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Introduction

There are these two young fish swimming along, and they happen to meet an older fish swimming the other way, who nods at them and says, "Morning, boys. How's the water?" And the two young fish swim on for a bit, and then eventually one of them looks over at the other and goes "What the hell is water?"

David Foster Wallace, Kenyon College Commencement Speech, 2005

The premise of this book is that the Big Bang of the Universe gave rise to inorganic and organic compounds alike. Both are formed by bonds, the former constituted by inertness, the latter doing quite the opposite by giving rise to life itself. Organic chemistry provided the physical space within which negentropy, chemiosmosis, and homeostasis all acted in concert to form the first primitive cells. Single-celled organisms dominated the Earth for the first 3 or 4 billion years, followed by the generation of multicellular organisms as exaptations. How and why this occurred provides the mechanism for the emergence of human biology, starting with the "first principles of physiology." Such a rendering is way overdue, since the human genome was published more than a decade and a half ago. Without such an effectively predictive working model for physiology, such information is of little value.

Mind the Gap

Let us go then, you and I,
When the evening is spread out against the sky
Like a patient etherized upon a table...

T.S. Eliot, The Love Song of J. Alfred Prufrock

The Michelson–Morley experiment (1887) refuted the notion of luminiferous aether, a theorized medium for the propagation of light, making way for novel thinking about the fundamental principles of physics at the close of the nineteenth century and the beginning of the twentieth. This second scientific revolution was crowned by Relativity Theory (1905), equating energy and mass, a counterintuitive relationship that changed not only the way we see the world around us, but also how we see ourselves. The understanding of the inner workings of the Bohr atom similarly gave insights to physics and chemistry

that were previously inaccessible and inconceivable. The twenty-first century has been declared the “age of biology,” given our foreknowledge of the genetic makeup of humans and an ever-increasing number of model organisms. Yet the promise of the human genome – the cure for all of our medical ills – has not transpired 15 years hence. We contend that this is symptomatic of our not having attained the level of knowledge in biology that the physicists had reached at the dawn of the second scientific revolution... we are still mired in the sticky, sludgy, stodgy “aether” of descriptive biology. Deep understanding of the inner workings of the cell, particularly as they have facilitated the evolution of multicellular organisms, will herald such breakthrough science. The way in which the cell acts at the interface between the external physical and internal biological “worlds,” authoring the script for Life, is a reality play without an ending, reiterative and reinventive. Thus life is formulated to continually learn from the ever-changing environment, making use of such knowledge in order to sustain and perpetuate it.

Duality, Serendipity, and Discovery

The field of biomedical research is characterized by paradoxes, serendipitous observations, and occasional discoveries. This is due to the lack of a central theory of biology, DNA notwithstanding. It is also the reason why we have been unable to solve the challenging “puzzle” of evolution. In lieu of guidelines and principles, we collect anecdotes and make up “Just So” stories based on associations and *a posteriori* reasoning. This book was written to elucidate how to understand biology based on its origins in unicellular life, evolving in the forward direction of biologic history, both ontogenetically (short-term history) and phylogenetically (long-term history). We use the figure-ground image (Figure 1.1), made popular by gestalt psychology, as a way to express the inherent problem in seeing biologic phenomena as dualities: inorganic-organic, genotype-phenotype, proximate-ultimate, structure-function, health-disease, synchronic-diachronic, ontogeny-phylogeny. It is the latter duality that was the breakthrough for us, realizing that ontogeny and phylogeny, looked at from a cellular perspective, are actually one and the same process, only seen from different perspectives. With that issue put behind us, we could address the “first principles of physiology,” beginning with the plasmalemma of protists as the homolog for all of the subsequent traits expressed by multicellular organisms.

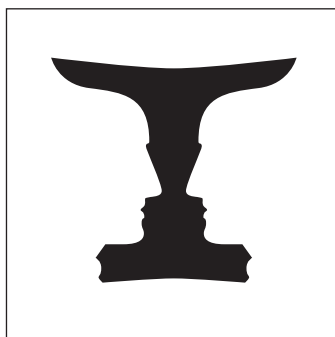


Figure 1.1 Figure-ground “faces.”

