Chapter 1

Oxygen: From Toxic Waste to Optimal (Toxic) Fuel of Life

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Abstract

Some 2.5 billion years ago, the great oxygenation event (GOE) led to a 10^5-fold rise in atmospheric oxygen [O_2], killing most species on Earth. In spite of the tendency to produce toxic reactive oxygen species (ROS), the highly exergonic reduction of O_2 made it the ideal biological electron acceptor. During aerobic metabolism, O_2 is reduced to water liberating energy, which is coupled to adenosine triphosphate (ATP) synthesis. Today, all organisms either aerobic or not need to deal with O_2 toxicity. O_2-permeant organisms need to seek adequate [O_2], for example, aquatic crustaceans bury themselves in the sea bottom where O_2 is scarce. Also, the intestinal lumen and cytoplasm of eukaryotes is a microaerobic environment where many facultative bacteria or intracellular symbionts hide from oxygen. Organisms such as plants, fish, reptiles and mammals developed O_2-impermeable epithelia, plus specialized external respiratory systems in combination with O_2-binding proteins such as hemoglobin or leg-hemoglobin control [O_2] in tissues. Inside the cell, ROS production is prevented by rapid O_2 consumption during the oxidative phosphorylation (OxPhos) of ATP. When ATP is in excess, OxPhos becomes uncoupled in an effort to continue eliminating O_2. Branched respiratory chains, unspecific pores and uncoupling proteins (UCPs) uncouple OxPhos. One last line of resistance against ROS is deactivation by enzymes such as super oxide dismutase and catalase. Aerobic organisms profit from the high energy released by the reduction of O_2, while at the same time they need to avoid the toxicity of ROS.

Keywords: oxygen, ROS, oxidative stress, oxyconformers, oxyregulators, adaptative metabolism

1. At the beginning, all life was anaerobic

The early Earth atmosphere contained high [H_2], [NH_3] and [CH_4], while [O_2] was less than 10^{-5} the present atmospheric level (PAL) [1, 2]. All life forms were anaerobic [3, 4]. Early redox reactions involved electron donors such as H_2, CO_2 or HS [5, 6], while electron acceptors were sulfur and NO_3 [7]. Eukaryotes were present before O_2 rose [8, 9] and contained anaerobic mitochondrion-like organelles [10, 11].

2. The massive increase in [O_2] and the need to counteract its toxicity

Approximately 2.5 billion years ago, the great oxygenation event (GOE) was precipitated by both geological processes [12] and by the photosynthetic activity of cyanobacteria [13, 14]. Today, O_2 is the preferred electron acceptor used by facultative microorganisms and the only one used by aerobes. The highly exergonic reduction of O_2 provided the energy needed for the development of multicellular organisms. In addition, the high energy of activation required for O_2 reduction ensures that this reaction occurs mostly through catalyzed reactions. For instance, oxidases bind their substrate tightly, preventing the liberation of reactive oxygen species (ROS) [15]. At low concentrations, ROS are useful as signaling molecules, while at higher concentrations ROS damage and kill cells. Cells need much less [O_2] than what is found in the atmosphere and thus, to prevent ROS production internal O_2 is kept at a low level [16]. Cells have developed two mechanisms to deal with surplus O_2: (1) avoiding it and (2) rapidly reducing it. Furthermore, cellular O_2 is found mostly bound to proteins such as hemoglobin, leg-hemoglobin and myoglobin. Early oxy-conformer organisms are permanent to O_2, and thus, at different stages in their life cycle, they have to migrate to microaerobic or anaerobic spaces (**Table 1**) to cope with variations in O_2. More evolved oxyregulator organisms from fish to mammals enveloped themselves in an O_2-impermeable epithelium, while at the same time developing highly specialized systems that control tissue [O_2] (**Figure 1**). Oxyconformers and oxyregulators display different strategies to manage O_2-by-product toxicity (**Figure 1**).

