5 Oxidative Stress, ROS Generation, and Associated Molecular Alterations in High Altitude Hypoxia

Aditya Arya and Shikha Jain

Abstract

High altitude especially above 3000 m of elevation is considered a potential risk for rapid ascent, while at elevation above 5500 m, it poses life threatening risk to non-adapted individuals. This threat is associated with hypoxia-induced rapid cardiopulmonary changes that impair the normal functioning of the body. It is well-evident that partial pressure of oxygen is much reduced at altitudes due to thinning of the atmosphere and therefore, the human body prefers to adapt against those depriving oxygen levels. In this attempt, some unbalanced changes in subcellular physiology may lead to alterations and hence cause reversible and irreversible damage. Among the most rapid cellular perturbations during altitude-associated hypoxia is the generation of reactive oxygen species (ROS). Although cells have mechanisms to succumb to those altered levels of ROS, the inability to quickly alleviate ROS leads to enormous damage to proteins, lipids, and other biomolecules. As cellular response cells readjust their redox milieu and strengthen antioxidant defence. The dietary intervention of antioxidants has also proven to be useful in clinical settings. This chapter describes the mechanism of ROS generation and ROS associated proteomic perturbation at the cellular level during hypobaric hypoxia.

Keywords

Reactive oxygen species · High altitude · Hypobaric hypoxia · Antioxidants

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5.1 Introduction

Environment plays a pivotal role in determining the well-being of organisms. The quality of life and longevity depends on the quality of the surrounding environment. Several environmental stressors are known to impact the quality of life and can lead to life-threatening diseases. Environmental stressors may be classified as natural or man-made. Man-made environmental stressors are primary pollutants that vary in severity and concentration depending on human activity. Some of the major man-made environmental stressors include high carbon monoxide in the air, pesticides in soil, and heavy metals in drinking water. These stressors may be avoided and their ill effects may be prevented by purification at the source. However, natural stressors are difficult to evade and they need suitable precautions in the form of individual adaptation or prophylactic modalities. Natural environmental stressors may arise from reduced air pressure at mountains (hypobaric hypoxia), increased pressure in deep-sea diving, cold temperature, high temperatures, UV radiations, etc. Figure 5.1 illustrates the major environmental stressors.

Among the natural environmental stressors, most of them are caused due to varying geological architecture of earth, primarily altitudes, deep oceans, or even latitudinal variations. Varying latitudes across the equator shows a gradation in temperature creating a huge variation of +55 °C maximum temperature in some

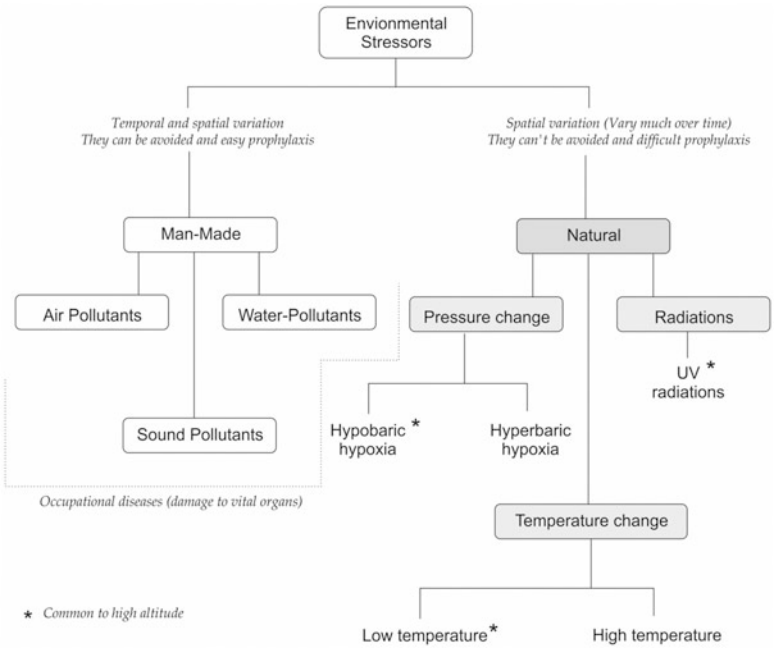

Fig. 5.1 Major types of environmental stressors: man-made stressors can be evaded while natural stressors are difficult to evade and need prophylactic or therapeutic interventions

