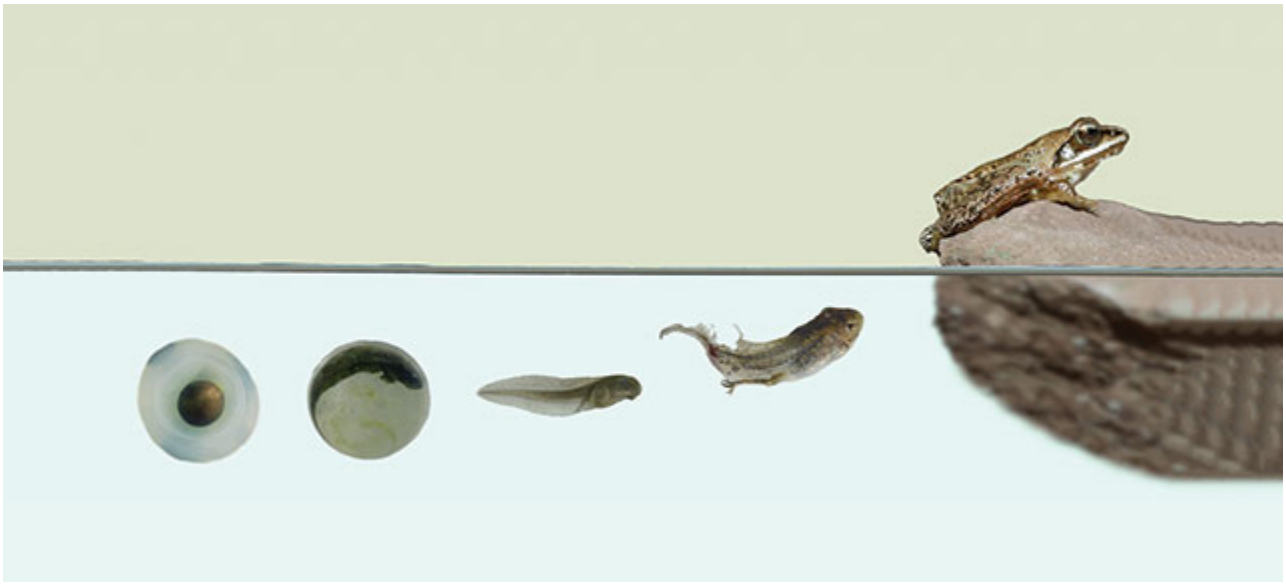
The Ever-Transcendent Cell

Deriving physiologic first principles

By John S. Torday | November 1, 2014



Both the developmental and phylogenetic histories of an organism describe the evolution of physiology—the complex of metabolic pathways that govern the function of an organism as a whole. The necessity of establishing and maintaining homeostatic mechanisms began at the cellular level, with the very first cells, and homeostasis provides the underlying selection pressure fueling evolution.

While the events leading to the formation of the first functioning cell are debatable, a critical one was certainly the formation of simple lipid-enclosed vesicles, which provided a protected space for the

evolution of metabolic pathways. Protocells evolved from a common ancestor that experienced environmental stresses early in the history of cellular development, such as acidic ocean conditions and low atmospheric oxygen levels, which shaped the evolution of metabolism.

As primitive protocells evolved to form prokaryotes and, much later, eukaryotes, changes to the cell membrane occurred that were critical to the maintenance of chemiosmosis, the generation of bioenergy through the partitioning of ions. The incorporation of cholesterol into the plasma membrane surrounding primitive eukaryotic cells marked the beginning of their differentiation from prokaryotes. Cholesterol imparted more fluidity to eukaryotic cell membranes, enhancing functionality by increasing motility and endocytosis. Membrane deformability also allowed for increased gas exchange.

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Acidification of the oceans by atmospheric carbon dioxide generated high intracellular calcium ion concentrations in primitive aquatic eukaryotes, which had to be lowered to prevent toxic effects, namely the aggregation of nucleotides, proteins, and lipids. The early cells achieved this by the evolution of calcium channels composed of cholesterol embedded within the cell's plasma membrane, and of internal membranes, such as that of the endoplasmic reticulum, peroxisomes, and other cytoplasmic organelles, which hosted intracellular chemiosmosis and helped regulate calcium.

As eukaryotes thrived, they experienced increasingly competitive pressure for metabolic efficiency. Engulfed bacteria, assimilated as mitochondria, provided more bioenergy. As the evolution of eukaryotic organisms progressed, metabolic cooperation evolved, perhaps to enable competition with biofilm-forming, quorum-sensing prokaryotes. The subsequent appearance of multicellular eukaryotes expressing cellular growth factors and their respective receptors facilitated cell-cell signaling, forming the basis for an explosion of multicellular eukaryote evolution, culminating in the metazoans.

