Evolution, atmospheric oxygen, and complex disease

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Submitted 23 February 2007; accepted in final form 26 April 2007

Koch LG, Britton SL. Evolution, atmospheric oxygen, and complex disease. Physiol Genomics 30: 205–208, 2007. First published May 1, 2007; doi:10.1152/physiolgenomics.00043.2007.—If evolution is an accurate statement of our biology, then disease must be tightly associated with its patterns. We considered selection for more optimal capacity for energy transfer as the most general pattern of evolution. From this, we propose that the etiology of complex disease is linked tightly to the evolutionary transition to cellular complexity that was afforded by the steep thermodynamic gradient of an oxygen atmosphere. In accord with this thesis, clinical studies reveal a strong statistical link between low aerobic capacity and all-cause mortality. In addition, large-scale unbiased network analyses demonstrate the pivotal role of oxygen metabolism in cellular function. The demonstration that multiple disease risks segregated during two-way artificial selection for low and high aerobic capacity in rats provides a remote test of these possible connections between evolution, oxygen metabolism, and complex disease. Even more broadly, an atmosphere with oxygen may be uniquely essential for development of complex life anywhere because oxygen is stable as a diatomic gas, is easily transported, and has a high electronegativity for participation in energy transfer via redox reactions.

thermodynamics; metabolism; health; biocomplexity

About twenty years ago we started an assessment of how to create an animal model that emulates the polygenic nature of a complex disease such as Type 2 diabetes or hypertension. We did not think that the commonly utilized animal models were complex disease. Physiol Genomics 30: 205–208, 2007. First published May 1, 2007; doi:10.1152/physiolgenomics.00043.2007.—If evolution is an accurate statement of our biology, then disease must be tightly associated with its patterns. We considered selection for more optimal capacity for energy transfer as the most general pattern of evolution. From this, we propose that the etiology of complex disease is linked tightly to the evolutionary transition to cellular complexity that was afforded by the steep thermodynamic gradient of an oxygen atmosphere. In accord with this thesis, clinical studies reveal a strong statistical link between low aerobic capacity and all-cause mortality. In addition, large-scale unbiased network analyses demonstrate the pivotal role of oxygen metabolism in cellular function. The demonstration that multiple disease risks segregated during two-way artificial selection for low and high aerobic capacity in rats provides a remote test of these possible connections between evolution, oxygen metabolism, and complex disease. Even more broadly, an atmosphere with oxygen may be uniquely essential for development of complex life anywhere because oxygen is stable as a diatomic gas, is easily transported, and has a high electronegativity for participation in energy transfer via redox reactions.

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About twenty years ago we started an assessment of how to create an animal model that emulates the polygenic nature of a complex disease such as Type 2 diabetes or hypertension. We did not think that the commonly utilized animal models were appropriate, and an updated version of this view can be summarized in four statements: 1) Chemical and physical maneuvers, such as administration of streptozotocin to mimic diabetes mellitus or ligature of coronary arteries to emulate arterial disease, more accurately reflect response to injury and not the progression of disease. 2) Single- or multiple-gene knockout approaches are problematic because complex diseases generally result from expression of combinations of allelic variants sensitive to a given environment (18). That is, gene knockout only reveals essentiality of a gene and biological reorganization subsequent to its loss. 3) Mutagenic approaches, such as that produced by administration of the gametic mutagen ethylnitrosourea (ENU), are random and provide no direct information as to what allelic variants or gene combinations are involved (20). 4) Superficially, it seems that disease models derived from selection would be highly useful. Yet selection for a particular disease is problematic if it is based on measurable traits or symptoms and not the full complement of underlying mechanisms. This problem is amplified because chronic diseases emerge not as discrete events, but as complexes, such as the cascade represented by the metabolic syndrome. These kinds of problems led us to consider a more fundamental and speculative approach to the development of animal models of complex diseases.

The initial idea was that disease must be associated closely with the strongest pattern of evolution. We defined this pattern operationally as selection for a more optimal capacity for energy transfer (2). From this, we propose that complex disease is linked tightly to the evolutionary transition to cellular complexity that was afforded by the steep thermodynamic gradient of an oxygen atmosphere. As a test of these possible connections, we hypothesized that artificial selection of rats based on low and high intrinsic aerobic treadmill running exercise capacity would yield models that contrast for disease risks. Here we first describe the models that emerged and then explain the underlying logic.