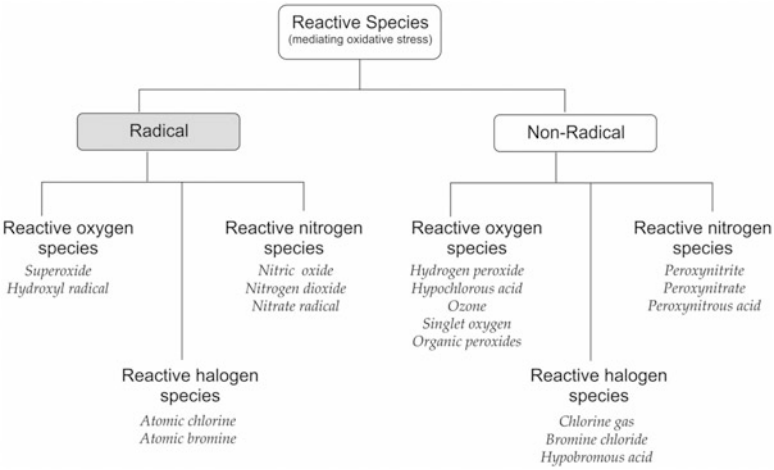

Fig. 5.2 Common Pro-oxidants explored in biological systems

countries of Africa while lowest temperatures of −50 °C at poles. High pressure exists as a potent stressor in deep oceans. Another factor is altitude, which poses two parallel threats, one in the form of reduced air pressure and another as elevated UV radiations, creating it one of the most difficult terrains for organism survival. These changes, above a threshold, induce the compensatory adaptive cardiopulmonary responses, primarily hyperventilation and generation of excess radicals as a result of an imbalance of glucose metabolism and oxygen availability resulting in the onset of high altitude sickness.

Chemically, various molecules such as oxygen have the ability to accept electrons are potentially called as oxidant or oxidising agents (Prior and Cao 1999) and this phenomenon of electron removal is called as oxidation. Although the process of oxidation is concurrent with reduction in another paired molecule or group, hence a more general term redox reaction is used. Redox reactions build the foundations of key biochemical pathways including biosynthesis and energy production. They are also important in understanding biological oxidation and radical/antioxidant effects. While the terms oxidant and reductant are primarily of chemical origin, in biological environments pro-oxidant and antioxidant terms are often preferred (Kohen and Nyska 2002). Pro-oxidants include both radical and non-radical species (Halliwell 2006). A few most abundant and common pro-oxidants are listed in Fig. 5.2.

A number of aforementioned environmental stressors are known to directly or indirectly influence the conventional redox milieu and impair the steady state of oxidant and antioxidants, this condition is referred to as oxidative stress (Halliwell 2006; Kalyanaraman 2013). Moreover, recently, the oxidative stress has been further elaborated to distinguish the thin line of difference between oxidative imbalance that causes pathological conditions called distress, while the one that constitutes an essential part of redox signalling is called oxidative eustress. A number of pathological conditions especially those influenced by environmental stressors are known to

have involvement of oxidative stress and are therefore characterised by the presence of hallmarks of oxidative stress or redox-biomarkers (Dalle-Donne et al. 2006). Among the two most common environmental stressors known to cause oxidative stress are hypoxemia and UV radiation. The former disrupts the oxygen flux in mitochondria and affects the steady flow of electrons via electron transport chain and hence promotes reactive oxygen species generation. While in case of UV radiations, the high energy photos are directly known to induce homolytic cleavage of bonds and therefore generation of radicals across various biomolecules.

