Why respiratory biology? The meaning and significance of respiration and its integrative study

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Synopsis Traditionally the process of respiration is divided into three phases: (1) cellular respiration, (2) transport of respiratory gases and (3) ventilation of the gas exchange organs (breathing). Thereby organisms assimilate chemical energy from the environment, and within their cells transfer it from molecule to molecule in a stepwise fashion. Although studied separately, these phases represent a continuum and cellular respiration in all life forms has much in common. Ironically, these respiratory foci have been artificially delineated by their own practitioners, who tend to publish in their own journals, and attend their own conferences. The goal of modern respiratory biology should be to understand biological connectivity and complexity by viewing an organism as a series of interconnecting systems from molecule to ecosystem. The future of science in general, and biology in particular, lies in disciplinary networking: combining the results of traditional disciplines to better understand the whole. Because of its universality, Respiratory Biology can best provide this bridge and improve interdisciplinary studies in biology generally. To this end, the First International Congress of Respiratory Biology was held from August 14 to 16, 2006, at Bonn, Germany. As evident from the success of this inaugural meeting, these are exciting times for Respiratory Biology. The explosion of "X-omics" and systems biology, the powerful genetic approaches to disease treatment, and the long-standing and newly emerging questions in evolutionary biology and ecology; all portend a continuing role of respiratory biology as a key integrative discipline.

Introduction

Just what does "respiration" mean? and "What is the significance of respiratory biology in the postgenomic phase of natural science?" To provide useful answers to these far-from-hypothetical questions, we must first define and characterize exactly what we are referring to when using the word "respiration." Do we imply a concept, a process or both? Secondly, it is useful to reflect on the "meaning" of respiration? On the one hand, "meaning" could be just the definition of the word, which for respiration includes all subcellular, cellular, and organismic ramifications. On the other hand, however, the "meaning" encompasses the impact of metabolism on biological systems at the most fundamental levels, as well both philosophical and applied aspects relating to the importance of respiration to human life, culture, and well being.

As a concept "respiration" is the motor of life. Life in all but the simplest of forms depends upon chemical energy being assimilated from the environment by cells, and then transferred from molecule to molecule in a stepwise fashion within them. In these metabolic, biochemical reactions, enzymes regulate which substrates are involved, specify the order of reactions and channel the flow of energy to and from the substrates. Respiration as a process in higher animals (Bilateria) falls into three phases: (1) cellular respiration, (2) transport of respiratory gases, and (3) ventilation of the gas exchange organs (breathing).

Cellular respiration occurs at the intracellular level. It is a complex and highly structured series of processes by which energy is converted to a form that can be used for metabolism, development, growth and maintenance of cells, tissues and organisms, and ultimately influence reproduction and fitness. Cellular respiration stores chemical energy in the form of phosphorylated nucleotides (primarily ATP) by means of oxidative reactions and makes it available to other reactions. In contrast to simple combustion, cellular respiration involves the step-wise release of energy in a tightly regulated fashion. What little heat that is produced as a byproduct is dissipated or, in endotherms, results in a constant body temperature. Given the staggering

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This paper summarizes one of the 22 symposia that constituted the "First International Congress of Respiratory Biology" held August 14–16, 2006, in Bonn, Germany.

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diversity of plants and animals, cellular respiration is quite conservative, with similar components of the ancestral metabolic pathways showing up regularly in a wide range of organisms. At the same time, however, genomic analysis reveals a very irregular distribution of key enzymes involved in aerobic and anaerobic respiratory pathways (Castresana, 2001). That strong selection pressures have operated on the enzymatic control of respiration underscores the importance of respiration as a key property of life.

Internal respiration involves gas transport and tissue gas exchange. This mass movement of oxygen and carbon dioxide between environment and tissues occurs by means of passive diffusion and energy-consuming perfusion. In multicellular organisms with a high metabolic rate, one or more gas-exchange organs have evolved that present a large surface area and a thin diffusion barrier, over which the respiratory-relevant gases are exchanged by diffusion along a partial pressure gradient between the (often internalized) environment and the circulatory system of the animal. The circulatory system transports these gases between the gas-exchange organ(s) and the tissues. There, the dissolved gases diffuse between the blood/hemolymph and the tissue cells. This arrangement also has strong evoluationarily conserved elements in both air and water breathers (Maina 2002; Perry and Sander 2004; Evans et al. 2005; Maina and West 2005).

