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Exploiting cellular-developmental evolution as the scientific basis for preventive medicine

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SUMMARY

In the post-genomic era, we must make maximal use of this technological advancement to broaden our perspective on biology and medicine. Our understanding of the evolutionary process is undermined by looking at it retrospectively, perpetuating a descriptive rather than a mechanistic approach. The reintroduction of developmental biologic principles into evolutionary studies, or evo-devo, allows us to apply embryologic cell-molecular biologic principles to the mechanisms of phylogeny, obviating the artificial space and time barriers between ontogeny and phylogeny. This perspective allows us to consider the continuum between the proximate and ultimate causes of speciation, which was unthinkable when looked at from the descriptive perspective. Using a cell–cell interactive 'middle-out' approach, we have gained insight to the evolution of the lung from the swim bladder of fish based on gene regulatory networks that generate both lung ontogeny and phylogeny, i.e. decreased alveolar size, decreased alveolar wall thickness, and increased alveolar wall strength. Vertical integration of cell–cell interactions predicts the adaptivity and maladaptivity of the lung, leading to novel insights for chronic lung disease. Since we have employed principles involved in all of development, this approach is amenable to all biologic structures, functions, adaptations, maladaptations, and diseases, providing an operational basis for preventive medicine.

Introduction

In the post-genomic era, we must broaden our perspective on biology and medicine to make maximal use of this technological advancement. Since evolution is all of biology [1], such an approach would accommodate our needs. How can we effectively apply evolutionary thinking to medicine? Like Darwin and Wallace, our understanding of Natural Selection continues to be based on retrospective, descriptive analysis, reasoning after the fact- if we think of the chronology of life as an "arrow of time" traveling from left to right, we must begin thinking about evolutionary complexity from its unicellular origins, progressing in time and space from left to right, rather than being seen in the conventional reverse direction from right to left. At best, Darwinian theory retrodicts phylogeny, but how do we move to evolution in the forward direction, reflecting how life evolved from unicellular organisms to metazoans? This paradox is a vestige of the view that the only evidence we have for evolution as scientists is the fossil record. But that has changed with the advent of evolutionary-developmental biology and the effective application of molecular biology to decipher both phylogeny and ontogeny.

Cellular-development and evolution

We know a lot about the cell-molecular mechanisms of embryogenesis- how genes determine structure and function- which can be used as an experimental platform for testing Natural Selection for gene regulatory networks (GRNs) that determine phylogenetic phenotypes. Exploitation of developmental models to experimentally test phylogenetic hypotheses would allow us to challenge evolutionary theory in Real Time, experimentally.

Abbreviations: ADRP, adiopocyte differentiation related protein; C/EBPα, CCAAT/enhancer-binding protein alpha; cAMP, cyclic adenosine monophosphate; Gli, glioma-associated oncogene homologue; GSK 3β, glycogen synthase kinase-3beta; GRN, gene regulatory network; LEF-1, lymphocyte enhancer-binding factor; PAI-1, platelet activator inhibitor-1; PTHrP, parathyroid hormone-related protein; PPARγ, peroxisome proliferator activated receptor gamma; Wnt, wingless/int.

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Unicellular organisms dominated the earth for the first 4.5 billion years- it is only during the last 500 million years that multicellular organisms have emerged [2]. The prevailing theory as to why this occurred is that unicellular organisms began experimenting with metabolic cooperativity [3], a process that is mediated by cell–cell signaling. That process resulted in a selection advantage, initially because the bigger the organism became, the less likely it was to be eaten. But beyond this simple explanation for increased size, as pro- and eukaryotes continued to compete, the development of progressively more complex systems conferred a further selection advantage through division of labor. D'Arcy Thompson had pointed out that the variability in animal size is not a function of cell size, which is fairly constant, but in cell morphologies, which are highly variable [4].

Morphogenesis is determined by cell–cell communication, which is the driving force behind vertebrate evolution. As such, it provides insights to the macro- and microevolutionary strategies that have succeeded over biologic time. Gene duplication has been a key genetic adaptational mechanism [5], but this is an obvious strategy, like increasing body size more is better at a very basic level in all systems. And increasing size and gene duplication describe processes without providing underlying mechanisms. As long as we continue to tell 'Just So Stories' [6], we legitimize intelligent design and fail to exploit genomics to advance our knowledge of biology and medicine [7]. One set of molecular mechanisms common to both development and phylogeny are the ligand–receptor interactions that mediate growth, differentiation, homeostasis and aging [8]. Sydney Brenner has referred to this as the 'Middle-Out' approach [9], though he did not suggest exploiting the ligand–receptor relationship as a way of deconstructing the evolved pathways. These mechanisms are plastic, and represent mechanisms that mediate the on-going interactions between the organism and its environment that are at the core of the evolutionary process [9,10]. Such a mechanistic strategy is superior to descriptive 'top–down' approaches like natural selection [11] or the great chain of being, or 'bottom–up' approaches like those of West [12,13] and Morowitz [14] based on hierarchical metabolic pathways.