5.2 Mechanisms of Oxidant Generation

Living organisms are continuously at the risk of being exposed to reactive oxidants of both extrinsic and intrinsic origin, some of which are related with the random interaction of molecular oxygen and its trade-off (Winterbourn 2008). Generation of RONS in living cells can be attributed to either direct emergence from interaction of high energy radiations (such as UV radiations at high altitude) or via mitochondrial route due to the leakage of electrons from electron transport chain (Novo and Parola 2008; Lin and Beal 2006). A detailed discussion on mitochondrial ROS generation system is provided in the following description.

5.2.1 Oxidants Generation in Mitochondria

Nearly, 1% to 5% of electrons flowing at a steady rate in electron transport chain could be diverted to the generation of superoxide radicals ($O_2^{\bullet -}$), which mostly occurs across the NADH/ubiquinone oxidoreductase or ubiquinol/cytochrome c oxidoreductase, otherwise commonly known as complex I and complex III of electron transport chain (Kohen and Nyska 2002). Superoxide radicals are then usually detoxified to hydrogen peroxide by mitochondrial superoxide dismutase enzymes. This hydrogen peroxide can now cross the mitochondrial membrane and reach cytoplasm, which could damage other biomolecules unless detoxified via several peroxidases (Cadenas and Davies 2000). Moreover, besides membrane bound complexes which contribute to the oxidant generation, several matrix proteins are also actively involved in oxidant generation such as alpha ketoglutarate dehydrogenase (KGDH), aminocycloproane-carboxylic acid oxidase (ACO), and pyruvate dehydrogenase complex (PDC), which involve the oxidation of NADH are primary matrix sources of radicals. Besides these common ROS-generating pathways which lead to the formation of either superoxides or hydrogen peroxides, several antioxidants counter the effect. These enzymatic or non-enzymatic antioxidant systems either independently (catalase, Mn-SOD, glutathione peroxidase) or operate as a cascade. Among a very common cascade is the oxidation–reduction cycling of Peroxiredoxins (PRX3), Thioredoxins (TRX2), Glutathione peroxidase (GPX), and Glutathione (GSH) as shown in Fig. 5.3.

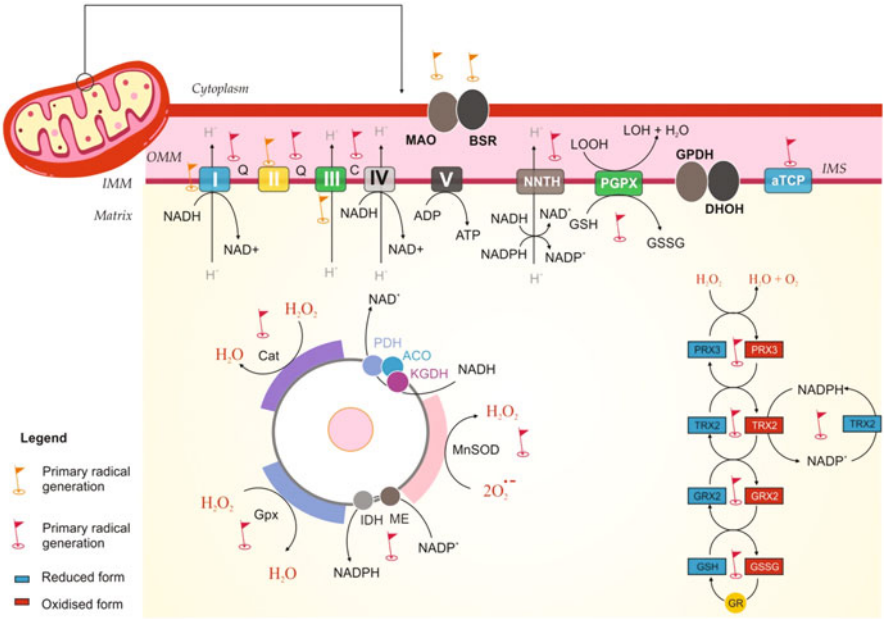

Fig. 5.3 Summary of major ROS generation systems and antioxidant defence inside mitochondria. (*OMM* outer mitochondrial membrane, *IMM* intermembrane space, *MAO* Monoamine oxidase, *PRX* peroxiredoxin, *TRX* Thioredoxin, *GPX* Glutathione peroxidase, *GSH* Glutathione (reduced), *GSSG* Glutathione (oxidised), *IDH* Isocitrate dehydrogenase, *Mn-SOD* Manganese superoxide dismutase

