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A Central Theory of Biology

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Abstract

The history of physiologic cellular–molecular interrelationships can be traced all the way back to the unicellular state by following the pathway formed by lipids ubiquitously accommodating calcium homeostasis, and its consequent adaptive effects on oxygen uptake by cells, tissues and organs. As a result, a cohesive, mechanistically integrated view of physiology can be formulated by recognizing the continuum comprising conception, development, physiologic homeostasis and death mediated by soluble growth factor signaling. Seeing such seemingly disparate processes as embryogenesis, chronic disease and dying as the gain and subsequent loss of cell–cell signaling provides a novel perspective for physiology and medicine. It is emblematic of the self-organizing, self-referential nature of life, starting from its origins. Such organizing principles obviate the pitfalls of teleologic evolution, conversely providing a way of resolving such seeming dichotomies as holism and reductionism, genotype and phenotype, emergence and contingence, proximate and ultimate causation in evolution, cells and organisms. The proposed approach is scale-free and predictive, offering a Central Theory of Biology.

Introduction

The underlying unity of nature has been sought ever since the time of the ancient Greek philosophers [1]. More recently, Whyte [2] formulated a way of thinking about Unitary Biology, but it lacked any scientific basis, making it untestable. Others, like David Bohm [3] and Herb Benson [4] have offered ways of generating unity, acknowledging the underlying problem of our own self-perception. The present hypothesis that complex physiologic traits evolved from the cell membrane of unicellular organisms offers a scientific basis for viewing biology as primarily being unicellular, multicellularity being an epiphenomenon (see definition in Table 1) [5,6]. This conceptualization is scale-free and predictive, offering a Central Theory of Biology.

The following is an exercise in Systems Biology, which can generally be viewed at several different levels – the gene, the transcript, the protein, the cell, the organ, the organ system, or the population – and clearly, evolution could have impacted these processes at any one of these levels. There are many such analyses in the literature, but they don't provide (vertically) integrated, functional genomic, evolutionary mechanisms that lead to novel

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insights to the underlying mechanisms, let alone to further experimentation, and ultimately to predictions. Selection pressure – intrinsic, extrinsic, or both – must be applied at a level where it can have the necessary homeostatic effect for survival, the level where the genetic expression is functionally integrated with the phenotype. The comprehensive 'middle-out, cellular-level-theory of evolution' approach described herein offers the advantage of minimizing *a posteriori* assumptions by focusing on Gene Regulatory Networks (GRNs). GRNs govern the expression levels of the mRNAs and proteins that generate form and function, particularly those that have evolved using the same conserved ontogenetic/phylogenetic, homeostatic, and regenerative cell-molecular motifs.

Vertebrate evolution chronicles the utilization of oxygen for ever-increasing metabolism [7]. Seen in their contemporary forms, one assumes that vertebrates evolved in direct response to metabolic drive, and yet this process is far more interactive than just evolution being 'fueled' by oxygen; the cellular mechanisms by which oxygen is intercalated into the biologic cellular mechanisms of ontogeny and phylogeny is a cipher [8–10]. When seen longitudinally as a functionally-linked continuum of emergent and contingent processes resulting from the recombination and permutation of genetic traits first expressed in unicellular organisms [5,6], a very different picture appears, like doing a crossword puzzle, and the answer spontaneously forms from the matrix.

Conventional Evolutionary Biology is teleological [11,12], undermining its mission in explaining the processes involved. Instead, by identifying mechanisms that were exapted [13] from seemingly unrelated ancestral traits is of particular value in avoiding such 'Just So Stories'.

In this regard, the events surrounding the water-land transition that fostered vertebrate adaptation to land are instructive, and are highly relevant to human physiology. Moreover, because they provide insight to the emergent and contingent mechanisms underlying endothermy/homeothermy in mammals and birds, they can be reverse-engineered to determine the intermediate physiologic steps in land vertebrate evolution.

Water–land transition as the catalyst for vertebrate evolution

Based on the Romer Hypothesis [14], land vertebrates emerged from water some 400 MYA in response to the desiccating effect of rising levels of carbon dioxide in the atmosphere [15], drying up bodies of water globally. Based on the fossil record, vertebrates breached land on at least five occasions, indicating the magnitude and direction of the selection pressure to 'Gain Ground' [16]. Remarkably, no attention has been paid to the obligatory, concomitant evolution of the visceral organs involved during this key transitional period, other than to document the phylogenetic differences between fish, amphibians, reptiles, mammals and birds [17]. The disconnect between such phenotypic observations and the underlying mechanisms of evolution is due to the systematic emphasis placed on random mutation and population selection by conventional Darwinian evolutionists [18]. In contrast to this dogmatic approach, Torday and Rehan [19] have pointed out the value added in determining the cellular–molecular adaptation to oxygenation in forming the mammalian lung through the specific cell–cell interactions that determine its embryogenesis. Such cellular mechanisms are mediated by soluble growth factors and their receptors [20], acting

iteratively in response to alternating external and internal selection pressures to generate form and function [21] based on homeostatic principles [5,6]. The history of such cellular–molecular interrelationships can be traced all the way back to the unicellular state by following the pathways formed by lipids in accommodating calcium homeostasis, and their consequent effects on oxygen uptake by cells, tissues and organs [6]. Through this *a priori* understanding of the fundament of evolution, the pitfalls of teleology and tautology can be avoided, and instead a predictive model of Evolutionary Biology can be formulated as follows.

