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Opinion

Adaptability Beyond Darwin: Microbial Evolution, Mitochondria, and the Thermodynamic Frontiers of Survival

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Abstract

Charles Darwin hypothesized that evolution is based on adaptations to a changing environment, and that organisms that developed even slightly favorable variations would ultimately be most likely to survive. This concept is clearly reflected in the life cycles of pathogenic species. While modern antibiotics, antiviral agents, and vaccines can successfully eliminate many pathogens and prevent infections, only susceptible strains are affected. Bacteria and viruses that can adapt and develop resistance mechanisms will survive and thrive in the absence of ongoing competition. We build on this framework by considering the evolutionary impact of microbial-mediated adaptations experienced by the host. For example, intracellular mitochondria, largely believed to be descendants of symbiotic ancestral bacteria, can be specifically targeted by viral pathogens. Taken one step further, we hypothesize that Darwinian theory may also apply to atoms and molecules, which are not "alive" by any conventional definition, but interact with one another and self-assemble according to the principles of thermodynamics that promote stability in defined environments. Building on these foundations, our hypotheses and conceptual framework will facilitate further exploration into the evolution of microbial mechanisms that modulate behavior, shape the development of the immune system, and promote host evolution.

Keywords: Charles Darwin; adaptability; pathogens; evolution; vaccines; antibiotics; mitochondria; bacteria; viruses

1. Introduction

In his 1859 book entitled "On the Origin of Species", the British naturalist Charles Darwin (1809–1882) proposed the theory of evolution, noting that adaptability, rather than superior physical strength or intellect, was critical for the ongoing survival and perpetuation of a given species. Although Darwin certainly had no direct knowledge of microbial pathogens in the modern sense, his foundational ideas on adaptation, natural selection, and survival remain conceptually applicable today [1]. This simple principle, as updated and modernized to a multi-level framework by Lewontin [2] and Szathmáry and Maynard Smith [3], has great importance toward our understanding of modern-day pathogens and infectious diseases. Successful pathogens exhibit extraordinary adaptability, most notably, their ability to circumvent natural host immune responses and environmental changes, including antimicrobials, antiviral agents, and vaccines [4] (Table 1). In this work, we apply Darwinian theory to our evolving understanding of the complex role of mitochondria in eukaryotic cells and extend these hypotheses to encompass the thermodynamic basis of the evolution of life on Earth. Our overall aim is to invoke Darwin's theories in this broader conceptual framework to create a realistic and meaningful basis for understanding microbial evolution in modern times.

2. Antigenic Variation and Darwinian Principle

Antigenic variation is the most immediate expression of Darwin's stress on adaptability. Seemingly minor modifications in surface proteins frequently allow pathogens to evade detection by endogenous host defense mechanisms. For example, influenza viruses experience antigenic drift, accruing point mutations that can alter the antigenicity of the surface hemagglutinin and neuraminidase [5], enabling them to evade detection by antibodies induced in response to earlier vaccination or infections. Likewise, mutations that accrue rapidly in the human immunodeficiency virus (HIV) envelope glycoproteins permit the virus to evade detection by the immune system [6]. In a collective sense, these observations imply that pathogen survival and transmission rely less on acute virulence in isolation and more on their capacity for sustained adaptability. As discussed in a theoretical consideration of parasite evolution published by Cressler *et al.* [7], virulence may evolve as a trade-off between transmissibility and the selective advantage conferred by rapid within-host growth, among other potential mechanisms.

3. Antimicrobial Resistance as Evolution in Action

Antimicrobial resistance can also be understood as an example of Darwinian adaptation. Frequent use and, in some cases, misuse of antibiotics has led to blanket selec-

Table 1. Pathogens that demonstrate adaptability in response to environmental constraints.

Pathogen	Family	Example in text
Influenza virus	*Orthomyxoviridae*	Experience antigenic drift that enables them to evade detection by circulating antibodies.
SARS-CoV-2	*Coronaviridae*	Alterations in viral surface spike (S) proteins permit virions to evade detection.
Methicillin-resistant *Staphylococcus aureus*	*Staphylococcaceae*	Modified penicillin-binding protein (PBP2a) facilitates resistance to beta-lactam antibiotics.
ZIKV	*Flaviviridae*	Key mutations likely facilitated conversion to a more virulent form.
Marek's Disease Virus	*Herpesviridae*	Vaccination blocks symptoms but permits ongoing virus replication, leading to greater virulence over time.
HIV	*Retroviridae*	Mutations accrue rapidly in envelope glycoproteins, facilitating immune evasion.