Biology as “Stamp Collecting”

As working scientists, the authors of this book have been involved in studies of developmental physiology for many decades. One of us (J.T.) was first introduced to the concepts of cell biology in reading Paul Weiss, one of the founders of the discipline, when he took advanced placement biology in high school. It was Weiss who admonished us not to ask “how or why” questions, but merely to describe biologic phenomena. That attitude prevailed in biology until the advent of molecular biology in the 1960s, which demanded that we ask how biologic mechanisms functioned, having finally “reduced” the problem to its smallest functional unit, the cell, like the Bohr atom in physics. Yet this reductionist approach has not solved some of the remaining fundamentals of physics, hence string theory, “branes,” and multiverses. By analogy, we are of the opinion that we must think in terms of the cell as the smallest functional unit of biology. Conversely, stripping away billions of years of biologic information to focus on DNA is a systematic error that is misleading and misguided, in our opinion. This book is intended to demonstrate how the cell-molecular approach to evolutionary biology provides novel insights to the how and why for the evolution of form and function.

The “why” question has emerged from the New Synthesis of evolutionary biology, particularly after it had embraced developmental biology as evo-devo. But even at that, the evolutionists were not delving into the mechanisms of evolution, seemingly content with random mutation and population selection as the mechanisms of evolution. For working scientists like ourselves, studying how organs develop across species, this didn’t seem like a reasonable process since we could see the common denominator between ontogeny and phylogeny at the cellular level, suggesting (to us) that some underlying organizing principle was at large. Not to mention that the ongoing serendipitous, anecdotal nature of both biology and medicine, even in the post-Human Genome Project era, was frustrating given that science is ultimately supposed to be predictive.

Then in 2004 Nicole King published her ground-breaking paper demonstrating for the first time that the complete multicellular genomic “toolkit” of sponges was expressed in the unicellular free-swimming amoeboid form during the life cycle. That reversed everything in biology because up until that point in time physiology was described based on biologic traits in their extant form, not based on how they evolved from the unicellular state. That perspective precipitated our hypothesis that the complete phenotypic toolkit was present in the plasmalemma of unicellular organisms, and raised the question as to how the genome determined complex physiology ontogenetically and phylogenetically, from unicellular organisms to invertebrates and vertebrates.

That question was made all the more pertinent because we had published a seminal paper on the cell-molecular basis of alveolar physiology that had emerged from decades-long study of how the fetal lung develops at the cell-molecular level. Those studies were catalyzed by two landmark observations – the physiologic acceleration of lung development by glucocorticoids, and the observation that parathyroid hormone-related protein (PTHrP) was necessary for alveolar formation. The linking of those two phenomena through the serial paracrine interactions between the lung endoderm and mesoderm culminated in our fundamental understanding of the physiologic principle of ventilation-perfusion matching – essentially how the distension of the alveolar wall molecularly coordinated surfactant production and alveolar capillary perfusion to maintain both local and systemic homeostasis.

The experimental evidence for the coordinating effects of cell stretching on PTHrP, leptin, and their cognate cell-surface receptors on surfactant production and vascular perfusion led to the first scientific documentation of the physiologic continuum from development to homeostasis. More importantly, it begged the question as to how these specific cell types evolved the mammalian lung phenotype, given that the molecular ligand and receptor intermediates involved were highly conserved, deep homologies that could be traced at least as far back as the origins of vertebrate phylogeny in fish, if not all the way back to the unicellular state. If that “story” could be told, it would provide insight to both lung physiology and pathophysiology based on first principles – a counterintuitive idea predicted by this cell-molecular approach.

More importantly, the functional genomic linkage between lung evolution in complex climax organisms – mammals and birds – and homologous mechanisms in emerging unicellular eukaryotes, formed the basis for fundamental insights into the evolution of all visceral organs. The advent of cholesterol, which Konrad Bloch referred to as a “molecular fossil,” was critical for the evolution of eukaryotes from prokaryotes. The insertion of cholesterol into the cell membrane of eukaryotes enabled vertebrate evolution by facilitating endocytosis (cell eating), increased gas exchange (due to the thinning of the eukaryotic cell membrane), and increased locomotion (due to increased cytoplasmic streaming). And vertebrate evolution is founded on those three biologic traits – metabolism, respiration, and locomotion. Therefore, all of the visceral organs – lung, kidney, skin, skeleton, brain, and so forth – likely evolved from the plasmalemmae of unicellular organisms, providing a unified, common homolog for all of these organs. The existence of vertebrate physiologic mechanisms based on functional cell-molecular homologies, rather than on the tautologic “Just So” stories for physiologic structure and function that currently prevail, would no longer hamper forward progress in understanding the “how” and “why” of biology and medicine.