Artificial Selection for Complex Disease

In 1996 we (14) started large-scale selective breeding to develop strains of rats that contrast for intrinsic (i.e., untrained) aerobic treadmill running capacity. After 11 generations of selection, the low-capacity runners (LCR) and high-capacity runners (HCR) differed by over 300% in aerobic running capacity (Fig. 1). The LCR scored higher on cardiovascular risks and features of the metabolic syndrome, including higher blood pressure, insulin, random glucose, fasting glucose, free fatty acids, visceral adiposity, and triglycerides when young adults. The HCR were higher for health factors (29) such as maximal oxygen consumption, heart function, endothelial nitric oxide formation, economy of oxygen use, and levels of transcription factors and oxidative enzymes required for mitochondrial function in skeletal muscle (Fig. 2).

The general divide in aerobic capacity and health status between LCR and HCR was confirmed in studies using rats from generations 15–19 of selection (10, 27). LCR rats from generations 15 and 17 were found to be more susceptible to ischemia-mediated cardiac ventricular tachycardia relative to HCR (16); although predictable from our general hypothesis, this is an important find because acute coronary artery occlusion that leads to ventricular arrhythmias is the leading cause of death in humans in developed countries (1).

Because of the interaction of environments with genetic predisposition to disease, it was of large interest to know whether LCR and HCR respond differentially to clinically relevant changes in environment. In the first trial of this possibility (22), the effects of a high-fat diet (HFD) on weight gain patterns, insulin sensitivity, and fatty acid oxidative capacity were evaluated in sedentary male rats. LCR rats fed normal chow were heavier, hypertriglyceridemic, and less insulin sensitive and had lower skeletal muscle oxidative capacity compared with HCR rats. LCR rats on a HFD gained...
Modified from Ref. 29.

40 m per generation in distance run to exhaustion. Values are means decreased 16 m per generation and the high-capacity runner (HCR) rats gained mice, and compared transcriptional profiles across aging in humans, considered the most relevant clinical phenotypes. Zahn et al. tive of oxidative stress. 

duction and decreased the availability of nitric oxide, suggest-

and increases dietary atherosclerosis without affecting choles-
terol levels. UCP-1 expression also increased superoxide pro-

expression in aortic smooth muscle cells causes hypertension 

They reported a 12% increase in survival for each 1-metabolic 

erful predictor of mortality than other established risk factors. 

Clinical Studies Provide Circumstantial Evidence 

Clinical investigations demonstrate dysfunctional oxygen 

energy metabolism in essentially all disease conditions such 
as Type 2 diabetes (18), cardiac arrhythmias (1), inflam-

ation (5), neurogenerative dysfunction (15), and cancer 

(17). In a study with over 6,000 subjects, Myers and colleagues 

(19) concluded that aerobic exercise capacity is a more pow-

erful predictor of mortality than other established risk factors. 

more weight and fat mass, and their insulin-resistant condition 

was exacerbated, despite consuming similar amounts of me-
tabolizable energy as chow-fed controls. Remarkably, these 

metabolic variables remained unaltered in HCR when shifted 

from normal chow to HFD.

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Our goal was to define the broadest possible feature me-

chanistically underlying the polygenic condition of complex 
disease and then artificially select for low and high forms of 
this feature. This led us to consider that disease is tightly 
associated with the patterns of evolution. For this we “bor-
rowed” heavily from a paper by Baldwin and Krebs entitled “The evolution of metabolic cycles” (2). This paper initiated 

our view that evolution is a thermodynamic event related to the 

more optimal use of resources. That is, selection weighs the 

benefit of a change for its worth in energy transfer.

Atmospheric Oxygen and the Evolution of Complexity 

There is general agreement that cellular life originated ~3.7 

billion years ago (Ga) in an anoxic environment. For anaerobic 

energy transfer early organisms developed glycolytic pathways 

that are extant for all known cells (26). The relatively modest 

energy transfer afforded by glycolysis was sufficient for life at 

the single-cell level, but there are no known examples of 

multicellular complex organisms that are exclusively anaerobic 

(6). Further complexity apparently required and awaited, pari 

passu, the development of pathways for larger energy transfer. 

Geochemical studies have assembled a reasonably well 

known history of Earth’s oxygenation (6, 9, 12) (Fig. 3). 