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ZIKV, Zika virus; HIV, human immunodeficiency virus.

tive pressure across entire microbial populations. From the perspective of "survival-of-the-fittest", bacterial strains that remain drug-resistant will survive and eventually predominate in the end. Bacteria have responded to antibiotic selection pressure with beta-lactamase production, target site alterations (e.g., methicillin-resistant *Staphylococcus aureus*), and upregulation of drug efflux pumps [8].

4. Acquired Immunity, Vaccination, and the Emergence of Escape Variants

In some cases, vaccination can be a selective constraint leading to pathogen adaptation and prolonged transmission. While critical mass vaccination strategies have undoubtedly saved lives especially in the current political climate, they have also, in some cases, facilitated pathogen transmission. One example of this phenomenon is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) "escape variants", i.e., Omicron variants that were only partially susceptible to initial vaccine-induced immunity [9]. Thus, in accordance with Darwinian predictions, virus strains with non-lethal mutations in critical epitopes might be less susceptible to natural or vaccine-induced immunity. However, it is important to recognize that general reactions to both vaccines and naturally-acquired immunity are virus-specific, vaccine-specific, and greatly dependent on the dynamics of a given vaccination campaign and the development of herd immunity. While rare, a remarkable example of an "imperfect vaccination" is the strategy of immunization applied in veterinary practice, aimed at the prevention of Marek's disease. While the vaccine largely prevented disease symptoms, it did not block replication and thus facilitated the diffusion of pathogens with increasing virulence [10]. Whereas our understanding of the process is far from comprehensive, Bernhauerová [11] suggested that the selective constraints promoting adaptation and virulence may be widely separated from one another. Similarly, Kun *et al*. [12] highlighted the contributions of the transmission-virulence tradeoff to explain the challenges involved in anticipating the virulence of future SARS-CoV-2 variants.

5. Adaptation to Ecological Niches and Host Competition

Apart from responses aimed at escaping endogenous and exogenous selection pressures, pathogens must adapt to fill ecological niches and compete for scarce resources [13]. Toward this end, dynamic epigenetic control and horizontal genetic transfer mechanisms can facilitate pathogen adaptation and encourage ongoing growth and survival [14–17]. When confronted with complex and evolving host defense mechanisms (e.g., pattern recognition receptors, phagocytosis), many pathogens adjust by developing dodges, manipulations, and even adaptive co-option of these pathways [18,19], engaging in a bi-directional "fight" for survival [20–23].

6. Viruses, Bacteria, and the Evolutionary Role of Mitochondria

Viruses and bacteria co-evolved with one another, engaging in the universal competition for existence [24]. Because viruses have no specialized metabolic machinery, they co-evolved with bacteria largely to facilitate expropriation of their reproductive and energy-producing systems.

Viruses that infect bacteria (i.e., bacteriophages) facilitate genetic transfer and can have a critical impact on target cell interactions with the host. Cholera, diphtheria, and Shiga toxins are all examples of bacteriophage-encoded sequences that alter the properties of host bacterial species [25]. While mitochondria most likely evolved from an ancient α-proteobacterial symbiotic species, the precise mechanisms and events involved in this process remain unclear [26]. Nonetheless, mitochondria maintain some properties suggesting that they remain independently "alive" [27,28], including their own genetic material, characteristic membrane components, and vulnerability to viral manipulation.

Mitochondria are susceptible to a unique set of virus pathogens (e.g., mitoviruses [29]) and can detect and respond to bacteria, similar to their ancestral counterparts [30]. Results from two recent studies highlighted tissue-specific transcription of nuclear-encoded mitochondrial genes [31,32]. Neurons can even shuttle mitochondria to-

wards adjacent malignant cells [33], an observation that highlights the potentially complex ramifications of mitochondrial function.

7. Zika Virus and Mitochondrial Targeting

Given the aforementioned theories on the origins of eukaryotic mitochondria [26], Zika virus (ZIKV)-mediated mitochondrial targeting can be viewed as an adaptive process derived from ancient virus-bacterial survival mechanisms. Several recent publications have addressed the mechanisms employed by ZIKV to target mitochondria and subvert host energy metabolism [34–38]. In infected states, ZIKV reprograms host target cell metabolism, driving its own propagation by increasing glucose uptake and redistribution to the pentose phosphate pathway and tricarboxylic acid cycle. ZIKV also subverts lipid metabolism, including modifications in lipid synthesis, transportation, and deposition, generating inflammation and cell stress. One of the hallmark consequences of ZIKV infection is the induction of mitochondrial stress, dysfunction, mitophagy, and eventually fragmentation, yielding bioenergetic advantages for the virus while suppressing the host antiviral mechanisms [37].