Up until now, the void between descriptive and mechanistic physiology has been filled by either top-down descriptive physiology, or bottom-up abstract philosophy and mathematics. With the insights gained from the “middle-out” ligand-receptor approach we have employed to understand lung evolution, we are now enabled for a paradigm shift from post-dictive to predictive physiology and medicine.

Historically, physicists became actively involved in biology after the Second World War as an alternative source of employment, having successfully developed and deployed the atomic bomb. The Greek philosophers understood the unity of life intellectually as far back in written history as the fifth century BCE, but had no scientific evidence for it. Beginning with quantum mechanics, physicists felt empowered to comment on the meaning of life, given that they had discovered the operating principle behind the atom and had unleashed its power. Bohr was the first modern physicist to address the question of “what is life” by applying the conceptual principle of the duality of light to biology in his Como lecture in 1927. He went on to explain that this seeming duality was a technical glitch due to the different ways in which the wave and packet forms of light were measured, a phenomenon he referred to as complementarity. This was a metaphor that poets such as Robert Frost (in his poem *The Secret Sits*) have reconciled more facily, in our opinion:

We dance round in a ring and suppose,
But the Secret sits in the middle and knows.

Or for that matter, the glib comment in Robert Frost's published notebook: "Life is that which can mix oil and water." Erwin Schrödinger later wrote a monograph, entitled *What is Life?*, in which he tried to apply physical principles to the question of the vital force. Others followed, such as the Nobelist Ilya Prigogine, and the polymath Michael Polanyi, who expressed their considered opinions that biology was "irreducible." More recently, in his Nobel Prize acceptance speech, Sydney Brenner stated that the problem of biology is soluble, citing his CELL project to map all of its intracellular pathways. Of course, the greatest of all physicists, Albert Einstein, kept the problem of "life" at arm's length, yet it was his intuitive insight that led him to $E = mc^2$, transcending the stigma of descriptive physics by equating mass and energy. He had already seen the "forest for the trees" at 16 years of age, dreaming that he was traveling in tandem with a light beam (see *Einstein* by Walter Isaacson). Like scientific feng shui, he was able to conceive of the fundamentals of the physical world – Brownian movement, the photoelectric effect, and relativity theory – all in his wunderjahr of 1905. Of course, he famously said that "G_d does not play dice with the Universe," so he would not have agreed with the conventional stochastic approach to evolution.

But perhaps the solution to the evolution puzzle is not based on random mutation and population selection – biology and medicine are on the threshold of a conceptual breakthrough on a par with such breakthroughs as heliocentrism and relativity theory. By subordinating descriptive biology to cell-molecular signaling in development, homeostasis, and regeneration as the essence of evolution, the fundamental mechanism of life, we will be able to understand the "Inner Universe" of physiology, starting from its origins, resynthesizing biology from the bottom up. Embracing this approach to physiology would be a game changer.

Galileo is widely considered to be the father of modern science because his ideas were not derived solely from thought and reason. He was guided by experimentation and observation. This was a revolutionary change in science – observational experience being the key method for discovering Nature's rules. By understanding how celestial bodies moved through the night sky, Galileo wrested power from the astrologers, placing it in the hands of the astronomers and their scientific heirs. That changed the course of human history.

A Cellular-Molecular Model of Evolutionary Biology

The formulation of Quantum Theory launched modern physics, providing a mechanistic explanation for the origin and formation of the Universe, beginning with the Big Bang. This represented a major transition from Newtonian mechanics, which was deterministic, to relativity theory, which is probabilistic. Yet biology remains wedded to descriptive mechanisms, not to the underlying mechanicism of biology. Evolution is the mechanism underlying all of biology, whereas natural selection, survival of the fittest, and descent with modification are all metaphors. In this book, we provide the biologic analog of Quantum Mechanics by showing how unicellular organisms gave rise to derivative multicellular organisms through the self-organizational cellular intersection of negentropy, information acquisition, and homeostasis. All of these components have been addressed in the biologic literature at one time or another over the course of the past 50 years, yet they have not been formulated as a mechanistic process that would explain evolution, especially as

it applies to non-fossilized tissues and organs. The advent of cell–cell interactive cellular-molecular embryology and phylogeny offers the opportunity to model vertebrate evolution. Herein, we provide a unique perspective on evolutionary biology.

