



Review Article

Oxygen in human health from life to death – An approach to teaching redox biology and signaling to graduate and medical students



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ABSTRACT

In the absence of oxygen human life is measured in minutes. In the presence of oxygen, normal metabolism generates reactive species (ROS) that have the potential to cause cell injury contributing to human aging and disease. Between these extremes, organisms have developed means for sensing oxygen and ROS and regulating their cellular processes in response. Redox signaling contributes to the control of cell proliferation and death. Aberrant redox signaling underlies many human diseases. The attributes acquired by altered redox homeostasis in cancer cells illustrate this particularly well. This teaching review and the accompanying illustrations provide an introduction to redox biology and signaling aimed at instructors of graduate and medical students.

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Contents

Oxygen and ROS sensing by the earliest life on earth.	124
Interaction of modern-day organisms with oxygen-derived species	126
Redox signaling in Bacteria.	126
Redox signaling in Eucarya.	126
Distinct chemical properties of ROS.	126
Cellular targets of ROS	126
Reversibility and specificity in redox signaling	126
ROS function at the start of life	127
Redox signaling for proliferation	128
Redox signaling for death.	129
Redox biology and signaling in cancer.	132
Aberrant regulation of proliferation, migration and invasion	132
Oxygen, ROS and cancer stem cells	132
Aberrant regulation of death	133
Aberrant regulation of metabolism	133
Mitochondria and metastatic potential	134
ROS and the hallmarks of cancer	134
Redox homeostasis: an old and emerging cancer target.	135
Future directions.	135
Acknowledgements.	135
References	135

Oxygen and ROS sensing by the earliest life on earth

A logical assumption is that antioxidant enzymes evolved with, or after the appearance of, aerobic metabolism on earth. The

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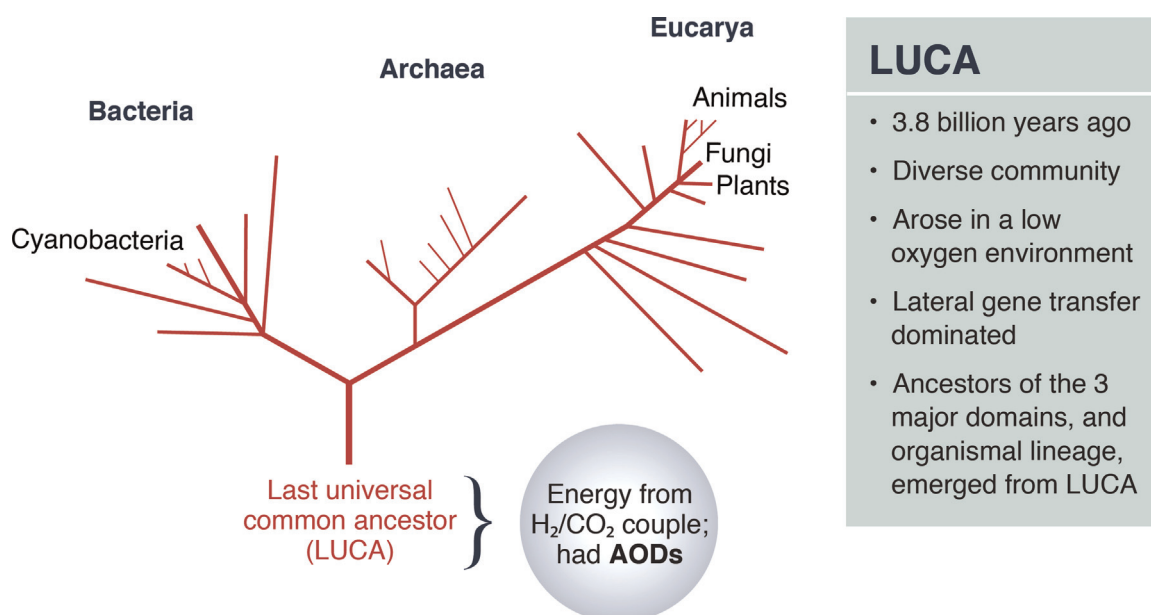


Fig. 1. Oxidative stress preceded oxygen metabolism. A phylogenetic tree developed from sequence analysis of ribosomal RNAs [1,2]. The first semblance of life is at the base of the tree and is referred to as the last universal common ancestor, or LUCA. Oxygen levels in the atmosphere did not increase appreciably until the appearance of the cyanobacteria. Yet, LUCA had genetic material encoding for antioxidant defenses.

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thinking is that these enzymes became necessary only when cells had to protect themselves from increased levels of reactive oxygen species (ROS) that were produced as by-products of respiration. Results from the quest for the earliest form of life on earth challenge this assumption. With modern sequencing technology, rRNAs from multiple species have been compared and used to construct a phylogenetic tree based on molecular rather than morphological similarities between organisms (Fig. 1). The tree has three domains: Bacteria, Archaea and Eucarya [1,2]. At the base of the tree is the last universal common ancestor (LUCA), which is

estimated to have appeared 3.5–4 billion years ago. Carl Woese postulates that LUCA was not a single organism but a community of primitive entities with a high frequency of lateral gene transfer [3]. Collectively, this community was genetically and metabolically complex, containing the molecular origins of all present life forms. Over time, the ancestors of three major domains emerged from LUCA.

LUCA was present a billion years before the rise of oxygen levels in the atmosphere. Yet, sequence analyses suggest that it was capable of detoxifying ROS [4]. The lack of an ozone layer at

LUCA	Bacteria	Eucarya
Hemoglobin-like molecule	SoxR/SoxS OxyR, PerR	AP-1 NF-κB Nrf2 p53 ASK1 BCL-2 HIFs RTKs HDACs
<ul style="list-style-type: none"> • Bacteria: direct regulation of transcription factors • Eukaryotes: multiple ways that redox signals change regulatory factors, including activity, expression level, stability and location 		

Fig. 2. Oxygen sensing and signaling in LUCA and modern-day organisms. LUCA had a hemoglobin-like protein that could have bound oxygen. Modern-day organisms have a number of regulatory systems that respond to oxygen, hydrogen peroxide or superoxide. Bacteria have redox-sensitive transcription factors that interact directly with superoxide (SoxR/SoxS) or hydrogen peroxide (OxyR, PerR) and regulate gene expression in response. In eukaryote cells, redox regulation frequently involves multiple proteins with one acting as the sensor and subsequently changing the location, activity or expression level location of a regulatory protein. The listed proteins have been shown to participate in different aspects of redox signaling.

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