8. Adaptability at the Molecular and Thermodynamic Level

We hypothesize that Darwin's theory (i.e., that adaptability is more important than strength or intelligence in ensuring the life of an organism) applies equally well to non-living systems. Atoms and molecules, which are not "alive" by any conventional definition, interact with one another and sort themselves out according to the principles of thermodynamics that promote stability in defined environmental contexts. We hypothesize that, over time, these interactions led to increasingly sophisticated biochemical systems capable of sharing energy, copying themselves, and storing information, all the hallmarks of life on Earth. Just as organisms adapt in response to selection pressures, biochemical pathways and molecular entities have adapted to changing environmental constraints, e.g., temperature, pH, available oxygen, and enthalpy gradients. While these traits cannot be inherited in the classic sense, we hypothesize that these primordial mechanisms build on one another, eventually leading to simple (e.g., primordial nucleic acids, coacervate-like droplets) and ultimately more complex structures. Thus, we suggest that many of the key features of eukaryotic biology (e.g., cell membranes, genetic material, host defense mechanisms) may be viewed as optimized "spinoffs" of advances made by primordial molecular systems [28,39]. Our current understanding of mitochondria clearly demonstrates this principle. In the face of physiological stresses (both ancient and modern), some of the negative sequelae of complex multicellular life (e.g., chronic inflammation, hypoxia, metabolic overloading) can overtake the key positive contributions of mitochondria. In these situations, mitochondria are no longer recognized for their capacity to generate ATP, but instead become major producers of reactive oxygen intermediates and pro-inflammatory signals, many of which contribute profoundly to neurodegeneration, vascular disease, and cancer. A consideration of mitochondrial dysfunction from both an evolutionary and thermodynamic viewpoint provides us with some perspective as to why such vulnerabilities persist, and also how they might be addressed therapeutically.

9. Conclusions

Our goal in this paper was to initiate new hypotheses that focus on microbial adaptability, mitochondrial behavior, and the evolution of host-pathogen interactions. Although pathogens and pathogenicity did not fall directly under Darwin's purview, the evolution-based tactics used by most infective agents bear witness to his key message. Bacterial and viral strains survive and reproduce not due to any inherent dominance, but because they can readily adapt to changing environments. Interestingly, virus adaptation is reflected in their capacity to infect organelles of bacterial origin (i.e., mitochondria) [40–43]. An in-depth understanding and appreciation of ongoing microbial evolution will permit us to identify more effective antiviral and antibacterial strategies.

Toward this end, we present a new thermodynamic and environmental selectivity-modeled mechanism to explain the co-evolution of viruses, bacteria, and eukaryotic cells. While horizontal gene transfer and molecular compatibility are well-established, we suggest that genetic openness is controlled by selective environmental conditions that promote innovation and biological compartmentalization. Thus, our viewpoint provides a unifying lens through which to interpret the conditional nature of genetic communication, survival, and the emergence of distinct biological identities.

While Neo-Darwinist theories typically emphasize competition and fitness, our perspective suggests that evolution as a whole is somewhat more complex. Given the recent evidence that has largely obscured the distinction between pathogen and symbiont, we recognize the growing need to view microbes as instruments of cooperation, of communication, and of systemic incorporation. Toward this end, we recognize Shapiro's [44] theories on natural genetic engineering and Ryan's [45] discussion of symbiotic individuality, positing that evolution involves both cooperation and competition. Similarly, we consider Villarreal's [46] reflections on viral creativity, in particular in the shaping of host genomes together with the ideas of Calvo *et al*. [47] concerning intelligence and cognition in cells beyond the neuron. Similarly, Levin's [48] work focused on bioelectric signaling and collective decision-making in cells, also improves our understanding of mitochondrial autonomy and distributed intelligence.

Building on these foundations, our conceptualization of host-pathogen interactions will be enhanced through a more explicit holobiont framework, specifically one that will explore how microbes positively modulate behavior, shape the development of the immune system, and promote host evolution. Integration of these concepts will expand the current conceptual horizons of microbiology and symbiosis and may transform our understanding of the mitochondria from simple intracellular organelles into fluid, semi-autonomous entities engaged in larger networks that support cell-based intelligence and evolutionary innovation.

Author Contributions

The single author was responsible for the conception of ideas presented, writing, and the entire preparation of this manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The author declares no conflict of interest.

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