Although the formation of a primary ROS, i.e., superoxides occurs in the respiratory chain from molecular oxygen. This is believed to follow first order kinetics with oxygen concentration. As a paradox, however, generating ROS in mitochondria in the cell remains constant or known to be elevated with a concurrent decrease in PO_2 which is often observed with hypoxic conditions, either normobaric or hypobaric. Interestingly, the reason behind aforementioned paradox is higher affinity of molecular oxygen to ROS-generating modules compared to conventional acceptor cytochrome oxidase or coenzyme Q. However, the generation of ROS predominates during oxygen limiting condition while the cytochrome oxidase is partially reduced. It is also noteworthy to mention that this paradox is absent in the isolated mitochondrial system.

5.2.2 Oxidant Generation in Phagocytic and Non-phagocytic Cells

Besides conventional mitochondrial route, yet another important radical generation route is through the catalysis of NADPH oxidase (NOX). Enzyme NOX is present in several phagocytic cells such as macrophages, neutrophils, and eosinophils, as well as non-phagocytic cells and its presence is associated with several diseases (Babior 1999; Vignais 2002; Lambeth 2007) particularly, chronic liver diseases (CLDs)

(De Minicis and Brenner 2007). There are two membrane bound components in classical NOX of phagocytic origin namely, p22phox and gp91phox/Nox2, each of which comprises flavocytochrome and four cytosolic components. The cytosolic components include p40 phox, p47phox, p67phox, and the GTPase Rac1/2. Stimulation of phagocytic cells leads to recruitment of NOX into the plasma membrane after which NOX interacts with Cyt b558. This interaction is known to increase activity and subsequent generation of reactive oxygen species.

On the other hand, NADPH oxidase of non-phagocytic cells is similar in structure and function as that of phagocytic NOX. However, gp91phox/Nox2 is substituted by another member of the same family, usually Nox1, Nox3, Nox4, Nox5, or Duox1/2, which are homologues of Nox2. In contrast, non-phagocytic NOX is different, as it results in relatively low levels of ROS. It is observed that presence of 5-Lipoxygenase (5-LOX), a mixed function oxidase, elevates the activity and ROS generation mediated by NOX. 5-LOX is known to catalyse the synthesis of leukotrienes from arachidonic acid after some exogenous stimulus and can therefore stimulate NOX (Novo and Parola 2008). The growth factors and cytokines lead to membrane ruffling and the generation of superoxide, leading to H_2O_2, through the intervention of the small GTPase Rac1 and a SOD isoform (Soberman 2003). ROS can also be generated enzymatically in many subcellular compartments by several oxidases, peroxidases, mono- and di-oxygenases and by isoforms of the cytochrome P450 superfamily. Here it seems relevant to mention nitric oxide synthase and xanthine oxidase (Vasquez-Vivar and Kalyanaraman 2000; Pritsos 2000), cyclooxygenase (COX), and other NAD(P)H dependent oxidoreductase are also able to generate superoxide radicals. Moreover, oxidases of peroxisomal origins such as D-amino oxidases, ureate oxidases, glycolate oxidases, and fatty acid-CoA oxidases can generate hydrogen peroxide (H_2O_2) during their routine metabolic reactions (Rojkind et al. 2002). Also, an enzyme lysyl oxidase that catalyses the formation of the aldehyde precursors forming cross-links in collagen and elastin can also give rise to H_2O_2 as a result of electron leakage (Fig. 5.4).

5.3 Defence Mechanism Against Oxidative Stress

Defence against oxidative stress or rapid surge in reactive oxygen and nitrogen species is effectively countered by antioxidants. It is evident from the evolutionary process, life witnessed and adapted according to the changing oxygen concentration, in fact mostly an increase and life adapted to emerge from reduced environment to the oxidised one, suggesting the origin and prevalence of strong intrinsic antioxidant defence in most organisms. The antioxidant defence system of living organisms contains two major arms or operations, enzymatic antioxidants, and non-enzymatic antioxidants.