Cells capable of anoxygenic photosynthesis were present 

about 3.3 Ga. By 2.4 Ga oxygenic photosynthesis became 

established and initiated the Great Oxidation Event (GOE) 

with atmospheric oxygen increasing to a partial pressure of ~15 mmHg by 2.0 Ga. During the next 1 billion years 

aerobic respiration and small noncomplex organisms became 

widespread in an atmosphere of oxygen that remained at ~15 

mmHg. From 1.0 to 0.5 Ga atmospheric oxygen rose to its 

current value of 150 mmHg. This increase was associated with 

an escalating development of complexity that included the 

Cambrian explosion during which all the major animal phyla 

appeared. Protein sequence data and molecular clock methods 

have been used to estimate the timing of the rise in the

Longevity and capacity at a given age can perhaps be 

considered the most relevant clinical phenotypes. Zahn et al. 

(30) compared transcripational profiles across aging in humans, 
mice, and Drosophila. Although expression changes were 

species specific (private) for several pathways, only the elec-

tron transport pathway was decreased in association with aging 

in all three species (public). These results suggest that changes 

in electron transport pathways may be the common signature 

that underlies aging.
The centrality of energy transfer pathways is revealed in three large-scale unbiased interrogations of biological connectivity. First, Jeong et al. (13) examined the core metabolic networks of 43 organisms in the WIT database (now merged into PUMA 2). The goal was to quantify the topological properties of metabolic networks with graph theory and statistical mechanics. Analysis yielded two conclusions: 1) biochemical reactions connect through nodes as scale-free networks, and 2) the most highly associated nodes were for pathways associated with energy transfer [top 15 nodes: H2O, ADP, phosphate, ATP, l-glutamate, NADP⁺, pyrophosphate, NAD⁺, NADPH, NADH, CO₂, NH₄, coenzyme A (CoA), AMP, and pyruvate].

Second, Barrett et al. (3) used a genome-scale in silico reconstruction of the integrated transcriptional regulatory and metabolic network for Escherichia coli (iMC1010v1) to computationally assess growth phenotypes. The visualized structure showed that the regulatory network governing metabolism in E. coli responds primarily to the available electron acceptor and to the presence of glucose as the carbon source.

Third, Raymond and Segre (25) evaluated the effect of the presence or absence of common biomolecules such as oxygen on the complexity of metabolic networks. They used a heuristic in which sets of compounds were allowed to react according to the rules of the Kyoto Encyclopedia of Genes and Genomes (KEGG) to create reaction networks. The first network was generated from a randomly chosen set of seed compounds. The second network was generated from that same seed set amended with the addition of one of these nine metabolites: NAD⁺, 3'-adenosyl methionine, CoA, ATP, O₂, CO₂, NH₄, pyruvate, or 2-oxoglutarate. Their analysis revealed the existence of four discrete groups of networks of increasing complexity. Groups I, II, and III were associated with a maximum of 2,800 reactions. The most complex group IV reactions were associated almost exclusively with the presence of oxygen and had about 1,000 more reactions than networks achieved in the absence of oxygen. This striking connection of oxygen with network complexity strengthens the argument that increases in atmospheric oxygen were permissive for evolution of advanced biocomplexity. In accordance with this, new evidence suggests that differences in atmospheric oxygen are explanatory for the large-scale biological events of insect gigantism (8), polar gigantism (7), and Romer’s Gap in vertebrate and arthropod terrestrialization (28).

In summary, our initial idea that major features of complex diseases are mechanistically underwritten by flaws in oxygen metabolism is consistent with current information assembled from a broad range. Simultaneous emergence of contrasting health profiles during two-way artificial selection for low and high aerobic capacity corroborates this notion. Nevertheless, evidence for the general idea that complex diseases are mechanistically associated with flaws in oxygen metabolism is circumstantial and direct tests remain a challenge. Recently, Pladevall and colleagues (23) used confirmatory factor analysis to conclude that the components of the metabolic syndrome are manifestations of a single common mechanistic factor. We suggest that alteration in oxidative capacity is that underlying factor.
ACKNOWLEDGMENTS

We gratefully acknowledge Lori Gilligan and Nathan Kanner for expert care of the LCR/HCR rat colony, Julie Stotler for preparation of the manuscript, and J. W. Britton for helpful discussions.

GRANTS

This work was supported by National Heart, Lung, and Blood Institute grant HL-6427 and National Center for Research Resources Grant RR-17718.

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