For example, the Creationist Michael Behe has suggested that for evolution to have generated novel protein features through point mutations it would have required a minimum of 10^9 individuals [15]. But the middle-out mechanism would require much smaller numbers since it is based on active selection for traits. The model also provides the basis for evolutionary experimentation. By examining GRNs that determine development of structure and function, one can identify other functionally related GRNs within that organism, and in homologous tissues in the same and phylogenetically-related organisms [16]. Such an analysis, based on adaptational strategies, is far more likely to provide useful information about evolution and physiology than the stochastic approach currently being used to elucidate systems biology [17]. For example, as depicted in the Schematic (Fig. 1) above, a GRN common to the phenotypes for development, homeostasis, repair and aging of a given structure/function (lung, kidney, liver, brain, etc.) can be depicted as changing over chronologic time (x axis) as a family of idealized parallel lines. Such a set of simultaneous equations can then be solved for these GRN/phenotype interrelationships in biologic time, or evolution, independent of chronologic time, i.e. all of the biological processes are now relative to one another, independent of chronologic time. Such a self-referential property of evolved structure and function reflects the modular nature of the cell–cell interaction principle. But that primary process of evolution is complicated by the fact that selection is for genes in specific cell populations as they relate to specific physiologic functions, such as breathing, locomotion, digestion, micturation, cognition, etc. But those same genes are expressed in all of the cells in the population, both for the primary structure/function site, and for all of the other tissues and organs where that cell population is present. The descriptive term for this phenomenon is exaptation, as coined by Gould and Vrba [18]. What they had not considered were the developmental implications of such a process. Such a mechanism would create scenarios in which cells of differing germline origins would be forced into spatiotemporal juxtapositions based on developmental principles, whereas the formation of novel gene regulatory networks would either create novel structures and/or functions, or not, depending upon whether they were compatible with viability limited/constrained by the reproductive process.

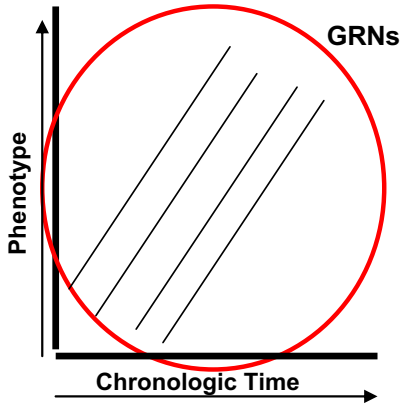

Fig. 1. Solving for evolutionary principles independent of chronologic time. By regressing gene regulatory networks (GRNs) mediating cell–cell interactions relevant to structure/function across ontogeny and phylogeny against chronologic time and phenotype, we can generate a family of parallel lines, or simultaneous equations. Using this approach, we can 'solve' for the underlying evolutionary principles involved independently of chronologic time, making the biologic processes self-referential.

Such a seemingly haphazard mechanism could explain why the fish swim bladder evolved into the vertebrate lung, for example, as follows: the swim bladder is a gas-filled out-pouching of the gastrointestinal tract in physostomous fish [19]. It has allowed fish to adapt to the force of gravity, maintaining equilibrium in order to forage efficiently at various levels in the water, rather than having to expend additional energy by constantly swimming, and to sleep at the bottom at night by emptying the bladder. The 'invention' of the surfactant, a lipid complex, further facilitated this mechanism by making the bladder more compliant [20]- selection pressure for the transition of vertebrates from water to land may have been facilitated by the overlapping of the processes of gas exchange and metabolic activity (feeding) through the production of surfactant, selecting for progressively greater surfactant production efficiency to increase the surface-to-volume ratio of the gas exchange organ [21].

Cell–cell signaling, evolution and the development of physiologic novelties

It is has been challenging to understand why evolution takes 'big leaps' from time to time [22]. Our prediction is that because the cell-molecular model for evolutionary novelty selects for genes within specific cell populations, the resultant genetic 'legacy' acquired by all cells in that population (e.g., endoderm, mesoderm, ectoderm), not just those of the structure/function being selected for, i.e. genetic adaptation spilling over into other structures/functions, creates opportunities for novelty by virtue of the fact that the genetic trait may become useful, i.e. adaptive, under emergent conditions. This process may explain why, for example, respiration and metabolism [23], photoreception and circadian rhythms [24], cerebration and radical oxygen species signaling [25], renal function and erythropoiesis [26], or the formation of eyes and ears [27] have