Parathyroid Hormone-related Protein signaling is key to understanding the evolution of the lung

The key empiric observation for understanding the evolution of the mammalian lung was the discovery that Parathyroid Hormone-related Protein (PTHrP) (Fig. 1), is necessary for the formation of alveoli [22], the gas exchange units that have fostered the evolution of the lung from the swim bladder of fish [23]. When the PTHrP gene is deleted from the developing mouse embryo, the lung does not form alveoli [22]. PTHrP is synthesized and secreted by the alveolar epithelial type II cell, binding to the neighboring lung fibroblast via the G Protein-coupled PTHrP Receptor (PTHrPR). This triggers the intracellular Protein Kinase A pathway, inducing the lipofibroblast phenotype [24,25]. These cells protect the lung against oxidant injury by actively accumulating and storing neutral lipids [26]. Lipofibroblasts subsequently evolved the capacity to actively provide neutral lipid substrate for lung surfactant phospholipid synthesis [27,28]. Paracrine signaling from the lipofibroblast to the alveolar type II cell is mediated by the locally-acting paracrine hormone leptin, which stimulates lung surfactant synthesis by the alveolar type II cell [29]. These mutually-interactive cell–cell interactions facilitate the molecular cross-talk between PTHrP and leptin for the mechanically-regulated production of surfactant, since PTHrP, leptin, and their respective cell-surface receptors are all coordinately stretch-regulated genes [30]. The Neutral Lipid Trafficking process [31] is orchestrated by Adipocyte Differentiation Related Protein [32], which mediates the uptake, storage and transit of neutral lipid from the lipofibroblast to the alveolar type II cell [33].

Once these cellular–molecular aspects of the functionally integrated mechanism for homeostatic regulation of lung surfactant were reconstructed [31], it became evident that they must have resulted from evolutionary selection pressure for specific cellular functions, i.e., since the lipofibroblast and alveolar type II cell each took a minimum of 3×10^9 years to evolve the mammalian lung [5,6], the probability of this occurring by chance alone would have taken the multiplicative product of the two, which is longer than the existence of the Earth, or the Universe itself for that matter ($>9 \times 10^{18}$ years). Therefore, understanding the functional interrelationships between the individual molecular mechanisms involved and their phenotypes lay in how the lung surfactant subserves the alveoli both ontogenetically and phylogenetically [5,6]. That is to say, the overarching process of lung evolution is characterized by the progressive decrease in alveolar diameter, which facilitates gas exchange by increasing the surface area-to-blood volume ratio between the alveolus and the alveolar capillaries that transfer oxygen to the peripheral tissues and organs.

The physics of lung evolution

The Law of Laplace dictates that surface tension is inversely proportional to the diameter of a sphere such as the alveolus. We know from extensive phylogenetic studies by Daniels and Orgeig [34–37] that the composition of the surfactant, and therefore its surface tension-reducing capacity has changed progressively to compensate for the increasing surface tension caused by the evolutionary decrease in alveolar diameter. But that begs the question as to what cellular–molecular mechanisms facilitated such accommodations. Given that epithelial-mesenchymal interactions are responsible for alveolar morphogenesis [38,39], culminating in surfactant-mediated alveolar homeostasis, the logical hypothesis was that the epithelial and mesenchymal cells generating the alveoli evolved under selection pressure to modify the composition and production of the surfactant, fostering both the phylogenetic and ontogenetic decreases in alveolar diameter [40].

The mammalian lung evolved from the fish swim bladder [24], which uses gases to regulate buoyancy for feeding and other bodily functions. The swim bladder of physostomous fish is an outpouching of the esophagus, connected to the alimentary tract by the pneumatic duct, which is homologous with the trachea [41]. For example, at the cell-molecular level both the pneumatic duct and trachea are formed from smooth muscle controlled by the interaction between Hedgehog and FGF10 [42,43]. Furthermore, the swim bladder is lined by gas gland epithelial cells that synthesize and secrete cholesterol, the most primitive form of lung surfactant [34–37]. Moreover, PTHrP is among the most highly expressed genes in Zebra Fish swim bladder development [23]. Therefore, the functional homology between the swim bladder and lung can be discerned as the utilization of lipid to facilitate gas exchange. Utilizing cholesterol, the most primitive surfactant [34–37] to lubricate the inner surface of the swim bladder facilitates buoyancy for feeding on algae, which are 90% lipid. This gas exchange mechanism is functionally homologous with the mammalian lung, utilizing surfactant phospholipids to facilitate gas exchange for efficient metabolism. This is essentially how Francois Jacob famously described evolution – as ‘tinkering’ [44]. However, up until now this process has been seen as the chance result of Darwinian mutation and selection, whereas in the present model structure and function have evolved from pre-existing cellular–molecular traits [5,6,23], determined by homeostatic changes in growth factor-mediated cell–cell communication. The mechanism of selection remains the traditional one of fitness.