The Evolutionary Continuum from Development to Physiologic Homeostasis, Repair and Reproduction

The central concept of this book is that there is a biologic continuum mediated by cell–cell communication that starts with the zygote, generating multicellular organisms, facilitating reproduction, culminating in the next generation of the organism, et cetera, et cetera. The experimental breakthrough in this way of thinking about biology occurred in 1978, when George Todaro discovered that cultured cells produce soluble growth factors. These substances allow cells to communicate with one another in space-time through specific signaling receptors, mediating the generation of structure and function. At birth, many of these signaling mechanisms become the agents that determine physiologic homeostasis and repair.

Evolution is said to be “emergent and contingent.” Moreover, newly evolved biologic traits are known to have their antecedents in earlier phylogenetic forms of the same species, what is referred to as preadaptation or exaptation. If you follow that precept back far enough, you end up in the unicellular state, which King, Hittinger, and Carroll have shown to be the origin of multicellular organisms.

And if we trace the evolution of eukaryotes all the way back to the single-celled form, we see homologies with prokaryotes, such as negentropy, bioenergetics, and homeostasis, that are common to both. In fact, bacteria express sterol-like hopanoids that are under control by oxygen, as is the case for sterols in eukaryotes, yet they do not serve the same fundamental purpose of rendering the cell membrane interactive with the environment. Instead, bacteria possess a hard exterior cell wall that isolates the internal milieu. In contrast to this, eukaryotes possess a compliant cell membrane that facilitates metabolism, respiration, and locomotion. And the endomembranes that derive from the cell membrane provide the cell with the ability to form compartments in which factors derived from the external environment that would otherwise have been harmful – oxygen, nitrogen, ions, heavy metals, gravity – are exploited for physiologic functions. These structural-functional relationships between prokaryotes and eukaryotes offer an opportunity to consider the possibility that we are still part of that continuum, particularly in light of the recent recognition that the microbiome is an integral component of the hologenome.

Resonance at the Denouement of this Book

If we may wax a bit poetic, once we determine the mechanisms that resonate throughout biology, we will truly be able to understand our origins, and predict our future as a species. Like the hierarchical relationships generated by the Big Bang, biology shares a oneness with the Universe because of its fundamental mimicking of the external environment, not unlike a great literary or musical composition, though that falls short because it is a creation of the human mind, unlike evolution. Biology resonates from

unicellular to multicellular life, derived from the Cosmos, as George Gurdjieff and the monk Teilhard de Chardin had proposed, culminating in the human mind and what Raymond Maslow referred to as “peak experiences.” That being said, once we determine the interrelationship between the physical world and the human mind, we will truly be able to act in harmony with our environment, organic and inorganic alike.

Why is Physiology?

It should be obvious to even the most casual observer that there are orthogonal patterns of inheritance, like those of physiology and physiognomy, that is, things just seem to “fit together.” After all, the physical Universe was generated by the Big Bang, creating an informational hierarchy by distributing the elements based on their mass. The biologic “Universe” was generated by mimicking that physical Universe. Even at the molecular level, we see that genes “fit together” into clusters, or cassettes. Perhaps the most striking examples are the homeobox genes, which align on the chromosome in the same sequence as they are expressed during embryology – how could this have happened by chance? I maintain that this cannot merely be the result of random variation and phenotypic selection, whereby over eons such associations occurred adaptively, so natural selection favored those organisms that expressed them as such.

Alternatively, this may have been the net result of ongoing interactions between internal and external selection, internal selection resulting from physiologic stress, generating radical oxygen species that are known, for example, to cause gene duplications closely associated with evolutionary change. The epitome of internal selection is Haeckel’s Biogenetic Law (Figure 1.2) – ontogeny recapitulates phylogeny – dismissed by contemporary evolutionists for lack of “hard” fossil evidence but rejuvenated by molecularists providing evidence for ghost lineages due to epigenomic inheritance mediated by genetic “marks.” We have suggested that perhaps the process of phylogenetic recapitulation during embryonic development is necessary in order to ensure that any given genetic change, particularly those due to epigenetic inheritance, is internally consistent with the subsequent homeostatic adaptations fostered by such an event – we see this repeatedly when experimentally manipulating genes, resulting in either some phenotypic developmental change, or embryonic lethality, which we refer to as either “proof of principle” in the case of the former, or casually dismiss as being incompatible with life in the case of the latter, without further delving into the underlying mechanisms involved.