Casting a cellular perspective on evolution highlights the integration of genotype and phenotype. Starting from the protocell membrane, the functional homolog for all complex metazoan organs, it offers a way of experimentally determining the role of genes that fostered evolution based on the ontogeny and phylogeny of cellular processes that can be traced back, in some cases, to our last universal common ancestor. (See "Ancient Life in the Information Age," *The Scientist*, March 2014.) It is commonplace for evolutionists to note that modern traits evolved from preexisting traits. The logical extension is that all the physiological traits of modern organisms evolved from their unicellular origins. Selection at the level of the cell was rejected by evolutionists as Lamarckian. Yet Lamarck is back in favor in the guise of epigenetics. His theory that the environment directly causes changes in animals is consistent with epigenetic inheritance. Therefore, invoking cell biology in the context of evolutionary theory is timely.

Return to the unicellular state

The reduction of evolution to cell biology may answer the perennially unresolved question of why organisms return to their unicellular origins during the life cycle in the form of zygotes. Maybe ontogeny does recapitulate phylogeny during embryogenesis to query the homeostatic mechanisms that evolved to facilitate the multicellular state. Without such a "fail-safe" mechanism, I speculate that all organisms would have drifted away from their foundational principles of evolution and away from those critical first principles that have granted them survivability on Earth, since all extant organisms ascribe to homeostatic principles.

Given that the unicellular toolkit is complete with all the traits necessary for forming multicellular organisms (*Science*, 301:361-63, 2003), it is

distinctly possible that metazoans are merely permutations of the unicellular body plan. That scenario would clarify a lot of puzzling biology: molecular commonalities between the skin, lung, gut, and brain that affect physiology and pathophysiology exist because the cell membranes of unicellular organisms perform the equivalents of these tissue functions, and the existence of pleiotropy—one gene affecting many phenotypes—may be a consequence of the common unicellular source for all complex biologic traits.

The switch from swim bladder to lung as vertebrates moved from water to land is proof of principle that stress-induced evolution in metazoans can be understood from changes at the cellular level.

If this concept is valid, then it's no wonder that we often see references to phylogenetic preadaptations, which are actually postadaptations of unicellular phenotypic traits. Because development is the only mechanism we know of that gives rise to structure and function, and that generates the adult from the zygote, why not consider this hypothesis? It's testable.

Evolutionary continuum from cell to organism

The cell-molecular homeostatic model for evolution and stability addresses how the external environment generates homeostasis developmentally at the cellular level. It also determines homeostatic set points in adaptation to the environment through specific effectors, such as growth factors and their receptors, second messengers, inflammatory mediators, crossover mutations, and gene duplications. This is a highly mechanistic, heritable, plastic process that lends itself to understanding evolution at the cellular, tissue, organ, system, and population levels, mediated by physiologically linked mechanisms throughout, without having to invoke random, chance mechanisms to bridge different scales of evolutionary change. In other words, it is an integrated mechanism that can often be traced all the way back to its unicellular origins.

Lung evolution as a model

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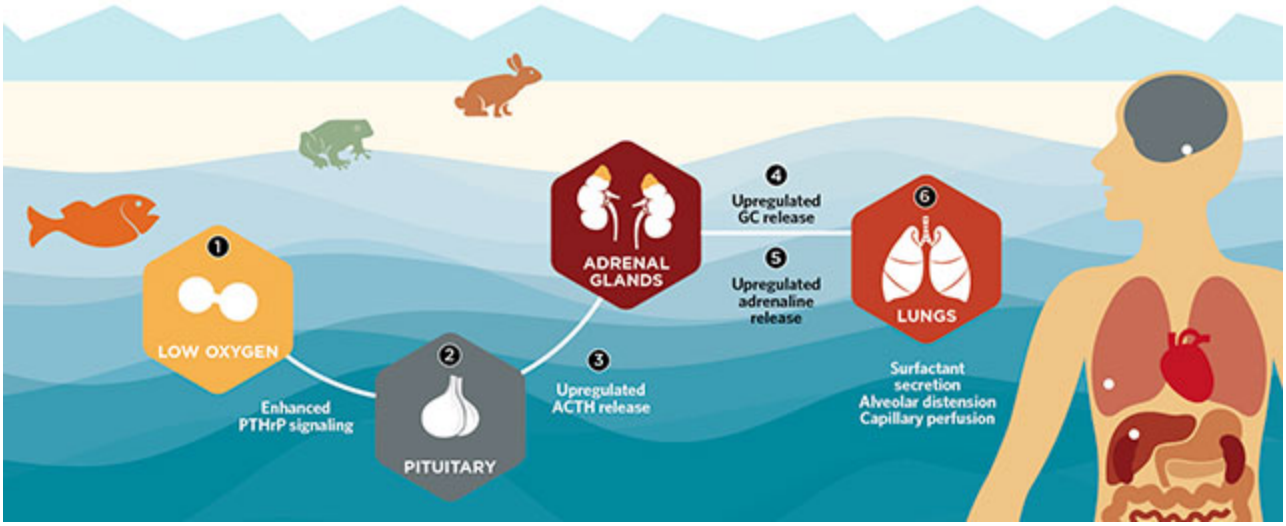