In oxyconformers, all cells are exposed to environmental [O_2]. O_2-permeable organisms do have O_2 transport proteins and intracellular O_2-binding proteins, but in addition, they need to implement diverse strategies to deal with changing O_2. These include searching for microaerophilic or anaerobic environments. Arthropoda, the most abundant and widely distributed phylum on Earth, are oxyconformers [17]; it comprises subphyla Chelicerata (spiders), Myriapoda (centi- and millipedes), Hexapoda (Insects) and Crustacea, all of them protected by an exoskeleton. Nonaquatic insects possess a hard waterproof cuticle and branched invaginated tubules forming a specialized respiratory structure that works well at constant

[O_2]. Aquatic organisms, including most of the crustacea, are exposed to highly variant [O_2], which may be 26 times lower than in the atmosphere [18, 19]. In water, [O_2] varies with temperature, depth, mechanical aeration and tidal movements. Only few invertebrates (Plathelmynthes, Nematoda, Molluska, Anellida and Sypuncula) have been thoroughly studied in regard to their mechanisms to deal with fluctuating [O_2] [20, 21]. Remarkably, very few studies on Crustacea are available.

Environment	O_2 concentration (μM)	References
Atmosphere	1000m ASL 256.0 Sea level 1028.0	[88]
Alveoles	143.0	[89]
Arteries	123.0 *Hb bound 120.5* *Not bound 2.5*	[89] [90]
Capillaries	130.0	[89]
Interstitial fluid	55.0	[89]
Tissue cells	31.0	[89]
Veins	59.0	[89]
Mitochondria	Minimal for coupling 0.1 Minimal reported 20.0	[91]
Distilled water	223.0	[92]
Sea water	Surface 198-397.0 250.0 MOZ < 20.0	[93] [34] [94]
Estuaries	Surface 375.0 Bottom 62.5	[95] [96]

Oxygen concentrations reported were modified from partial pressures to micromolar concentration (μM) using Henry's law at 310.15K ASL (above sea level).

Table 1. Oxygen concentrations in different environments.

In order to control the release of ROS oxyconformers reduce aerobic activity during hypoxia/anoxia cycles, marine crustaceans display different responses to hypoxia/anoxia. To avoid hyperoxygenated or anoxic waters, crustaceans migrate between open sea and coastal lagoons (**Figure 2**), or migrate vertically through the water column to flee the O_2 minimum zone (OMZ) and into [O_2] compatible with their metabolic needs [22, 23]. Some shrimp species, such as the burrowing thalassinids *Upogebia major* and *Callianasa japonica*, which commonly inhabit the extremely hypoxic or even anoxic intertidal flats, can reduce their respiratory rate in dugout burrows, surviving up to 5 h of anoxia for *U. major* and 19 h for *C. japonica* [24]. *Artemia franciscana* is well known for its high tolerance to anoxia; the embryos of this species survive without O_2 for years through the complete depression of their metabolic rates [25, 26]. Metabolic rate depression is also observed in ectotherms, which lower their mitochondrial activity in function of temperature adjusting their O_2 consumption machinery accordingly [27]. However, it is not clear how mitochondria from oxyconformers respond to hypoxia, how respiratory activity adapts to reduced metabolic rates and how the cellular redox balance and energetic homeostasis are preserved [28, 29].