Breathing is the act of ventilating the external surface of the gas exchange organ with water or air, and has been studied for several centuries (Farnsworth 1997). Critical to the efficiency of the gas exchange process is the pattern of flow of the respiratory medium past the blood on the opposite side of the respiratory membrane. In this respect, a wide variety of flow patterns have emerged—infinite/ventilated pool, cross-current, counter current, etc.—that transcend taxonomic lines.

It is critically important to emphasize that these three phases of respiration—cellular respiration, internal respiration, and breathing—represent a continuum both conceptually and in process. Yet, ironically, these respiratory foci have been artificially delineated by their own practitioners, who publish in their own journals, and attend their own conferences. Our hope is that the three phases of respiration will become more integrated, and the margins of the three definitions mentioned earlier will increasingly merge as we become capable of expressing effectively the continuity of the respiratory process. One way by which this can be achieved is to emphasize the significance of Respiratory Biology as a distinct, integrative discipline

Significance of respiratory biology

Respiration as a key "integrating discipline" in biology

Our view of the biological road map is that all roads pass through respiration. We argue that respiration is the ultimate integration of all biological processes, from two perspectives: organ systems physiology and systems biology.

The centrality of respiration to life dates at least as far back as Lavoisier's (1789) demonstration that metabolism is equivalent to combustion. Of course, lacking neural or endocrine regulation, organ systems will fail; if the gut digestive system isn't processing food, nutrients become limiting; but renal disposal of nitrogenous wastes and excess water are also essential for life; and so on. Obviously, every organ system and its attendant processes have an ultimately critical role. But respiration, through its direct energetic support of all other functions, is the "meta-system." Moreover, respiration is ultimately a "coal miner's canary for metabolism." If the endocrine system is dysfunctional, for example, this won't be revealed by examination of the kidneys or the nervous system. In fact, examination of no single organ system accurately reflects overall physiological well-being. But breakdown of any the innumerable processes along the (cellular/internal/breathing) respiratory continuum, may be immediately evident in altered function of all other organ systems.

Because of its universality, respiration also may be considered a key "integrating discipline" for biology in general. We are witnessing the emergence of an exciting Systems Biology[2] perspective in which the goal is to understand biological connectivity and complexity by viewing an organism as a series of interconnecting systems from molecule to ecosystem (for just a few of many interesting articles see Ho and Ulanowicz 2005; Toscano and Oehlke 2005; Huang and Wikswo 2006; Nicholson 2006; Goodacre 2007). There are many concepts that bridge more than one position on this vertical span (e.g., information, form–function interdependence). However, energy—its storage, release and flow—is one factor that truly spans molecules-to-ecosystem

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[2] "Systems Biology" currently has many different definitions. Among the original views was a molecular approach heavily dependent upon computational methodology, but an expanding view of Systems Biology (certainly one now promulgated by the US National Science Foundation) is a vertically integrated flow of information between cellular and molecular, physiological, and ecological/evolutionary fields of study.

gap, linking all the elements in a broad systems biology network. If energy is the linking factor, then *respiration* is the linking process.

Health and respiratory biology

Respiratory biology is at the center of modern health study and practice. When pulmonary ventilation or diffusion becomes insufficient, the respiratory system fails and life is in jeopardy. (An insufficiency in pulmonary perfusion would be classified as cardiac failure.) One cause of ventilatory failure involves central nervous control of breathing or inhibition of transmission of neuronal impulses to the respiratory musculature. Ventilation can also fail due to blockage of the airways by choking, or in such diseases as obstructive sleep apnea, COPD (chronic obstructive pulmonary disease), emphysema, or asthma. Diffusion is inhibited in pneumonia, pulmonary edema, cystic fibrosis, or hyaline membrane disease of the lung. Lung cancer, depending on the type and severity can affect all of the above functions. In addition to all this, the lung can serve as a port of entry for toxic substances and airborne disease vectors.