Functional homology between membrane lipids and oxygenation

These cellular–molecular homologies raise the question as to what atavistic unicellular trait or traits might have formed the basis for the functional interrelationships between membrane lipids and oxygenation. Early in the evolution of unicellular organisms, oxidant stress caused endoplasmic reticulum stress [45], resulting in the release of potentially toxic levels of stored calcium into the cytoplasm. To compensate for this, de Duve hypothesized [46] the advent of the peroxisome in unicellular organisms, an organelle that utilizes lipids to protect against such excesses in intracellular calcium [47]. This ancient relationship between the peroxisome, the endoplasmic reticulum stress and calcium homeostasis may underpin the ubiquitous effects of Peroxisome Proliferator Activated Receptor gamma (PPARγ) in preventing and treating a wide variety of inflammatory diseases [48–50]. And this same

receptor is crucial to longevity in laboratory mice [51], life span being determined by the same cell–cell communications that evolved to maintain calcium-lipid homeostasis [5,6]. PPARγ is the nuclear transcription factor that determines the adipocyte phenotype [52], which protects against oxidant injury [53]. When PPARγ is inhibited [54], the adipocyte re-expresses its atavistic muscle phenotype [55], characterized by alpha smooth muscle actin (αSMA). The contrast between the adipocyte and muscle phenotypes reprises the seminal role of cholesterol in facilitating the evolution of eukaryotes [5]. As for the evolutionary origins of this relationship, Barbara Wold's research [56] has shown that cultured muscle cells will spontaneously differentiate into adipocytes in 21% oxygen (room air), but not if cultured in 6% oxygen, bespeaking the role of atmospheric oxygen in the origins of the adipocyte phenotype.

Another functional indication for the role of lipid-calcium epistasis (see definition in Table 1) in evolution is the homology between the lung and skin (Fig. 2). Both organs synthesize and secrete lipid-containing lamellar bodies in combination with host defense peptides to form watertight, antimicrobial 'barriers'. In the case of the skin, the stratum corneum secretes such an extracellular lipid-antimicrobial barrier [57]. In the case of the alveolus, the alveolar type II cell secretes the surfactant film, termed tubular myelin [58], a lipid–protein complex composed of phospholipids and Surfactant Protein A (an antimicrobial peptide), similar in composition and structure to the lipid barrier formed by the stratum corneum.

So there is a fundamental homology between lipids, anti-microbial peptides and barrier function exhibited by both the lung and skin. These structural–functional homologies refer as far back as the unicellular state, in which the cell membranes of eukaryotes were populated by cholesterol [5,59,60]. In turn, the advent of cell membrane cholesterol promoted gas exchange, motility and metabolism [5,6], the major evolutionary characteristics of all vertebrates [61]. And since we now have experimental evidence that the unicellular form expresses the complete 'toolkit' for multicellular organisms [62,63], it is feasible that the lipid-oxygen-barrier homology between the lung and skin evolved from the plasma lemma of unicellular organisms. Experimentally, manipulation of cell membrane cholesterol has shown that increasing the cholesterol content is cytoprotective [64], whereas loss of membrane cholesterol can cause cell death [65].

Atmospheric oxygen, physiologic stress, gene duplication and lung evolution

As indicated at the outset, the hypothesis to be tested is that visceral organ changes during the water-land transition were caused by physiologic stress. Based on the adaptive changes cited above, consider the consequences of episodic fluctuations in environmental oxygen [66], initially protected against by sterol hopanoids found in prokaryotic bacteria. Mechanistically, oxygen stimulates the SREBP/Scap family of enzymes that regulate sterol biosynthesis in prokaryotes and eukaryotes alike [67], reflecting the depth of this evolved trait. Konrad Bloch had hypothesized that the synthesis of cholesterol was due to the increased availability of atmospheric oxygen, since it takes six molecules of oxygen to make one molecule of cholesterol [68]; however bacteria do not produce cholesterol, so the oxygen-sterol connection must have some other origin.

For example, Deamer has written extensively on the role of polycyclic hydrocarbons, omnipresent throughout the Universe, in the origins of life [69]. Aromatic molecules delivered to the young Earth during the heavy bombardment phase in the early history of our solar system [70] were likely to be among the most abundant and stable organic compounds available. The Aromatic World hypothesis [71] theory suggests that aromatic molecules might function as container elements, energy transduction elements and templating genetic components for early life forms. These molecules can experimentally stabilize fatty acid vesicles [72] much like cholesterol does in contemporary cell membranes, and can foster the biosynthesis of nucleotides [73].

During the Phanerozoic period, much larger fluctuations in atmospheric oxygen, ranging between 12% and 35% [66] are widely recognized to have caused dramatic increases in animal body size [74]; what has not been addressed previously are the physiologic consequences of the concomitant, episodic decreases in oxygen that followed the increases, documented by Berner et al. [66]. The effect of hypoxia, the most potent physiologic stressor known, is mediated by the Hypothalamic–Pituitary–Adrenal Axis in vertebrates. Pituitary ACTH stimulating corticoid production by the adrenal cortex subsequently stimulates catecholamine production by the downstream adrenal medulla [75]. This physiologic mechanism is of evolutionary significance because catecholamines cause surfactant secretion from the lung alveoli, which would acutely have alleviated the hypoxic stress on the lung by further reducing surface tension, consequently increasing the distention of the alveolar wall. In turn, that would have stimulated alveolar type II cell PTHrP production [30], coordinately increasing both alveolarization [22] and alveolar vascular perfusion. PTHrP is both a potent vasodilator [76], and an angiogenic factor [77], thus comprehensively promoting the physiologic increase in gas exchange surface area over the course of evolutionary time.