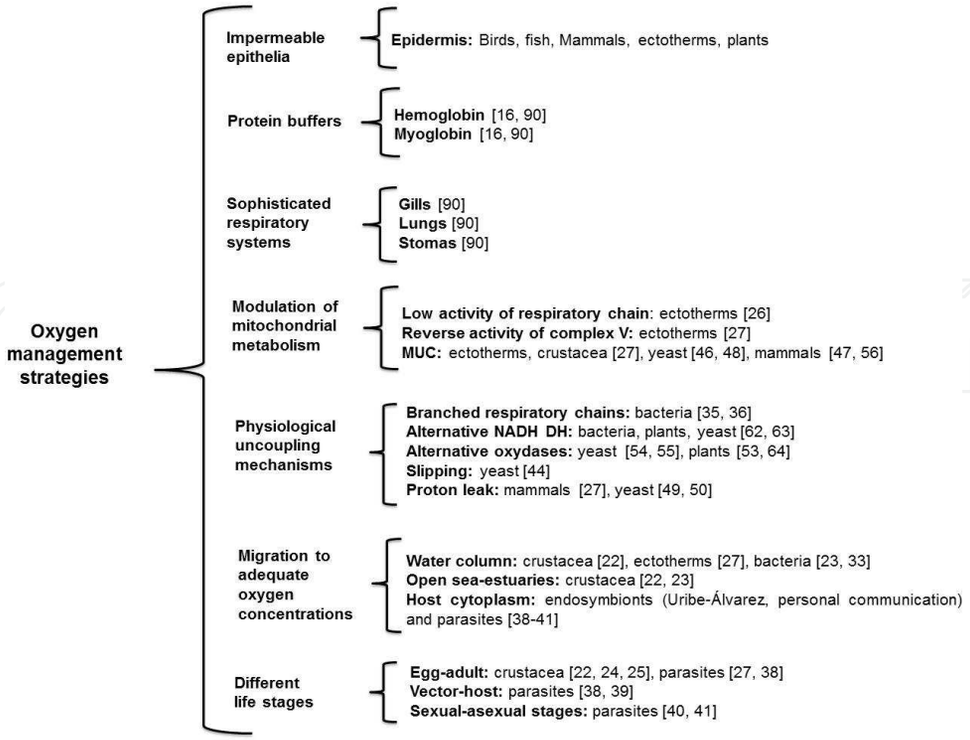

Figure 1. Oxygen management strategies in different organisms. Organisms need to adapt to the O_2 concentration in the environment. Therefore, either they move to environments with adequate O_2 or they engineer different mechanisms to process O_2 at varying rates (electron transport chain (ETC) activity, mitochondrial unspecific channels (MUC), uncoupling proteins (UCPs). Additionally, oxyregulators have developed O_2-excluding mechanisms such as impermeable epithelia, external respiratory systems (lungs, gills, stomas) and O_2-transporting proteins (hemoglobin, myoglobin).

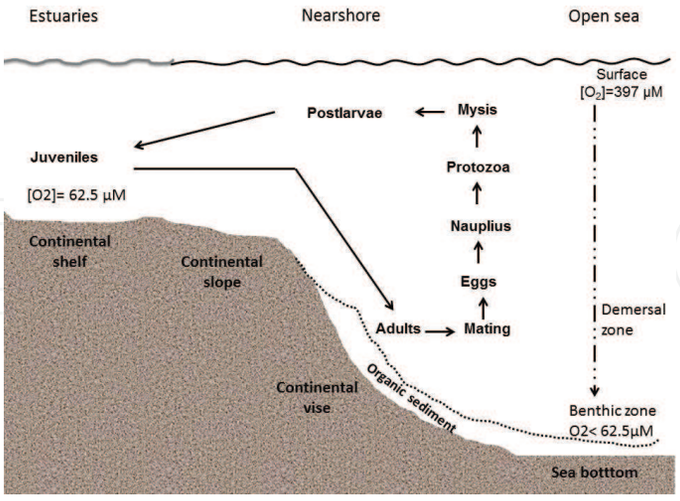

Figure 2. Migration of shrimp during their life cycle. Shrimp spend most of their life in the open sea, where they mate and lay eggs which hatch and undergo different larval stages (Nauplius, Protozoa, Mysis). Once in the postlarval stage, they travel to estuaries where they mature reaching the juvenile stage, and burying themselves in the sand for long periods. Once maturity is reached, they begin the cycle again returning to the open sea. This migration pattern takes shrimp to waters with widely different O_2 concentrations.

Among unicellular organisms, diverse yeast species can survive at almost any [O_2]. *Saccharomyces cerevisiae* can thrive at very low [O_2] through fermentation, although it does possess a facultative aerobic metabolism. The anaerobic metabolism of *S. cerevisiae*, *D. hansenii* and other yeast species is the basis for the fermentation industry of bread, wine and cheese. For example, during wine fermentation, *S. cerevisiae* produces large amounts of ethanol, while *D. hansenii* produces volatile products conferring the characteristic aroma of wine [30]. Also, *S. cerevisiae* participates in cheese fermentation, whereas *D. hansenii* protects against other filamentous fungi during ripening [31, 32]. Yeast and other organisms have developed diverse systems to detoxify oxygen through physiological uncoupling and these are discussed later.

