to the emergence of living cells in alkaline vents [30].

These three discoveries—the role of mitochondria in apoptosis, the chimeric origins of eukaryotes and alkaline hydrothermal vents—may seem at first to have little in common, but all are linked by the close association of proton gradients with genomes—chemiosmotic energy transduction and genome function. Naturally occurring proton gradients may have driven the origin of genomes in micro-porous alkaline vents [31]. The requirement for local genome outposts to control chemiosmotic coupling in mitochondria may have freed the first eukaryotes from the

bioenergetic constraints facing bacteria [32]. And many physiological traits of modern eukaryotic organisms, including apoptosis, may reflect the tortured evolutionary history of assimilating two genomes into the same cell [22]. These traits in turn could be responsible for common age-related diseases, and perhaps for ageing itself [33].

In short: energy and genes have gone hand in hand throughout all biological evolution. We argue that it is impossible to understand genes without understanding energy flow. Equally, we cannot understand energy flow in eukaryotes and prokaryotes without appreciating the need for core genomes in mitochondria and chloroplasts, which we think maintain redox poise, as postulated in the CoRR (Co-location for Redox Regulation) hypothesis [34,35]. This in turn requires the interaction of two or three genomes in all eukaryotic cells. Yet, while similar themes of energetics and genome function cut through many fields, the perspectives are disparate. Medical molecular biology has almost no intersection with deep phylogenetics, or with the geochemistry of the early Earth. In our view, it should. Pleasingly, one of the few scientists who is recognized in each of these fields is Peter Mitchell himself. He is our inspiration in this evolutionary synthesis.

The Discussion Meeting on which this Special Issue is based aimed to bridge the gap between fields as disparate as the origin of life and ageing, and, in doing so, to lay the foundations of a new evolutionary synthesis grounded in the principles of thermodynamics. Not all the papers delivered at the meeting are included in this issue; several are published elsewhere and not reproduced here [3,32]. Nonetheless, this Special Issue fully conveys the breadth of the meeting, and we hope it will give a sense of the wider themes of energy and genes that permeate all these fields. This timely collection of papers should strengthen the foundations of the synthesis.

The first four papers deal with the origin of life from a thermodynamic and bioenergetic point of view. Amend *et al.* [36] bring an overarching thermodynamic perspective to the synthesis of organic molecules under hydrothermal conditions, in the presence of gases such as H<sub>2</sub>, CO<sub>2</sub> and NH<sub>3</sub>. They report that, remarkably, the energetic cost of autotrophic synthesis of all cell biomass monomers is exergonic between 50°C and 125°C, so long as conditions are anoxic (standard redox potential of −0.27 eV, as in methanogenesis). In contrast, under microoxic conditions the synthesis of all biomass monomers is endergonic, with a 13-fold increase in energetic costs for amino acid synthesis at a redox potential of +0.77 eV, equivalent to 0.1 per cent oxygen.

Given the favourable thermodynamics under strictly anoxic hydrothermal vent conditions why have empirical efforts to synthesize organics from CO<sub>2</sub> and H<sub>2</sub> proved difficult? The answer may be one of kinetics—the catalysts or conditions that break down thermodynamic or kinetic barriers are elusive—or of properly emulating the extreme conditions of deep sea hydrothermal systems. One sign of the growth of this field is that several possible answers are currently being examined empirically. Their theoretical basis is laid out here in papers by Russell *et al.* [37], Nitschke & Russell [38] and Sousa *et al.* [39]. Nitschke and Russell argue that organics were synthesized in part from methane, in the presence of high-potential electron acceptors such as NO, via a form of anaerobic methanotrophy. In contrast, Sousa *et al.* [39] favour the synthesis of organics from H<sub>2</sub> and CO<sub>2</sub> via reactions essentially identical to those found today in the acetyl CoA (Wood–Ljungdahl) pathway of CO<sub>2</sub> fixation, with no

requirement for high-potential electron acceptors, hence requiring a less oxidized ocean. Better constraints on Hadean Ocean chemistry and direct experimentation should discriminate which, if either, possibility is correct.