Starting with the generation of unicellular organisms, life forms have internalized and mimicked the external physical environment, “fueled” by negentropy, perpetuated and molded by homeostasis, structurally realized through endomembrane compartmentation...or perish. For example, early in the evolution of primitive cells, cytoplasmic calcium had to be drastically reduced in concentration to avoid the denaturing of proteins, nucleotides, and lipids. This was achieved by cholesterol forming calcium channels in the cell membrane, fostering integrated physiology, from unicellular to multicellular eukaryotes.

We have observed and documented this phenomenon for the evolution of the lung, genetically annotating the processes of lung ontogeny and phylogeny at the cellular-molecular level. As a result, we have documented a seamless, alternating pattern of internal and external selection for specific functional traits, accommodating both

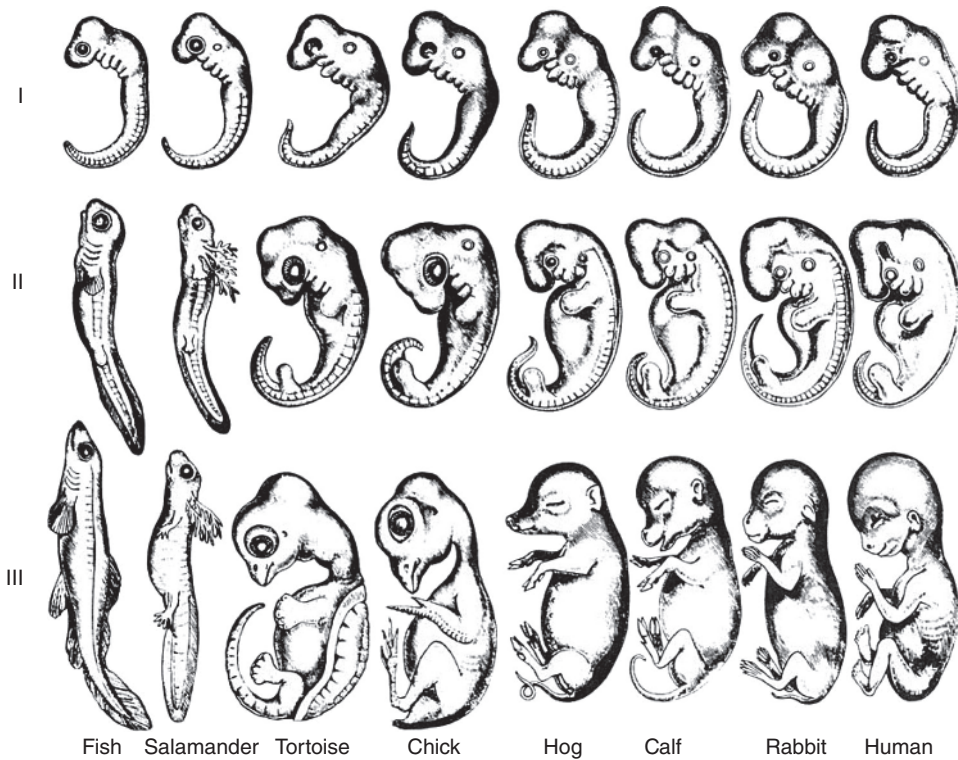


Figure 1.2 Haeckel's Biogenetic Law. Note the similarity between the early stages of all the organisms pictured. Such similarities are lost as these species grow and differentiate. From Blancke, 2010. Reproduced with the permission of John Wiley and Sons.

external and internal selection pressure. Since this mechanism of lung morphogenesis is determined by cell–cell interactions, the physical compartmentation of the genes expressed by the endoderm and mesoderm determines the ontogeny and phylogeny of the lung, providing a self-referential, self-perpetuating interactive mechanism for constantly monitoring and gleaning information from the environment, resulting in optimized physiologic adaptation on an ongoing basis.