According to a WHO study in 2002, all diseases of the respiratory system taken together constitute the leading cause of death worldwide. Not surprisingly, then, in 2006 the National Institutes of Health in the United States alone spent more than 3 billion dollars investigating respiratory-related diseases.

In addition to the treatment of diseases, a greater knowledge of respiratory biology can help improve and optimize respiratory performance in elite athletes, visitors to high altitudes, SCUBA divers, musicians and singers, and in many more professions that require modified respiratory or sound production function. Indeed, the field of respiratory physiology began with the vocational mining studies of J.B. Haldane in 19th-century England.

Industrial synthesis of consumer goods

Many respiratory biologists focus on oxygen-based respiration. Yet so-called ‘‘anaerobic respiration’’ plays a key role in the biology of unicellular and metazoans alike, and no commentary on respiratory biology would be complete without its consideration. Respiration, in the form of fermentation that releases either alcohol or lactic acid, is increasingly important in the industrial-scale production of a variety of consumer goods, including ethanol, organic acids, antibiotics, vitamins, and tanned leather (Streit and Entcheva 2003; Schallmey et al. 2004; Piel 2006; Teusink and Smid 2006). Many food items, including bakery (Lacase et al. 2007) and dairy products and alcoholic beverages, depend upon fermentation (Cedeño 1995; Piscur et al. 2006). As world-wide energy prices climb, the fermentation-based production of alcohol from sugar cane, soybeans, corn, and other agricultural crops, especially in heavily energy consuming areas such as Europe and North America, holds the dual promise of both significantly reducing demands for fossil fuels, while moving more internal combustion engines to cleaner energy sources (Hahn-Hagerdal et al. 2006; Ragauskas et al. 2006). Finally, as we consume more goods, we increasingly pollute our environment. Consequently, the roles to be played by bioremediation, which typically depends upon microbial respiration (Plaza et al. 2001; Daims et al. 2006; Munoz and Guieysse 2006) become more important.

The impact of biotechnology on industrial production of consumer goods is far-reaching indeed (Soetaert and Vandamme 2006), but one should not lose sight of the fact that respiration of microbes—both natural and genetically engineered—underlies this proliferation of new products and services.

The need for a respiratory biology now: the First International Congress of Respiratory Biology and the special section

The future of science in general, and biology in particular, lies in disciplinary networking: combining the results of partial disciplines to better understand the whole. The success of neurobiology and developmental biology lies in this molecule-to-organism approach and also in the close integration of human health and wellbeing issues with basic biological research. Respiratory biology has an even greater potential because virtually every life form respires and the conservative nature of cellular respiration makes direct comparison of processes in fungi, plants, and animals possible.

Historically, branches of respiratory biology have tended to remain separate: for example, botanists, zoologists, medical researchers, and others with similar respiratory interests attend different meetings and read different journals. To counteract this tendency, and to improve interdisciplinary activities in respiratory biology, the First International Congress of Respiratory Biology was held August from 14 to 16, 2006, at the Seminaris Congress Hotel in Bad Honnef and at the Rheinische Friedrich-Wilhelms-University in Bonn, Germany. The goal was to bring together researchers worldwide who work on respiration and to create a forum for them to interact. The emphasis was on promoting interdisciplinary collaboration and creating vertical networking—from molecule to ecosystem—within respiratory biology. Other goals were to lay the groundwork for further such meetings and for founding an International Society of Respiratory Biology.

This highly successful inaugural meeting was attended by approximately 250 persons—200 delegates with advanced degrees and some 50 graduate students—representing 25 nations. The ICRB organized around 22 symposia, each with from 5 to 23 speakers, and took place in four parallel sessions. In addition, there three were plenary lectures and a keynote address. Krogh's Principle, namely that for every physiological question there is an ideally suited animal in which it can be studied—was in evidence at every turn.

For this special section of *Integrative and Comparative Biology* the authors were asked to depart from the traditional practice of publishing individual symposium contributions and instead to summarize and integrate entire symposia in a single publication. Thus this issue has contributions from more than 90 co-authors and represents a cross-section of the whole three-day meeting. The articles have been updated and integrated to emphasize the interaction of various contributions within symposia. The result is a unique view into the breadth and depth of respiratory biology today. Access to abstracts from the ICRB and contact with the organizers are possible through the website: http://www.respirbiol.org.