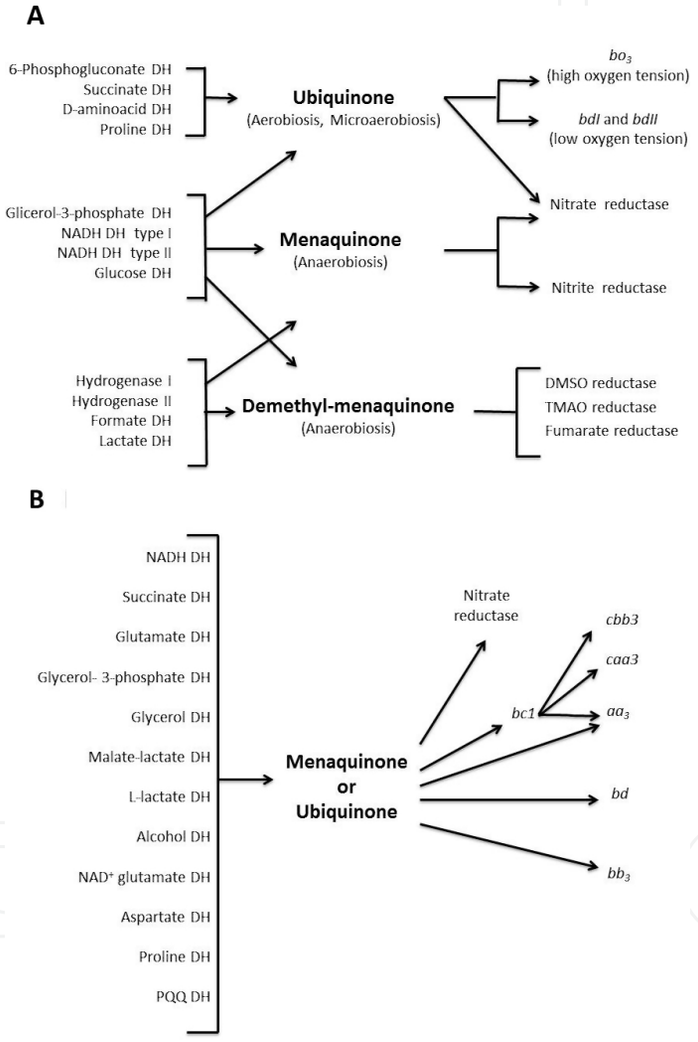

Figure 3. Diversity of bacterial respiratory chains at different [O_2]**. A**. The respiratory chain from *Escherichia coli* during aerobiosis, micro-aerobiosis and anaerobiosis. Modified from [35, 36]. Ubiquinone is expressed at high [O_2] and NADH DH type II is overexpressed as compared to the NADH DH type I, which in turn is expressed at low [O_2]. The major final oxidase is cytochrome *bo*. During anaerobiosis, the respiratory chain in *Escherichia coli* succinate dehydrogenase is not expressed, whereas fumarate reductase or nitrate reductase may be the final electron acceptors. **B**. Hypothetical respiratory chain of *Wolbachia pipientis* constructed from BLAST and genome sequences reported in [76, 77]. At high [O_2] cytochrome, bc1 and different cytochrome oxidases are expressed. Under microaerobic conditions, cytochrome *bd* is expressed. Then, under anaerobiosis, nitrate reductase is expressed.

Many bacteria are facultative. Among these, *Escherichia coli* is a very illustrative representative that may thrive both in microaerobic environments such as the intestinal lumen and in the external environment in a wide range of [O_2]. Bacteria respond to environmental [O_2] variations or other conditions such as the need to fixate N_2 [33, 34] by varying the composition of their branched respiratory chains (**Figure 3A**), which vectorially transport from 0 to 10 protons, as many as those in orthodox respiratory chains [35, 36]. Still, when motile, bacteria will swim toward environments containing the ideal [O_2].

Obligate endosymbionts, such as *R. prowazekii*, *Wolbachia sp.* or *Sodalis,* live in cytoplasmic vacuoles of multicellular organisms. The cytoplasm is a microaerophilic environment equipped with O_2-consuming organelles and ROS-detoxifying enzymes. Remarkably, most endosymbionts contain a respiratory chain that at least in the case of *Wolbachia* seems to aid host mitochondria to deplete intracellular O_2 (**Figure 3B**).

