Redox Biology 5 (2015) 124–139

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Review Article

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

Margaret M. Briehl

Department of Pathology, University of Arizona, PO Box 24-5043, Tucson, AZ 85724-5043, USA

ARTICLE INFO

Article history:
Received 8 April 2015
Accepted 8 April 2015
Available online 11 April 2015

Keywords:
Superoxide
Hydrogen peroxide
Proliferation
Apoptosis
Mitochondria
Cancer

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.

Contents

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

E-mail address: mmbriehl@pathology.arizona.edu

http://dx.doi.org/10.1016/j.redox.2015.04.002

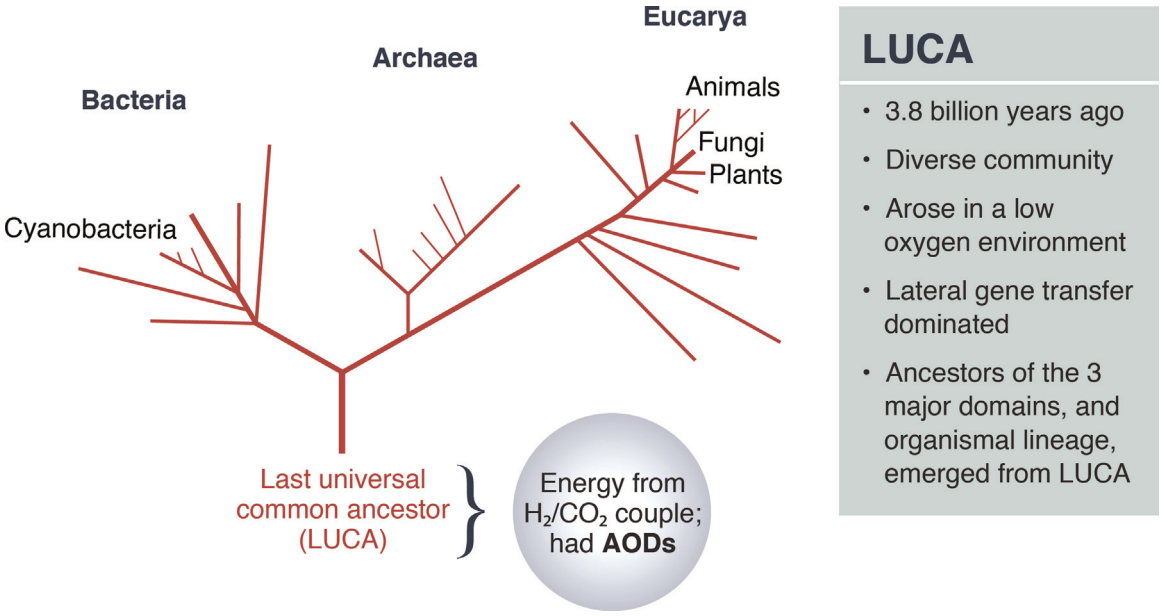

Fig. 1. Oxidative stress preceded oxygen metabolism. A phylogenetic tree developed from sequence analysis of ribosomal RNAs [1,2]. The first semblance of life is at the base of the tree and is referred to as the last universal common ancestor, or LUCA. Oxygen levels in the atmosphere did not increase appreciably until the appearance of the cyanobacteria. Yet, LUCA had genetic material encoding for antioxidant defenses.
From Knoll A.H. (1999) Science 285: 1025–1026; http://www.sciencemag.org/content/285/5430/1025. Reprinted with permission from AAAS.

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

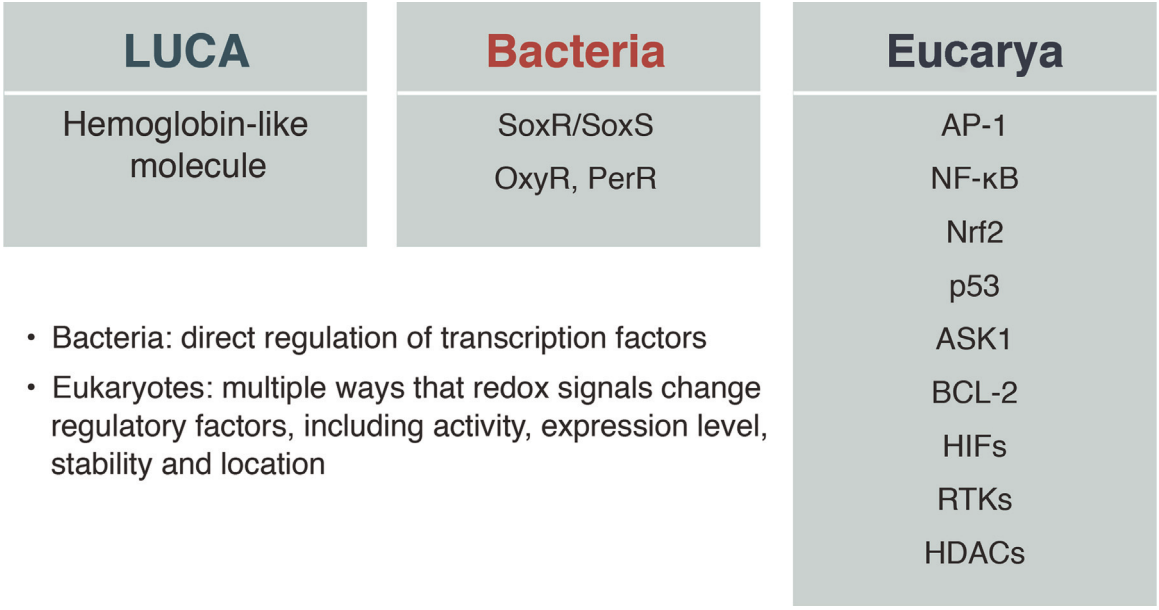

Fig. 2. Oxygen sensing and signaling in LUCA and modern-day organisms. LUCA had a hemoglobin-like protein that could have bound oxygen. Modern-day organisms have a number of regulatory systems that respond to oxygen, hydrogen peroxide or superoxide. Bacteria have redox-sensitive transcription factors 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.