Experimental evidence for such an interactive cellular-molecular process (Figure 1.3) comes from studies to determine the effect of gravity on fundamental phenotypic cellular expression. In organs as disparate as the skeleton (fossil evidence shows that vertebrates attempted adaptation to land on at least five separate occasions), lung, and uterus, PTHrP signaling is mechanosensitive; those reiterative attempts to breach land must have concomitantly caused physiologic stress on the visceral organs, resulting in microvascular shear stress within the capillaries, generating radical oxygen species known to cause gene duplications; and perhaps even the PTHrP receptor and β -adrenergic receptor gene duplications that occurred during the water–land transition. We hypothesized that the resultant amplification of PTHrP signaling promoted the various organ-level adaptations for land habitation – lung, skin, bone, kidney – as exaptations of ancient biologic adaptations to gravity, which is the most ubiquitous, unidirectional, unrelenting environmental effector of vertebrate biology. For example, microgravity

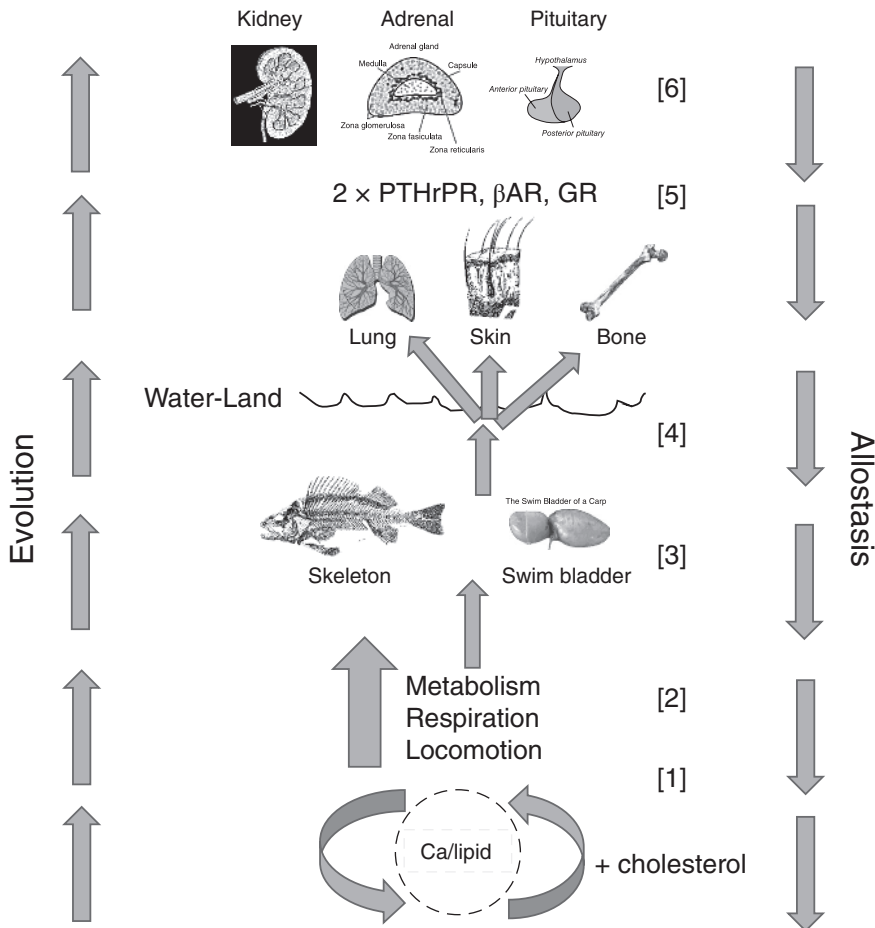


Figure 1.3 Vertical integration of PTHrP signaling. The ontogenetic and phylogenetic integration of calcium-lipid homeostasis, [1] from protocell incorporation of cholesterol into the plasmalemma for [2] metabolism, respiration, and locomotion, the foundation of vertebrate evolution. [3] Coevolution of the skeleton and swim bladder of physostomous ray-finned fish [4] under physiologic stress of the water–land transition gave rise to the lung, skin, and bone phenotypes of land vertebrates, [5] largely through the duplication of the parathyroid hormone-related protein (PTHrP), beta-adrenergic (β A), and glucocorticoid (G) receptors. [6] Expression of PTHrP in the pituitary, adrenal cortex, and kidney glomus gave rise to endothermy and the glomerulus.

causes both cellular depolarization and failure to form buds in yeast. Cell polarity is necessary for integrated physiology, whereas budding is the means by which yeast reproduce. Hence, there are deep homologies between the simplest and most complex eukaryotic traits that are mechanistically linked through the effects of gravity.