Most importantly, the PTHrPR duplicated during the water-land transition [78], amplifying the PTHrP signaling pathway, thus validating this hypothetical evolutionary mechanism based on empiric evidence. One might wonder why the PTHrPR gene duplicated at this critical juncture in vertebrate evolution [79]. As mentioned above, the visceral adaptive changes occurred in concert with at least five independent skeletal changes in order to breach land. The success of this path may specifically relate to the PTHrP signaling pathway, which directly affects bone formation and remodeling. Bone will re-conform structurally in response to physical force, referred to as Wolff's Law. The only known mechanism for this effect is mediated by PTHrP [80], a gravisensor that regulates calcium uptake and accumulation by bone locally [81].

Duplication of the β adrenergic receptor and the glucocorticoid receptor genes

In further support of this hypothetical mechanism for physiologic adaptation, the other two gene duplications known to have occurred during the water–land transition were the βAdrenergic Receptor (βAR) [82] and the Glucocorticoid Receptor (GR) [83], both of which facilitated vertebrate land adaptation. The increase in βARs alleviated the constraint on pulmonary blood pressure independent of systemic blood pressure. The GR evolved from the Mineralocorticoid Receptor (MR), likely due to the constraint of the orthostatic increase

in blood pressure due to the increased force of gravity on land adapting vertebrates; this was exacerbated by the effect of stress on mineralocorticoid stimulation of blood pressure, now offset by diverting some MR expression to the GR. This, combined with the synergistic effect of adrenocortical glucocorticoid production on adrenomedullary βAR production synergized integrated physiology.

Increased PTHrP signaling in soft tissues such as the lung during the water-land transition would initially have promoted positive selection for those members of the species adapting to land having higher levels of PTHrP to facilitate bone adaptation. Moreover, physiologic stress is known to cause microvascular capillary shear stress, which causes genetic mutations, including gene duplications [84]. Such an effect, particularly on the nascent pulmonary microvasculature was critical for land adaptation, increased breathing causing stress on the lung microvasculature in particular.

Evolution of endothermy/homeothermy as evidence for the effect of stress on vertebrate physiologic evolution

One can easily argue whether these physiologic adaptations were causal since there is no ‘hard’ fossil evidence for this sequence of events, though the functional relationships are consistent with their contemporary roles in ontogenetically forming and phylogenetically maintaining homeostasis *a posteriori*. There is also an *a priori* scenario for the subsequent evolution of these integrated physiologic traits that is internally consistent with their ontogeny and phylogeny through the advent of endothermy/homeothermy. Since a non-teleologic explanation for the evolution of endothermy/homeothermy has not previously been formulated [85–87], by exploiting the above-mentioned gene duplications, a mechanism that entails such pre-existing physiologic traits that may conditionally have given rise to endothermy/homeothermy is proposed. In the scenario cited above for the selection advantage of catecholamines alleviating the constraint on air breathing, catecholamines would secondarily have caused the secretion of fatty acids from peripheral fat cells, consequently increasing metabolism and body temperature.

In tandem with the effect of intermittent hypoxia on catecholamine release of fatty acids from fat cells, adrenaline has also been shown to stimulate leptin secretion by adipocytes [88]. Leptin, in turn, has been shown to increase the basal metabolic rate of ectothermic Fence Lizards [89], consistent with the putative role of adrenaline in the evolution of endothermy.

The increase in body temperature would have interacted synergistically with the evolved mammalian lung surfactant, composed of saturated phosphatidylcholine, which functions 300% more actively to reduce surface tension at 37 °C than at 25 °C. This effect is due to the elevated phase transition temperature of saturated phosphatidylcholine (41 °C), the temperature at which the lung surfactant film collapses, no longer acting to reduce surface tension. The selection pressure for the co-evolution of saturated phosphatidylcholine production by the alveoli and endothermy/homeothermy may have been due to the pleiotropic effects of catecholamines, stimulating both surfactant secretion by the alveoli, and coordinately increasing the unsaturated fatty acid composition of peripheral cell membranes [90], thereby increasing oxygen uptake by increasing membrane fluidity. The

progressive phylogenetic increase in the percentage of saturated phosphatidylcholine in lung surfactant [34–37] is indicative of the constitutive change in adaptation to endothermy/homeothermy. These fundamental changes in lipid composition in service to metabolism are exaptations of the events that initiated eukaryotic evolution [5]. Considering the severe conditions generated by Romer's Gap [91], during which vertebrates were virtually wiped off the face of the Earth, it should not be surprising that such deep homologies were recruited [5,6] during this critical phase of vertebrate evolution.

Hibernation as reverse evolution

The causal nature of the interrelationship between physiologic stress, catecholamines and endothermy/homeothermy is validated by the reverse effects of hibernation or torpor on lung surfactant lipid composition and cell membrane fatty acid composition. Under such conditionally low stress conditions, decreased catecholamine production results in both increased surfactant cholesterol [92], rendering lung surfactant less surface active, and decreased unsaturated fatty acid content of cell membranes [93], adaptively reducing oxygen uptake.