A MECHANISTIC BASIS FOR LUNG DEVELOPMENT: Stress from periodic atmospheric hypoxia (1) during vertebrate adaptation to land enhances positive selection of the stretch-regulated parathyroid hormone-related protein (PTHrP) in the pituitary and adrenal glands. In the pituitary (2), PTHrP signaling upregulates the release of adrenocorticotropic hormone (ACTH) (3), which stimulates the release of glucocorticoids (GC) by the adrenal gland (4). In the adrenal gland, PTHrP signaling also stimulates glucocorticoid production of adrenaline (5), which in turn affects the secretion of lung surfactant, the distension of alveoli, and the perfusion of alveolar capillaries (6). PTHrP signaling integrates the inflation and deflation of the alveoli with surfactant production and capillary perfusion.
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From a cell-cell signaling perspective, two critical duplications in genes coding for cell-surface receptors occurred during this period of water-to-land transition—in the stretch-regulated parathyroid hormone-related protein (PTHrP) receptor gene and the β adrenergic (βA) receptor gene. These gene duplications can be disassembled by following their effects on vertebrate physiology backwards over phylogeny. PTHrP signaling is necessary for traits specifically relevant to land adaptation: calcification of bone, skin barrier formation, and the inflation and distention of lung alveoli. Microvascular shear stress in PTHrP-expressing organs such as bone, skin, kidney, and lung would have favored duplication of the PTHrP receptor, since sheer stress generates radical oxygen species (ROS) known to have this effect and PTHrP is a potent vasodilator, acting as an epistatic balancing selection for this constraint.

Positive selection for PTHrP signaling also evolved in the pituitary and adrenal cortex (see figure on this page), stimulating the secretion of ACTH and corticoids, respectively, in response to the stress of land adaptation. This cascade amplified adrenaline production by the adrenal medulla, since corticoids passing through it enzymatically stimulate adrenaline synthesis. Positive selection for this functional trait may have resulted from hypoxic stress that arose during global episodes of atmospheric hypoxia over geologic time. Since hypoxia is the most potent physiologic stressor, such transient oxygen deficiencies would have been acutely alleviated by increasing adrenaline levels, which would have stimulated alveolar surfactant production, increasing gas exchange by facilitating the distension of the alveoli. Over time, increased alveolar distension would have generated more alveoli by stimulating PTHrP secretion, impelling evolution of the alveolar bed of the lung.

This scenario similarly explains βA receptor gene duplication, since increased density of the βA receptor within the alveolar walls was necessary for relieving another constraint during the evolution of the lung in adaptation to land: the bottleneck created by the existence of a common mechanism for blood pressure control in both the lung alveoli and the systemic blood pressure. The pulmonary vasculature was constrained by its ability to withstand the swings in pressure caused by the systemic perfusion necessary to sustain all the other vital organs. PTHrP is a potent vasodilator, subserving the blood pressure constraint, but eventually the βA receptors evolved to coordinate blood pressure in both the lung and the periphery.

Predicting evolution

Because the model described above for the vertebrate water-land transition is largely based on ubiquitous developmental principles, the evolution of all other tissues and organs is also amenable to the same analytic approach. The cellular-molecular ontogenetic/phylogenetic method can be applied moving both forward and backward at any given phase of vertebrate evolution to systematically fill in the gaps between unicellular and multicellular genotypes and phenotypes. The model organisms and molecular tools to test these hypotheses are now available, enabling us to ultimately observe evolution in the forward direction. Undoubtedly, this approach will yield a *priori* knowledge about the first principles of physiology, and how they have evolved to generate structure and function. ☐

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Tags

unicellular state, swim bladder, PTHrP, protocell, physiology, multicellularity, lung evolution, homeostasis, evolution, environmental stress, cell biology and beta-adrenergic receptor

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