In the lung, mechanotransduction via fluid distension of the airways *in utero* determines the epithelial-mesenchymal interactions underlying gene regulatory mechanisms for alveolar barrier formation, including surfactant biosynthesis, intracellular matrix production, and tubular myelin formation. When lung alveolar epithelial cells are cultured under $0 \times g$ conditions the cells round up, losing their polarity, and their PTHrP

signaling capacity declines, reaching a newly established, stable baseline of expression several orders of magnitude less than in unit gravity several hours later, resulting in the loss of cell–cell signaling for lipid metabolism. As noted above, uterine PTHrP expression is also stretch-regulated during pregnancy, regulating the rate of calcium flux between the mother and fetus. Hence, there appear to be highly conserved mechanisms common to cellular polarity, metabolic homeostasis, and reproduction alike that have evolved in adaptation to gravity. Even a simple eukaryotic yeast will lose both its polarity and ability to duplicate, or bud, in $0 \times g$. In retrospect, this should not be surprising, given that actin and tubulin are common to mitosis, meiosis, and homeostasis alike.

These physical adaptations may have originated from the cytoskeleton, since it is homologous to both unicellular organisms and to bone, the latter regulating calcification through PTHrP in compliance with Wolff's law. That is to say, the skeletal adaptation to the water–land transition may have created the selection pressure for PTHrP signaling in other visceral organs, fostering the phenotypic adaptations seen in the lung, skin, and bone alike.

In support of this hypothesis (see Figure 1.3), PTHrP is also expressed in the anterior pituitary, where it regulates Adrenocorticotrophic Hormone (ACTH), and in the adrenal cortex, where it controls corticoid synthesis. The net effect of such a PTHrP-dependent hypothalamic-pituitary-adrenal (HPA) axis would be increased adrenaline production by the adrenal medulla, due to the corticoid stimulation of the rate-limiting step in catecholamine synthesis in response to physiologic stress. The most potent naturally occurring physiologic stressor is hypoxia, which would have occurred transiently due to fluctuations in atmospheric oxygen during the Phanerozoic eon (Figure 1.4) as the lung evolved from the swim bladder of bony fish to the lungs of amphibians, reptiles, mammals, and birds; that is, the gradual increase in lung surface area occurred in response to metabolic demand, and would periodically have been constrained, resulting in periods of hypoxia, stimulating the HPA and adrenaline production, and releasing the bottleneck on the lung by increasing surfactant production ad hoc. Therefore, there appears to have been a mechanism of physiologic evolution arising from external environmental stress, from unicellular to multicellular organisms, contingent on cellular compartmentation of genetic expression.

Using this cellular approach, even the evolution of the central nervous system can be traced from unicellular to multicellular organisms. Both paramecia and neurons communicate environmental information through calcium flux, in the case of the former as hyperpolarization, in the case of the latter as polarization and depolarization. Therefore, the evolution of the human brain can be seen as an arc of consciousness, beginning with the simplest organisms, culminating in creativity – “first there were bacteria, now there is New York” (Simon Conway Morris in *Complexity and the Arrow of Time*).

As independent corroboration of this foundational conceptualization for the origins of physiology, Jack Szostak has shown that lipid-based protocells can generate nucleotides, whereas nucleotides cannot produce lipids. This indicates that micelles preceded DNA–RNA, which may have evolved in supporting the evolutionary effort by providing a “long-term” memory for the adaptational strategy. That is to say, the nucleotide “memory mechanism” would have put those organisms that evolved DNA at an advantage due to their “reference library” for adaptive strategies rather than random selection. The obvious efficiency of the former would have put such organisms at an advantage, ultimately becoming the mode of life to the exclusion of non-DNA-based life forms.