The next three papers concern the ensuing phase of early evolution in global oceans and ecosystems: the origins of the oxidoreductase proteins involved in respiration and nutrient cycling [40], the way these impact on the ecology and distribution of microbial life [41], and the intricate control of tetrapyrrole biosynthesis [42]. Kim *et al.* [40] construct an electronic circuit diagram of life, tracing the structural relationships between the transition-metal-binding sites of oxidoreductase enzymes. They infer, on the basis of hydrogen bonding strength and evolvability, that the polypeptide loops of ferredoxins and molybdopterins preceded proteins with mixed alpha helices and beta sheets such as Mo–Fe–S nitrogenases, which in turn preceded proteins with more structured alpha helices (e.g. haems) or beta sheets (e.g. rubredoxins, Mn and Cu proteins)—all in broad agreement with the view that FeS minerals and Mo were essential catalysts of the origin of life. Macalady *et al.* [41] demonstrate that subtle differences in the ratio of external electron donors and acceptors can dramatically shape the structure of microbial ecosystems. The massive scale of taxonomic discovery enabled by molecular methods has revealed many new microbial phyla with no cultured representatives. There are many more taxa than energy-yielding redox or light-harvesting reactions. Macalady *et al.* show that in some sulfur and iron oxidizing lithotrophs, population dominance is predictable on the basis of resource ratios. Yin & Bauer [42] consider the interactions between the three major tetrapyrrole biosynthesis pathways, for haem, chlorophyll and cobalamin. The restriction of chlorophyll biosynthesis to eubacteria indicates that it arose later than haem and cobalamin biosynthesis. The use of cobalamin cofactors in haem synthesis and vice versa suggests a tight coevolution of these pathways. However, alternate routes of haem biosynthesis in eubacteria and archaeabacteria hint at independent origins [39,42], possibly from a more ancient sirohaem pathway, used for the reduction of sulfur and nitrogen, as suggested by Rolf Thauer four decades ago [43].

These papers all concern the metabolic virtuosity of prokaryotes, much of which is built up from modular sub-units—often oxidoreductases containing transition metal cofactors, and very often involving tetrapyrroles—adapted to specific resource ratios in predictably structured ecosystems. Raven *et al.* [44] consider how these metabolic niches influence genome size in eubacteria, archaeabacteria and eukaryotes. In general, more genes are required for autotrophy (chemolithotrophy and phototrophy) than for osmotrophy (excluding phagotrophy in eukaryotes), and autotrophs usually have the largest minimal genome sizes. The diversion of a large proportion of resources into the photosynthetic apparatus also means that phototrophic organisms exhibit slower growth rates than chemoorganotrophs. But while there is some overlap, eukaryotic genomes are often several orders of magnitude larger than equivalent prokaryotic genomes (e.g. eukaryotic algae versus cyanobacteria). The entire eukaryotic domain encompasses no more metabolic versatility than is present in a single eubacterium [45]; yet despite this extreme metabolic limitation, eukaryotes have explored morphological and protein sequence space on an unprecedented scale. The finding that eukaryotes have orders of magnitude more energy per haploid gene copy, attributable to their extreme

genomic asymmetry (in which tiny mitochondrial genomes energetically support a massive nuclear genome) goes a long way to explain why eukaryotes were able to become complex while prokaryotes were not [32]. By virtue of their mitochondria, eukaryotes could afford, energetically, to experiment with the origin and expression of new genes in a way that no prokaryote ever could. The few remaining mitochondrial genes are needed to control oxidative phosphorylation locally, as proposed by the CoRR hypothesis [34,35], but virtually all other genes were lost or transferred to the nucleus. The energy savings gained by eliminating redundant protein synthesis from multiple endosymbionts enabled burgeoning genome complexity in the host cell, and the origin of the thousands of eukaryote-specific gene families [17,32].

A critical corollary is that eukaryotic cells arose in an endosymbiosis between prokaryotes, and have almost invariably retained at least two genomes per cell—nuclear and mitochondrial—which must coadapt to each other over evolutionary time. The next three papers concern different aspects of the coadaptation of mitochondria and their eukaryotic host cells. Blackstone [46] takes a levels-of-selection view of eukaryotic origins, specifically considering the selection pressures acting on the lowest and most stringent level of selection—the mitochondria themselves. Blackstone views the cytosol as an emergent entity that exerts metabolic control over individual mitochondria, usually preventing them from acting in their own selfish interests, and therefore facilitating the loss of genes required for independent replication. The problematic evolution of metabolic controls that curbed the selfish behaviour of endosymbionts may explain why eukaryotes arose only once; also, intriguingly, the multiple origins of multicellularity, as the mechanisms of conflict resolution were easily repurposed to mediate levels of selection conflicts between cells in multicellular organisms.