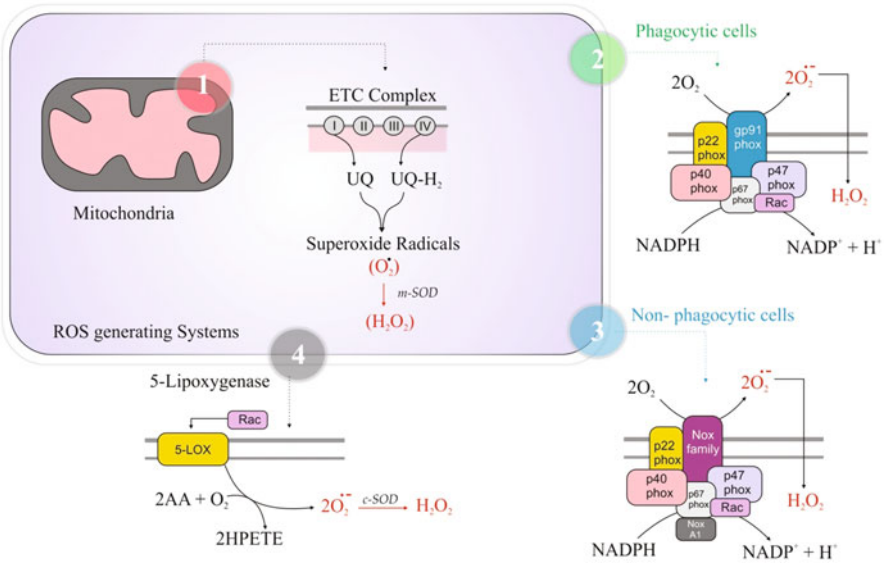

Fig. 5.4 Major endogenous sources of cellular oxidants in phagocytic cells, non-phagocytic cells, and peroxisomes

5.3.1 Enzymatic Antioxidants

A number of enzymes present in the human body are able to confer antioxidant abilities by catalysing the reduction process. One of the first lines of antioxidant defences in the cell include the activity of superoxide dismutase (SOD) which catalyses the conversion of superoxide into less reactive peroxides. SOD is compartmentalised as two different isoforms, namely Mn-SOD (SOD I), that is localised in mitochondria, second Cu-Zn-SOD (SOD II), localised in cytoplasm and EC-SOD (SOD III) localised in extracellular spaces. Among the most common dismutation of superoxides is the formation of hydrogen peroxide (H_2O_2) or sometimes organic peroxides. These peroxides are then detoxified with the help of catalase, and peroxidases in various compartments. Catalase is the key enzyme that catalyses this neutralisation of hydrogen peroxide, perhaps due to its high K_m value which allows it to remain active even at high concentrations of H_2O_2. In contrast to catalase, another enzyme peroxidase has relatively lower K_m and therefore remains active at low H_2O_2 concentrations. Peroxidases, depending on the requirement of glutathione are further grouped as glutathione (GSH) dependent peroxidase and glutathione independent peroxidase, the latter class includes, thioredoxin (Trx) dependent called peroxiredoxin (Prx). Peroxiredoxins are particularly important for antioxidant defence in erythrocytes (Rhee et al. 2005). Some of the commonly occurring cellular antioxidant enzymes, their activities and associated enzyme commission numbers are summarised in Table 5.1.