There is a phylogenetic precedent for lung surfactant facultatively accommodating ambient temperature. For example, in a study by Lau and Keogh [94] it was found that maintaining Map turtles at different ambient temperatures adaptively altered the composition of their lung surfactant. Ultimately, the ability to optimize lung alveolar physiology at various environmental temperatures may have been the precursor to endothermy/homeothermy. Experimental evidence for the causal interrelationships between body temperature [95], surfactant composition [96] and catecholamine regulation of surfactant secretion [97] supports this hypothesis.

The cellular accommodation of environmental temperature by lipids is hypothetically an exaptation for the fundamental enabling effects of cholesterol at the origins of eukaryotic evolution. That this is not merely an association is corroborated by the evolution of the alveolar lipofibroblast in mammals. These adipocyte homologs, located within the alveolar wall contiguous with the alveolar epithelial cells that produce surfactant [98] provide a ready source of substrate for increased surfactant phospholipid production under physiologic demand for oxygen via the stretch-regulated mechanism described above. As further evidence for this hypothetical evolutionary mechanism, when cholesterol synthesis by alveolar type II cell is experimentally inhibited in the developing mouse lung alveolar type II cell by deleting the Scap gene, the lung alveoli effectively compensate by increasing the number of lipofibroblasts [99]. This compensatory mechanism is apparently due to the observed concomitant increase in PPARγ expression by these cells [100], likely due to endoplasmic reticulum stress, reprising how peroxisomes evolved in the first place [45]. It is precisely such atavistic traits which can be exploited for the diagnosis and treatment of disease, as well as understanding what constitutes 'health' [9].

As further evidence in support of the hypothesized role of hypoxia-induced endothermy/homeothermy, there are other significant mammalian-specific changes that occurred during vertebrate evolution that are functionally consistent with this mechanism. First, PTHrP appears in both the mammalian pituitary [101] and adrenal cortex [102], thus amplifying the

fight-or-flight mechanism (Fig. 3). Furthermore, Richard Wurtman [103] has discovered that there are complex vascular arcades in the mammalian adrenal medulla, which act to amplify the production of catecholamines under stress conditions, as follows. In response to ACTH stimulation, Glucocorticoids produced in the adrenal cortex pass down through the adrenal medulla, where they stimulate the rate-limiting step in catecholamine biosynthesis, Catechol-O-Methyl Transferase, enhancing adrenaline production for the stress reaction. This expansion of the medullary microvasculature may itself have been caused by the adrenocortical secretion of PTHrP, which is directly angiogenic [77]. Speculatively, the combined effects of PTHrP on the adrenal cortex and medulla may have fostered the structural integration of the independent cortical and chromaffin tissues of fish in transition to the amphibian corticomedullary configuration, as shown in Table 2.

It is also feasible that this complex cascade of physiologic stress-mediated cellular mechanisms gave rise to the kidney glomerulus, which is largely absent in fish [104], but is ubiquitous in amphibians, reptiles, mammals and birds. PTHrP is the mediator of fluid and electrolyte balance in the glomerulus, being secreted by the podocytes lining this compartment, binding to its receptor on the mesangium, which regulates the amounts of fluid and electrolytes entering the kidney tubules [105]; as is the case for the lung, the distension of the glomerulus is sensed by the podocyte, which then transduces that signal for fluid and electrolyte balance via PTHrP signaling. Here again is a functional homology between seemingly structurally and functionally disparate tissues and organs based on descriptive biology, representing the pleiotropic distribution of the same cellular–molecular trait for both breathing and for fluid and electrolyte balance. This trait may also have evolved under the influence of increased catecholamine production due to physiologic stress, since epinephrine inhibits loss of water and salt from the kidney [106,107] in adaptation to land.

In further support of this complex scenario for the evolution of land vertebrate physiology, it has been observed that the genome decreased by about 80–90% after the Cambrian Extinction (Fig. 4) [108]. The advent of endothermy may explain this phenomenon because ectotherms require multiple isoforms for the same metabolic enzyme in order to function at variable ambient temperatures [109], whereas the uniform body temperature of endotherms only requires one metabolic isoform to function optimally [110]. Since metabolic genes account for 17% of the human genome [111], representing a fraction of the number of metabolic genes expressed by ectotherms, this reduction in metabolic enzyme heterogeneity would have contributed to the dramatic decrease in post-Cambrian genomic size [112].

Predictive power of the cellular–molecular approach to evolution

Starting with the unicellular perspective on the life cycle as the primary level of selection [6], and the necessity of returning to it as the adaptive strategy for epigenetic inheritance, the cellular–molecular approach is highly predictive in comparison to the conventionally dogmatic descriptive view of biology that we have held for thousands of years. The recognition that the cell membrane is the homolog for all complex physiologic traits [6] forms the basis for understanding the First Principles of Physiology [6]. And by focusing on the mechanistic transition from the unicellular state to the multicellular organism during

both ontogeny and phylogeny, such seemingly insoluble properties of life as pleiotropy [5], the stages of the life cycle, [6] and the aging process [5] can all be understood as one continuous process in service to emergence and contingence.