Bernard *et al.* [47] trace some of the early history of mitochondrial assimilation through pathways of FeS cluster assembly using *Arabidopsis*. FeS clusters are assembled using pathways that are distinct and independent in mitochondria and plastids. FeS clusters are also found in cytosolic and nuclear proteins. Bernard *et al.* [47] show that cytosolic aconitase activity is unaffected by plastid function, but depends on mitochondrial proteins, suggesting that cytosolic FeS cluster assembly arose before the second endosymbiosis in plants leading to plastids. In another example of the tight coevolution of mitochondria and eukaryotes, mutations in the cytosolic FeS cluster assembly pathway undermine nuclear genome integrity, apparently because replicative DNA polymerases require an FeS cluster. Puthiyaveetil *et al.* [48] examine the chloroplast sensor kinase system, which adjusts photosystem stoichiometry in response to changes in the wavelength of incident light, as indicated by the reduction state of the plastoquinone pool. This provides a concrete example of precisely the kind of redox regulation that was predicted by the CoRR hypothesis [34,35]. In a nutshell, the CoRR hypothesis posits that chloroplasts and mitochondria retain genes because local transcription and translation enables a swift, proportionate response to abrupt shifts in substrate availability, oxygen tension and light intensity, thus maintaining effective coupling of electron flow to ATP synthesis and carbon fixation. Puthiyaveetil *et al.* [48] show here that the ancient redox sensor kinase signalling pathway has been partly ‘rewired’ in chloroplasts, as compared with cyanobacterial two-component signalling, for reasons as yet unknown.

The final two papers in this Special Issue relate to the evolution and physiology of animals, and in particular to the problems of ageing and disease, in relation to bioenergetics. de Paula *et al.* [49] present new evidence demonstrating that oocyte mitochondria are transcriptionally and functionally inactive in the ovaries of the common jellyfish. This finding is significant because only the female passes on mitochondria; sperm mitochondria, which are active, and whose DNA is therefore at high risk of oxidative damage through use, are not inherited. This difference is predicted to be a general distinction between anisogamous sexes in metazoans [19]. Early sequestration of inactive 'template' mitochondria in the female germ line impedes the accumulation of mitochondrial mutations. Insofar as mitochondrial mutations are linked with ageing, sequestration of inactive germ line mitochondria should prevent the inheritance of 'aged' phenotypes and therefore delay ageing [16]. The final paper by Wallace [50] provides a synthesis of the central role of mitochondria in human adaptation and disease. The high evolution rate of mitochondrial DNA (up to 40× faster than the nuclear mean in humans [51]) facilitates physiological adaptation to different climates and diets, with nuclear genes encoding mitochondrial proteins being forced to coadapt to new mitochondrial haplotypes. However, sudden changes in diet and environment linked with modern life creates gene-environment mismatches that manifest in humans as prevalent metabolic diseases such as diabetes. Wallace argues here that the missing genetic

information (not detected by genome-wide association studies) is primarily mitochondrial DNA variation plus regional nuclear DNA variants that are by definition missed by large inter-population linkage studies.

Are we witnessing a bioenergetic synthesis in evolutionary biology? The 'modern synthesis' of the past century linked Mendel's genes and the process of mutation with Darwin's theory of natural selection to explain how new species come to be. While the mechanisms of natural selection are correct, and increasingly well understood, they do little to explain the actual trajectories taken by life on Earth. These trajectories are constrained by thermodynamics. No energy; no evolution. There is nothing in evolutionary theory that explains why life arose very early on Earth, nearly 4 billion years ago; why there was then a delay of 2–3 billion years before more complex eukaryotic cells first arose; why the origin of eukaryotes was apparently a singular event; or why eukaryotes share so many complex traits such as sex, phagocytosis and the nucleus, traits which show no tendency to evolve in prokaryotes at all. Yet all these major evolutionary transitions have an energetic basis, and, in some cases, an energetic cause.

A synthesis of energetics and genetics can help us view cell evolution in a new light, one that also illuminates central aspects of human health and ageing. This volume contributes to that synthesis, and we thank the Royal Society and all those involved for putting together the meeting and these pages.

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