Many parasites exhibit various life-cycle stages, which have different sensitivities to ROS engineered to endure attacks from macrophages. *Leishmania sp.* undergoes a relatively simple life cycle with two stages: the flagellated mobile promastigote living in the gut of the sand fly vector and the intracellular amastigote within phagolysosomal vesicles of the vertebrate host macrophage [37]. Promastigotes contain respiratory complexes I, II, III and IV, while it is not clear whether amastigotes possess an oxidative phosphorylation (OxPhos) machinery. Strikingly, amastigotes exhibit a succinate-dependent, uncoupler-sensitive transmembrane potential. Differences in sensitivity to oxidants are also observed between them, *in vitro*, promastigotes are more resistant to H_2O_2 than amastigotes [38].

In the bloodstream, *Trypanosoma cruzi* trypomastigotes contain high complex II and III activities. Interestingly, cytochrome *c* oxidase (COX) activity decreases creating an "electron bottleneck" that favors an increase in electron leakage, thus overproducing ROS. The oxidative preconditioning provided by this mechanism confers protection to bloodstream trypomastigotes against ROS liberated by the host immune system. These changes in mitochondrial activity, during the *T. cruzi* life cycle, are probably a key metabolic adaptation for survival in different hosts [39].

Malarial parasites are vulnerable to oxidative stress during their intraerythrocyte life stages. They contain the canonical respiratory chain (complex I, II, III and IV) plus an alternative electron transport pathway. Moreover, malarial mitochondria coordinate the biosynthesis of pyrimidine, heme and coenzyme Q [40]. *Plasmodium falciparum* possesses genes for two different superoxide dismutases (SOD), a cytosolic, Fe^{2+}-dependent, (SOD-1) expressed throughout the intraerythrocytic life of the parasite. The second, SOD-2, is mitochondrial and possesses a reminiscent apicoplast-targeting sequence. The host immune response to malaria involves phagocytosis and the production of nitric oxide and ROS that end up contributing to the pathology of the disease [41].

Regardless the organism studied, cytoplasmic [O_2] can vary widely, so damage control is needed at two levels. Either O_2 is reduced independently of adenosine triphosphate (ATP) production in a process known as physiological uncoupling, or the ROS-handling enzymes are activated. We shall briefly describe only physiological uncoupling as many reviews on

ROS-handling enzymes, such as superoxide dismutase and catalase are found elsewhere [42, 43].

3. Physiological uncoupling as an O_2-depleting mechanism and prevents ROS production

Both in oxyconformers and in oxyregulators, once O_2 enters the cell it has to be reduced at a high rate. When ATP is needed the respiratory chain rapidly catalyzes this reduction. When there is energy surplus, O_2 consumption has to be uncoupled from ATP synthesis with the aim of preventing ROS overproduction [44]. A review on the physiological uncoupling mechanisms observed in mitochondria from different species of yeasts has been published recently [45]. Yeast mitochondrial uncoupling mechanisms may be (a) proton sinks, such as the mitochondrial unspecific channels [46–48] and the uncoupling protein (UCP) [49, 50], or (b) nonpumping redox alternative enzymes found in branched respiratory chains [51–55].

(a). Proton sinks: The opening of the mitochondrial permeability transition pore (MPTP) leads to mitochondrial uncoupling and to the activation of signaling events leading to apoptosis [56], which was first detected in mammalian mitochondria as a response to the disruption of intracellular calcium homeostasis. In crustaceans subjected to hypoxia, mitochondrial functions are downregulated [57, 58, 20] and there is an anoxia-triggered intracellular increase in both calcium and phosphate, while ATP production is inhibited, probably as a result of the opening of a MPTP. In *Artemia franciscana* [26] and in the ghost shrimp *Lepidophthalmus louisianensis* [59], the proteins needed to form the MPTP are present. However, whether these crustaceans possess MPTPs is to be defined. Both in crustacean mitochondria and in other known hypoxia-tolerant invertebrates (mussels, oysters, and cnidarians among others), the role of a putative MPTP is an interesting question.