Perhaps more to the point, regarding the predictive power of the cellular approach to evolution, it has recently been hypothesized that among amniotes, the alveolar lung of mammals may have been the earliest adaptation for land life, followed by its simplification in snakes and lizards [109]. There is no mechanistic basis for such speculation, as interesting as this idea is; in fact, it runs counter to the developmental pattern of the mammalian lung, which begins as simple sacs that become progressively more structurally complex, consistent with the phylogeny of the lung evolving from the swim bladder [23]. I have previously pointed out the systematic error made in showing associations in evolution without offering a mechanistically causal relationship to environmental factor(s) [110], particularly at the cellular–molecular level in an attempt to determine relationships to other related evolutionary mechanisms [9], given the complex nature of this process. In that spirit, I have applied the hypothetical role of physiologic stress in mammalian lung evolution to other amniotes with ‘simple’ lungs. The simple sac-like lungs of other amniotes is associated with a lack of an adrenaline response to corticoid-mediated stress due to the fundamental difference in the configuration of the adrenal glands in mammals versus other amniotes; it is helpful here to keep in mind that the fish adrenal is composed of two separate organs for the elaboration of corticoids and catecholamines [101]. In mammals, the adrenal cortex lies on top of the medulla as a separate structure, and the corticoids secreted by the cortex pass down through the medulla, amplifying adrenaline production by stimulating Catechol-O-methyltransferase, the rate-limiting step in adrenaline synthesis [111]. In all of the other amniotes, the chromaffin cells that synthesize catecholamines are interspersed within the cortical tissue, and the relationship between stress and adrenaline production is not as well delineated [112]. Clearly, non-mammalian amniotes evolved another mechanism to cope with the physiologic stresses of land adaptation, and seemingly as a consequence, their adaptation for breathing as well. The comparators are birds, which have a ‘stiff’ lung composed of large air sacs [113]. The lungs are attached to the dorsal wall of the thorax during embryogenesis [114]. Furthermore, air entering the lung flows in only one direction [115], unlike the reciprocating nature of the mammalian lung, indicating a fundamentally different way of adapting to air breathing in birds. Embryonic alligators also exhibit the attachment of the lung to the chest wall during embryogenesis (personal observation), and in the adult (Thomas Owerkowicz, personal communication) in association with unidirectional air flow, in further support of the speculation that the fixing the lung to the chest wall during development is in service to the unidirectional flow of air. This supposition is further supported by the fact that birds have blood glucose levels 10–15 times higher than mammals [116], suggesting that instead of secreting fatty acids from fat stores in response to adrenaline for metabolic ‘fuel’ on an ‘as-needed’ basis via the fight-or-flight mechanism used by mammals, birds are constantly in a ‘metabolically-on’ mode.

Moreover, it is noteworthy in the context of metabolic evolution that both birds and humans are bipedal, which may have been a consequence of their both being endotherms. Being upright is metabolically costly [117], but by increasing their body temperatures in adaptation to land, both birds and humans have become much more metabolically efficient-cold-

blooded organisms require multiple isoforms of the same metabolic enzyme to survive at ambient temperatures, whereas endotherms usually have only one isoform. Bipedalism may have resulted, freeing the forelegs to evolve into wings and hands with prehensile thumbs through common genetic motifs.

The hypothesized evolutionary physiologic interrelationship between stress, metabolism and endothermy may underlie the effect of meditation on hypometabolism [118]. It has long been known that Yogis have the capacity to regulate their metabolism at will [119], and formal study of this phenomenon has validated it scientifically. Functionally linking to ever-deeper principles of physiologic evolution through meditation and bio-feedback may prove to be of wider benefit in healing, both conventional and self-healing alike.

Conclusion

By focusing on the necessity and utility of lipids in initiating and facilitating the evolution of eukaryotes [5,6], a cohesive evolutionary strategy becomes tenable. In fostering metabolism, gas exchange, locomotion, and endocytosis/exocytosis, cholesterol in the cell membrane of unicellular eukaryotes formed the basis for what was to come [5,6]. The basic difference between prokaryotes and eukaryotes is the soft, compliant cell membrane of the latter, interacting with the external environment, adapting to it by internalizing it using the endomembrane system as an extension of the cell membrane. This iterative process was set in motion by competition with prokaryotes, which can emulate pseudo-multicellular behaviors like Biofilm [120] and Quorum Sensing [121]. All of the examples cited in this paper-peroxisomes, the water-land transition, lipofibroblasts, endothermy/homeothermy – are functional fractals of the originating principle of lipids in service to the evolution of eukaryotes.

Following the course of vertebrate physiology from its unicellular origins instead of its overt phenotypic appearances and functional associations provides a robust, predictive picture of how and why complex physiology evolved from unicellular organisms. This approach lends itself to a deeper understanding of such fundamentals as the First Principles Physiology. From these emerge the reasons for life cycles and why all organisms always return to the unicellular state, pleiotropy, homeostasis. A coherent rationale is provided for embryogenesis and the subsequent stages of life, offering a context in which epigenetic marks are introduced to the genome.

From the beginning of life, there has been tension between calcium and lipid homeostasis [5,6,45–47], alleviated by the formation of calcium channels by exploiting those self-same lipids [47], yielding a common evolutionary strategy. The subsequent rise in atmospheric carbon dioxide, generating carbonic acid when dissolved in water, caused increased calcium leeching from rock [122]. Calcium is essential for all metabolism, and it is through calcium-based mechanisms that the inception of life is marked by a calcium spark kindled by sperm fertilization of the ovum [123], a process that sustains the processes of life until the time of death [124]; perhaps the aura that near-death experiences have chronicled is that very same calcium spark.