Table 5.1 Description of common enzymatic antioxidant defence operating during hypoxia

Enzyme	Reaction catalysed
Superoxide dismutase (EC 1.15.1.1)	Conversion of superoxide radicals in less toxic hydrogen peroxide
Catalase (EC 1.11.1.6)	Neutralisation of hydrogen peroxide in water (with a high K_m or low affinity)
Glutathione peroxidase (1.11.1.12)	Detoxification of organic peroxides (especially PUFA-OOH) into fatty acid and water
Glutathione S-transferases (2EC .5.1.18)	Reduction of proteins and other active molecules by addition of reducing groups of glutathione
Phospholipid-hydroperoxide glutathione peroxidase (EC 1.11.1.9)	Detoxification of organic peroxides (especially PUFA-OOH) into fatty acid and water
Ascorbate peroxidase (EC 1.11.1.11)	Neutralisation of hydrogen peroxide in water with concurrent oxidation of ascorbate into dihydroascorbate
Gualacol type peroxidase (EC 1.11.1.7)	Neutralisation of organic peroxides, halides or sulphates into less toxic forms
Monodehydroascorbate reductase (EC 1.6.5.4)	NADH mediated and recycling of dihydroascorbate (oxidised ascorbate) to ascorbic acid
Dehydroascorbate reductase (EC 1.8.5.1)	Glutathione mediated and recycling of dihydroascorbate (oxidised ascorbate) to ascorbic acid
Glutathione reductase (EC 1.6.4.2)	NADPH mediated recycling of oxidised glutathione (GSSG) into reduced glutathione (GSH)

5.3.2 Non-Enzymatic Antioxidants

Glutathione and thioredoxin are the most abundant among the non-enzymatic antioxidants. Glutathione is a dipeptide having cysteine in its structure that augments glutathione peroxidase activity and maintains cellular proteins in their reduced state. This process is expensive for the cells as NADPH is consumed during the conversion of oxidised glutathione (GSSG) to reduced glutathione (GSH) by an enzyme glutathione reductase (GR). Thioredoxin is another protein that augments peroxiredoxin activity and maintains protein thiolation. The intracellular picture of radical generation and its scavenging mechanisms is illustrated in Fig. 5.4.

Apart from these non-enzymatic antioxidants, especially metabolites such as melatonin and uric acid and dietary organic molecules such as vitamin E, lycopene, vitamin C, carotenes, and several polyphenols have shown potentials to scavenge the radicals and therefore alleviate oxidative stress above the basal threshold (Seifried et al. 2007; Catoni et al. 2008). On the basis of the above discussion, the entire antioxidant defence system may be stratified into four layers, the first is the immediate defence at the source that directly scavenges ROS, the next could be the first line of defence that depends on antioxidant enzymes. Then, the second line of defence including ancillary factors that augment conventional antioxidant defence and finally, the third line of defence including small metabolites and dietary antioxidants such as metal chelators and vitamins (Fig. 5.5).