(b). Branched respiratory chains: Bacteria do not exhibit a permeability transition. This seems to be a mitochondrial trait. Instead, bacteria (and many mitochondria) exhibit branched respiratory chains. Indeed, different species of mitochondria may exhibit from none to three alternative enzymes. In contrast, bacteria may contain as much as twenty electron entry ports and as many exits. Thus, in most prokaryotes, branched respiratory chains seem to be the mechanism of choice to maintain a high rate of O_2 consumption, while adjusting ATP production to the energy requirements of the cell. In this regard, the bioenergetic efficiency for each entry point is defined as the stoichiometry of H^+ pumped per e^- traveling through the respiratory chain [60]. In addition, terminal oxidases are remarkably varied and their active site orientation, to the cytoplasm or to the periplasm determines their pumping efficiency [36].

Alternative oxidoreductases is the term designating all components of the respiratory chain different to the usual complexes I through IV. Most alternative oxidoreductases lack proton-pumping activity and may coexist with, or substitute for the respiratory proton-pumping complexes. Alternative enzymes catalyze the rapid, uncoupled flow of electrons towards O_2. Alternative NADH dehydrogenases may either substitute for (*S. cerevisiae*) or coexist with (bacteria, plants and diverse fungi) complex I [61, 62].

Alternative oxidases (AOXs) catalyze the oxidation of ubiquinol to quinone and the reduction of O_2 to H_2O in the absence of proton translocation [53]. Although highly represented among plants, fungi and protist species, animal AOXs have been predicted to exist only in Molluska, Nematoda and Chordata [63]. Recently, the number of phyla that probably possess AOX has increased including Placozoa, Porifera, Cnidaria, Annelida, Echinodermata, Hemichordata and Chordata. In some marine vertebrates, such as sipunculids, annelids (*Nereis pelagica,* and *Arenicola marina)* and in bivalves (*Arctica islandica),* AOX has been detected [64–66]. However, there are no confirmed reports for AOX in mitochondria from crustaceans [51]. In different plant and animal species, cells lacking AOX show an increased susceptibility to death due to H_2O_2, hypoxia and pathogens [67]. The ultimate decoupling of electron flow occurs when NADH dehydrogenases act in concert with alternative oxidases. The yeast *Yarrowia lipolytica* is a strict aerobic organism for which several biotechnological applications have been developed, such as in the cheese fermentation, obtention of extracellular enzymes [68], production of organic acids [69] and interconversion of fatty acids and alkenes [70]. In *Y. lipolytica,* metabolism occurs in a complex network between compartments, such as peroxisomes, endoplasmic reticulum, lipid bodies and mitochondria [69]. Mitochondria play an important role in ATP production, as well as in the maintenance of the NADH/NAD^+ redox ratio [71]. The respiratory chain is composed of the classic complexes: I, II, III and IV, one alternative NADH dehydrogenase external (NADH2) [72] and two isoforms of AOX [73]. During the logarithmic growth phase, NADH2 interacts with supercomplexes III–IV channeling the electrons to oxygen, while pumping protons at both complex III and IV [74]. In contrast, during the stationary growth phase, electrons are directly transferred from alternative NDH2 to AOX, thus uncoupling oxidative phosphorylation and decreasing the production of ROS [54, 55]. This is a very illustrative example, which suggests that physiological uncoupling systems are present in all living organisms. Furthermore, in *Y. lipolytica,* both proton sinks and branched chains are observed [50, 54].

Bacterial cytochrome-containing oxidases are many. These enzymes are differentially expressed in response to different oxygen concentrations and on whether an organism is an obligate aerobic or a facultative species. In addition, oxidases may coexist depending on the species under study and they may play different roles in the cell [75]. In *E. coli*, different oxidases are expressed depending on [O_2]. At high O_2, bo3 is expressed, while at low O_2, bd cytochromes are observed. Furthermore, *E. coli* is capable of growth under anaerobiosis, using respiratory chains reminiscent of the early Earth that use ubiquinone, menaquinone or demethylmenaquinone to donate electrons to enzymes that use terminal acceptors different to O_2 (**Figure 3A**) [35, 36]. Branched respiratory chains provide the possibility of consuming O_2 without producing ATP. In the yeast *Y. lipolytica*, in the bacterium *E. coli* and probably in the Rickettsial *Wolbachia sp*., the arrangement of the respiratory chain varies such that when [O_2] is high, or ATP is needed, high proton pumping efficiency is observed. In contrast, factors such as arrival to the stationary phase or microaerophilic conditions probably trigger overexpression of the alternative NADH dehydrogenase and/or the AOX leading to the futile reduction of O_2 [61]. A possible arrangement of the respiratory chain of *Wolbachia* sp is illustrated (**Figure 3B**) where a large number of possible electron-donating enzymes reduce