A cohesive, mechanistically integrated view of physiology has long been sought. Whyte described it as Unitary Biology [2], but the concept lacked a scientifically causal basis, so it remained philosophy. But with the advent of growth factor signaling as the mechanistic basis for molecular embryology in 1978 [125], Whyte's vision of a singularity may now be realized.

Throughout this article, the contrast between conventional descriptive physiology and the deep mechanistic insights gained by referring back to the epistatic balance between calcium and lipids, mediated through homeostasis has been highlighted. It is emblematic of the self-organizing [1], self-referential [127] nature described for the origin of life itself. Using this organizing principle avoids the perennial pitfalls of teleology [11], conversely providing a way of resolving such seeming dichotomies as genotype and phenotype, emergence and contingence, unicellular organisms and vast multicellular organisms. Insight to the fundamental interrelationship between calcium and lipid homeostasis was first chronicled in Evolutionary Biology, Cell–Cell Communication and Complex Disease [5]. Further research will solidify the utility of focusing on the advent and roles of cholesterol in eukaryotic evolution, extending from unicellular to multicellular organisms and provide novel insights to the true nature of the evolutionary continuum in an unprecedented predictive and reproducible manner.

This understanding of the 'how and why' of Evolution provides the unprecedented basis for a Central Theory of Biology, which is long overdue. Many have given up on the notion of a predictive model for biology [128,129] akin to those for chemistry or physics [128,129]. This is largely due to the failure to realize that contemporary biology is descriptive [6,11], i.e. that describing a mechanism is not the same as actually determining causation based on founding principles, like Quantum Mechanics and Relativity Theory. This may seem surprising in the wake of the publication of the Human Genome, which is only 19% of the predicted size [130]. That alone should have generated criticism of the prevailing way in which biology is seen as a *fait a complete*, characterized by correlations and associations [5,6]. John Ioannidis has declared that 'most published research findings are false' [131]. This may be because we are using a descriptive framework, which generates associations and correlations, but ultimately will not allow for predictions.

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Further reading

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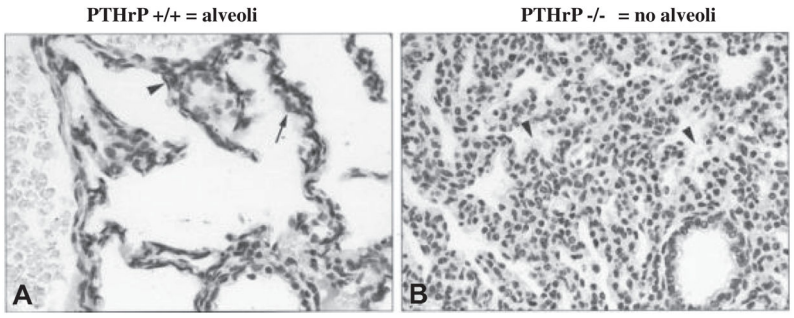

Fig. 1.
PTHrP.