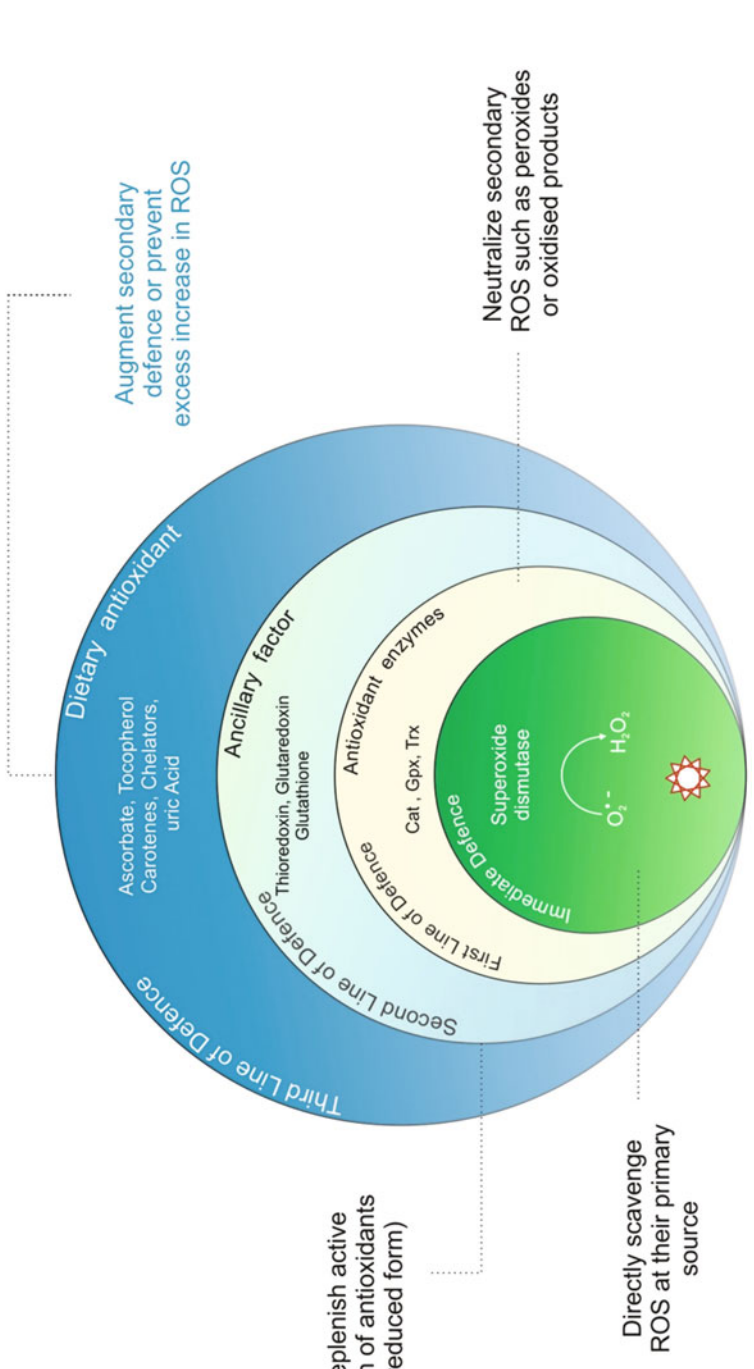

Fig. 5.5 Defence against oxidative stress can be broadly stratified into three levels, primary, secondary, and tertiary. The first level directly dimutates highly evanescent ROS such as superoxides by the presence of enzymes like superoxide dismutase, while the next level operates at neutralising peroxides, either hydrogen peroxide or organic peroxides by the action of peroxiredoxins, glutathione peroxidases, or catalase. The third strata of antioxidant defence mostly relies on dietary antioxidants including uric acid ascorbate, tocopherol, or carotenes

5.4 Organ-Level Oxidative Damage Manifested by Cellular ROS

Although the generation of ROS and RNS is manifested by alterations in the intracellular redox centres, the effects are manifested at organ levels. There are several reports of tissue level and organ level damage due to oxidative stress caused by hypobaric hypoxia. Among the most vulnerable organs are the lung and brain. The brain contains a large proportion of lipids that are at the direct risk of modification by oxidants, while lungs which stay at the interphase of atmosphere and body remain vulnerable due to change in external pressure.

5.4.1 Oxidative Damage in Lungs

Hypoxia, especially hypobaric hypoxia caused by a rapid ascent to altitudes is also associated with organ-level oxidative damage and one of the most affected organs is lung. Lung lies at the interphase of human physiological systems and outer atmosphere, any perturbation in the partial pressure of air leads to a cardiopulmonary burden and thereby leads to molecular changes in lungs. However, it is not well understood that molecular perturbations are primary or physiological that lead to molecular perturbations. Albeit, it is well established that lung cells experience a significant change during hypoxia, both in humans and animal models. Several studies including those conducted by the author are a good demonstration of these findings. In one of the studies, we and others have demonstrated the inflammation of lung concurrent with elevated cytokines in rat lung simulated to hypobaric hypoxia (Arya et al. 2016), which could be effectively managed using interventional of novel classes of antioxidants suggesting the oxidant mediated origin of inflammation. Furthermore, changes in physiological parameters such as ventilatory responses, cardiopulmonary blood transport mechanisms have also been observed. In a recent review by Siques et al., the possible mechanism has been illustrated in greater detail. It has been reported that the most common mechanism involved in the relationship of reactive oxygen species and pulmonary vascular cells under hypobaric hypoxic conditions include several factors, where not only ROS play a role but the complex interplay of calcium within sarcoplasmic reticulum, serotonin, endothelin-1, and interleukins. Moreover, some of the crucial transcription factors or protein interactors such as signal transducer and activator of transcription (STAT3), hypoxia-inducible factor 1 (Hif1a), and enhancer-binding protein modulate the transcriptional regulation of hypoxia-induced perturbations (Siques et al. 2018).