menaquinone or ubiquinone that in turn reduce final electron-accepting enzymes that are expressed according to the presence of O_2 in the cytoplasm of the host [76, 77].

4. N-fixating bacteria are a special case

Nitrogen-fixating bacteria may be facultative as *Klebsiella pneumonia* or strict aerobics as *Azotobacter vinelandii* or *Gluconobacter diazotrophicus*. As they contain fragile, oxygen-sensitive nitrogen-fixating enzymes that need to be protected, these bacteria have developed many strategies to detoxify [O_2]. Thus, in N-fixating bacteria, both N-reductases and different oxidases are expressed: *A. vinelandii* contains a highly active respiratory chain and is able to adjust the expression of its three oxidases to a wide range of [O_2]. Among these, cytochrome *bd* has high O_2 affinity (KmO_2= 5 μM) and becomes active during N fixation [15, 78–80]. Indeed, during N fixation the H^+/O index is low, at 1 [81]. In *Ga. diazotrophicus* different periplasmic membrane enzymes such as glucose-, acetaldehyde- or ethanol-dehydrogenase reduce a quinone, which in turn donates its electrons to two different oxidases, *ba* which is coupled to ATP synthesis and bb_3 which is not coupled, but its role is to deplete O_2 in the vicinity of nitrogen reductases [82].

5. ROS detoxification

In spite of the production-prevention mechanisms outlined earlier, ROS may reach high concentrations, for example, during ischemia-reperfusion. The last line of defense is detoxification. Enzymes such as superoxide dismutases (SODs) and catalases deactivate ROS. SODs have been grouped on the basis of the metal cofactor, which can be Fe, Mn, Ni or Cu/Zn [83]. The Fe-SODs are mostly found in microaerophiles and anaerobes. Microorganisms in aerobic environments prefer Mn-SOD [84]. Catalase dismutates hydrogen peroxide to water plus O_2 [85]. Several genes capable of H_2O_2 dismutation evolved from ancestral genomes. The most abundant was heme-containing enzymes spread among bacteria, Archaea and Eukarya [86].

In *Clostridium acetobutylicum*, a strict anaerobic that survives little time when exposed to O_2, no catalases are found [87], and a function has yet to be found for the annotated SODs.

6. Conclusion

During the early paleoproterozoic period, a massive death toll resulted from a 10^5 times rise in atmospheric O_2. In order to survive, organisms had to learn to cope with O_2 toxicity while profiting from the large energy release coupled to its reduction. Several O_2-management strategies are revised here. Among these is hiding away from O_2, moving to adequate O_2

concentrations or excluding O_2 with impermeable epithelia. Once O_2 enters the cell, other mechanisms are designed to handle it. Its reactivity is controlled by O_2-quenching proteins or by rapidly reducing it with specific oxidases. In order to avoid side reactions, the rate of reduction had to be kept at optimal pace, independently of ATP production and thus several mechanisms of physiological uncoupling of oxidative phosphorylation evolved. Physiological uncoupling was achieved either by opening proton sinks or by using O_2 independently of the proton gradient. Today, these mechanisms are expressed in many cells. Proton sinks include unspecific channels and uncoupling proteins, while proton gradient-independent consumption of O_2 involved alternative oxido-reductases found in the branched respiratory chains of fungi, plants and arthropods. In spite of the function of all these O_2-management machines, O_2 can still react unspecifically to form ROS, which destroy the cell through processes such as aging, apoptosis or necrosis. Once formed, ROS may still be eliminated by enzymes such as SOD and catalase, which are reviewed elsewhere [43] O_2 is a great source of energy for the cell, but its high toxicity has to be dealt with, through mechanisms that we are only beginning to understand.

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