These are exciting times for respiratory biology, broadly defined. The explosion of "X-omics" and systems biology, the powerful genetic approaches to disease treatment, and the long-standing and newly emerging questions in evolutionary biology and ecology all portend a continuing key role for all aspects of respiratory biology in the ever broadening kaleidoscope of life sciences.

References

Castresana J. 2001. Comparative genomics and bioenergetics. Biochim Biophys Acta 1506:147–62.

Cedeño M. 1995. Tequila production. Crit Rev Biotechnol 15:1–11.

Daims H, Taylor MW, Wagner M. 2006. Wastewater treatment: a model system for microbial ecology. Trends Biotechnol 24:483–9.

Evans DH, Piermarini PM, Choe KP. 2005. The multifunctional fish gill: dominant site of gas exchange, osmoregulation, acid-base regulation, and excretion of nitrogenous waste. Physiol Rev 85:97–177.

Farnsworth WE. 1997. Figuring out why we breathe. Med Hypotheses 48:229–36.

Goodacre R. 2007. Metabolomics of a superorganism. J Nutr 137(1 Suppl):259S–66.

Hahn-Hagerdal B, Galbe M, Gorwa-Grauslund MF, Liden G, Zacchi G. 2006. Bio-ethanol—the fuel of tomorrow from the residues of today. Trends Biotechnol 24:549–56.

Ho MW, Ulanowicz R. 2005. Sustainable systems as organisms? Biosystems 82:39–51.

Huang S, Wikswo J. 2006. Dimensions of systems biology. Rev Physiol Biochem Pharmacol 157:81–104.

Lacaze G, Wick M, Cappelle S. 2007. Emerging fermentation technologies: development of novel sourdoughs. Food Microbiol 24:155–60.

Lavoisier AL. 1789. Mémoire sur la respiration des animaux. Paris.

Maina JN. 2002. Fundamental structural aspects and features in the bioengineering of the gas exchangers: comparative perspectives. Adv Anat Embryol Cell Biol 163:1–108.

Maina JN, West JB. 2005. Thin and strong! The bioengineering dilemma in the structural and functional design of the blood-gas barrier. Physiol Rev 85:811–44.

Munoz R, Guieysse B. 2006. Algal-bacterial processes for the treatment of hazardous contaminants: a review. Water Res 40:2799–815.

Nicholson JK. 2006. Global systems biology, personalized medicine and molecular epidemiology. Mol Syst Biol 2:52.

Perry SF, Sander M. 2004. Reconstructing the evolution of the respiratory apparatus in tetrapods. Respir Physiol Neurobiol 144:125–39.

Piel J. 2006. Bacterial symbionts: prospects for the sustainable production of invertebrate-derived pharmaceuticals. Curr Med Chem 13:39–50.

Piskur J, Rozpedowska E, Polakova S, Merico A, Compagno C. 2006. How did Saccharomyces evolve to become a good brewer? Trends Genet 22:183–86.

Plaza G, Ulfig K, Hazen TC, Brigmon RL. 2001. Use of molecular techniques in bioremediation. Acta Microbiol Pol 50:205–18.

Ragauskas AJ, et al. 2006. The path forward for biofuels and biomaterials. Science 311:484–9.

Schallmey M, Singh A, Ward OP. 2004. Developments in the use of *Bacillus* species for industrial production. Can J Microbiol 50:1–17.

Soetaert W, Vandamme E. 2006. The impact of industrial biotechnology. Biotechnol J1:756–69.

Streit WR, Entcheva P. 2003. Biotin in microbes, the genes involved in its biosynthesis, its biochemical role and perspectives for biotechnological production. Microbiol Biotechnol 61:21–31.

Teusink B, Smid EJ. 2006. Modelling strategies for the industrial exploitation of lactic acid bacteria. Nat Rev Microbiol 4:46–56.

Toscano WA, Oehlke KP. 2005. Systems biology: new approaches to old environmental health problems. Int J Environ Res Public Health 2:4–9.