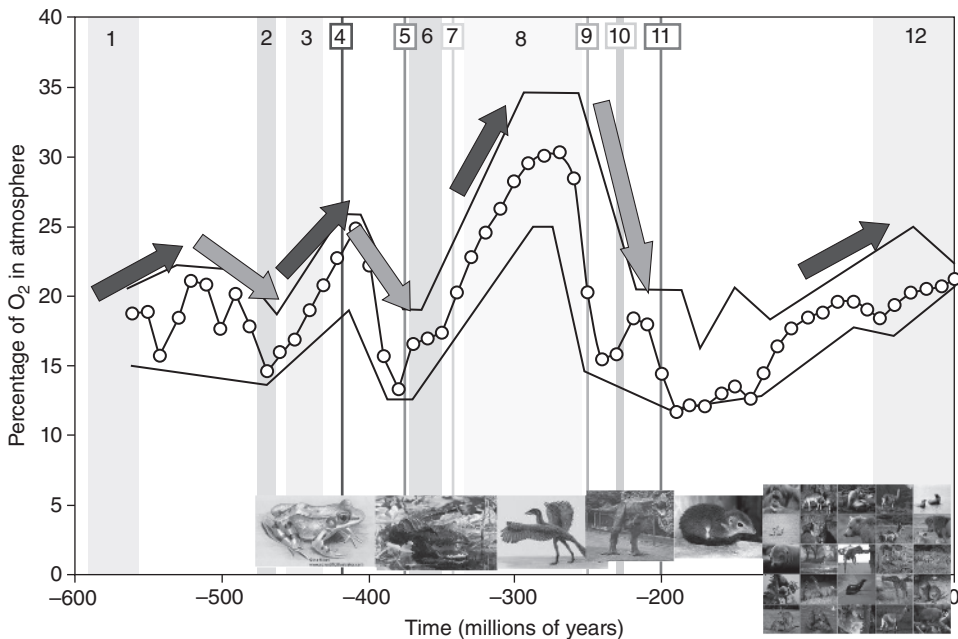


Figure 1.4 Phanerozoic oxygen, hypoxia and physiologic stress. Over the course of the last 500 million years, called the Phanerozoic eon, atmospheric oxygen levels have varied between 15% and 35%, fluctuating fairly drastically. The increases have been shown to foster metabolic drive, but the physiologic effects of the decreases have been overlooked. Hypoxia is the most potent physiologic agonist known, so the episodic decreases in atmospheric oxygen would have fostered remodeling of the internal organs. (See insert for color representation of the figure.)

These ontologic insights to the origin, creation, and perpetuation of physiology suggest a long-awaited approach to elucidating mechanisms for what Aristotle referred to as *entelechy*, a factor that directs the individual regularities of organisms; what Rupert Riedl referred to as *burden*, the responsibility carried by a feature or decision; what Wallace Arthur called *bias*; and what L.L. Whyte referred to as *coordinative conditions*: “The coordinative conditions hold the clue to the relation of physical laws to organic processes and to the unity of the organism.” Many have invoked the existence of an internal principle as the basic problem of evolutionary theory without providing a mechanistic understanding. Yet, we know that evolution is not a conscious process. The power of Darwinian evolution is in usurping the vitalists, yet they are encroaching yet again as creationists and intelligent designers!

The supporters of Synthetic Theory, on the other hand, hold that no causal mechanism has yet been proven. They are also concerned that the search for it would allow for such unproven phenomena as finality and entelechy. Entelechy, a concept taken from Aristotelian metaphysics, is assumed to be a factor that directs the individual regularities of organisms, specifically, their orderliness, harmony, plan, or goal. Entelechy would arise from the pre-established harmony of living organisms, which is outside the realm of science. Instead, these biologists tend to discount the problem, which is unfortunate. In some cases, they even claim that there is no place in the modern synthesis for an internal principle. However, it is important to note that even the authorities on this

viewpoint, such as Theodosius Dobzhansky, Curt Kosswig, and Ernst Mayr, acknowledge that the epigenetic system confers a fundamental, but not fully understood, ordering effect. They also ask whether this pattern of mutual gene effects will ever be understood, because of its complexity.

We maintain that the cellular-molecular, ontogenetic/phylogenetic approach provides the solution to this age-old quandary. Our working hypothesis is that the unicellular stage of the life cycle is the level of selection, going from zygote to zygote. This perspective has several advantages. It is based on the functional origin of life from the unicellular state, which naturally would integrate genotype and phenotype. And the iterative return to the unicellular state by metazoans during reproduction would provide the “filter” for newly acquired epigenetic marks from the environment, using ontogeny to recapitulate phylogeny as a means of determining the fidelity of any given mutation – reprising Haeckel’s Biogenetic Law (see Figure 1.2) after laying fallow for more than 200 years.

Additionally, all three states of unicellular organisms – homeostatic, mitotic, and meiotic – are determined by signaling from the cytoskeleton, which is ubiquitous in eukaryotes. Therefore, the unicellular state is self-organizing and autonomous.

In this Chapter, we have set the stage for a paradigm shift in the way we think about the evolution of vertebrate physiology based on mechanisms of cell–cell interactions. Chapter 2, entitled “On the Fractal Nature of Evolution,” will attempt to show the value added in the cellular-molecular approach to evolution, beginning at the origins of life. It is predicated on the balancing selection of calcium and lipids as the fundament of vertebrate evolution.

Selected Reference

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