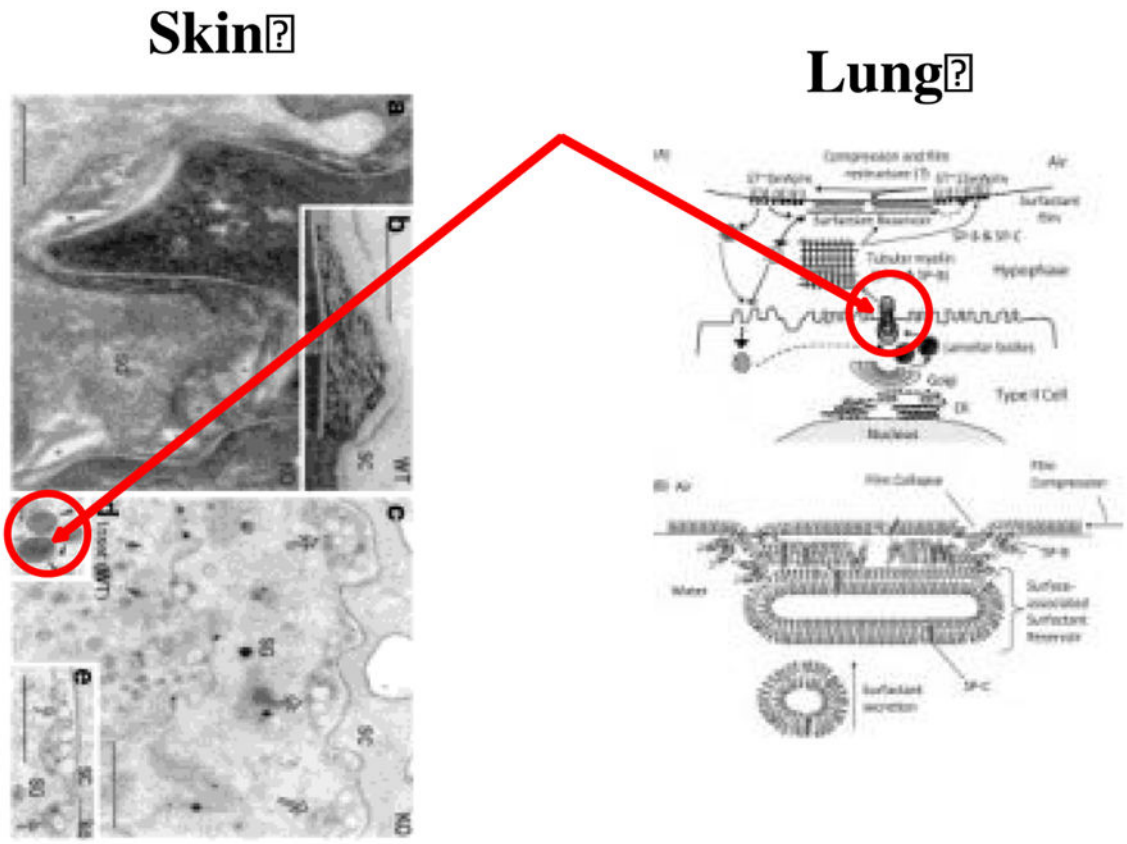

Fig. 2.

Skin–lung homology. Both organs synthesize and secrete lipid-containing lamellar bodies in combination with host defense peptides to form a watertight, antimicrobial barrier.

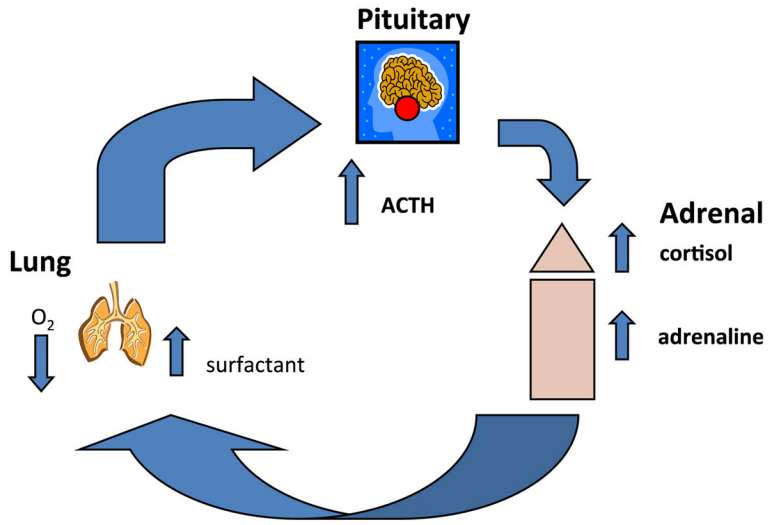

Fig. 3.

On the evolution of endothermy. It is hypothesized that intermittent hypoxia occurred during vertebrate adaptation to land, causing increased adrenaline production by the adrenal gland, relieving the constraint on the alveoli by stimulating surfactant production. The distension of the alveoli stimulated Parathyroid Hormone-related Protein production within the alveolar wall, ultimately increasing alveolarization.

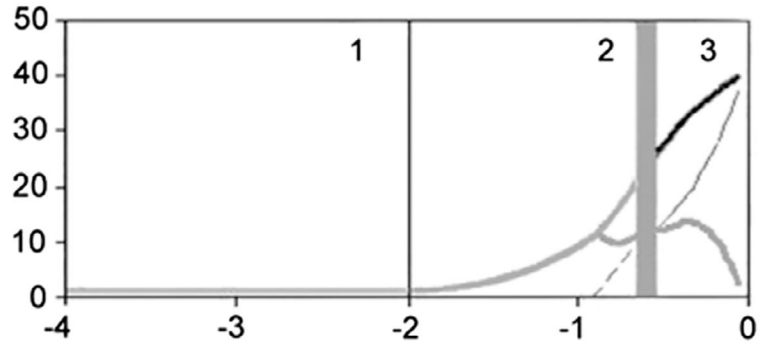

Fig. 4.

Decrease in genome size after the Cambrian Extinction. It is hypothesized that the decrease in minimum genome size after the Cambrian Extinction was caused in large part by the evolution of endothermy.

Table 1

Parathyroid Hormone-related Protein (PTHrP) deletion causes failed alveolarization. Deletion of the PTHrP gene in developing mice causes failure to form lung alveoli.

Contingence: an event that may occur but that is not likely or intended; a possibility
Emergence: is the process of complex pattern formation from more basic constituent parts
Epiphenomenon: is a secondary phenomenon that occurs alongside or in parallel to a primary phenomenon
Epistasis: a phenomenon that consists of the effect of one gene being dependent on the presence of one or more ‘modifier genes’
Homeostasis: the tendency of a system, especially the physiological system of higher animals, to maintain internal stability, owing to the coordinated response of its parts to any situation or stimulus that would tend to disturb its normal condition or function

Table 2

The combined effects of Parathyroid Hormone-related Protein on the adrenal cortex and medulla may have fostered the structural integration of the independent cortical and chromaffin tissues of fish in transition to the amphibian corticomedullary configuration.

Lung phenotype	Adrenal phenotype	Epinephrine effect on lung evolution
Alveolar	Cortex–medullar separate	+
Non-alveolar	Medullary tissue in cortex	−