5.4.2 Oxidative Damage in Brain

Hypoxia, especially hypobaric hypoxia that is known to be prominent at an altitude above 5500 m, has been proven to be an external stressor affecting brain functioning. The severe decline in the blood oxygen due to lowered partial pressure of oxygen is

the leading cause of affected brain functions. A well-known effect on brain functioning is the loss of memory and loss of cognition, which has been documented in several studies. We and others have observed in simulated hypoxic conditions, the loss of cognition and learning abilities in experimental rats, using Morris water maze experiments and found these changes to be concurrent with elevated reactive oxygen species in the brain (Arya et al. 2016). Moreover, these findings related to high altitude hypoxia have also been corroborated with simple hypoxia in conjugation with exercise. Devebec et al. showed that increased oxidative stress caused molecular damage and disruption of redox signalling and was found to be linked with numerous pathophysiological processes and known to exacerbate chronic diseases. Prolonged systemic hypoxia that was generally elevated by exposure to terrestrial altitude or a reduction in ambient O_2 availability was found to enhance oxidative stress and thereby modifying redox balance in healthy individuals (Debevec et al. 2017). Nevertheless, a reversal of the hypoxic condition, i.e. by utilising hyperbaric conditions, the changes might be reversed. Such experimental outcomes have recently been demonstrated that hyperbaric conditions can induce neuroplasticity and improve cognitive functions in patients suffering from anoxic brain damage (Hadanny et al. 2015).

5.4.3 Oxidative Damage in Heart

The heart is the next most vulnerable organ to hypobaric hypoxia after brain and lung. Although the changes in pulmonary ventilation patterns directly influence heart functioning both at the physiological and cellular levels. Most of the damage to the heart is due to hypobaric hypoxia. Christopher Jon Boos et al. recently provided an excellent context of hypobaric hypoxia-induced perturbations in the heart in comparison with normobaric and other physiological states. Their study showed that genuine high altitude (GHA), normobaric hypoxia (NH), and hypobaric hypoxia (HH) generate similar adaptations in the heart following acute exposure despite the reduced levels of SpO_2 with GHA and HH as compared with NH (Boos et al. 2016). The reactive oxygen species are pivotal in the development of several cardiac abnormalities and functioning. ROS levels up to a certain extent also play a role in intracellular signalling and homeostasis, but, elevated ROS, particularly after an exogenous or chemical stimulus has deleterious effects and the effects are exacerbated when the rise in ROS is not compensated by the endogenous antioxidant defence system. Several studies indicate that alteration in reactive oxygen species and therefore closely associated with inflammation and progression of cardiac infarction or hypertrophy or both. This has been confirmed in several animal models post-hypoxic exposure simulating to an altitude of 3600–7620 m (or 13–8% O_2). Among the common redox-mediated signalling pathways in the heart is hypoxia-inducible factor 1 a (HIF-1α) mediated changes, which are known to lead to hypertrophic stimuli via mitogen-activated kinase superfamily. Among a few well-established redox-regulated kinases and transcription factors are JNK, p38, and ERK which control the apoptosis and inflammation in cardiac cells.

Furthermore, recent studies suggest that redox imbalance and therefore oxidative stress can activate nuclear factor-kappa B (NF-kB) in cardiac tissue and lead to cardiac inflammation and in some cases complete cardiac failure (Pena et al. 2020).

5.5 Oxidative Perturbations Mediated Changes in Proteome

Organ-level proteomic studies have been carried out by us and other researchers on subjects exposed to hypobaric hypoxia either in natural high altitude or simulated hypobaric hypoxia. Most of these studies indicate a significant change in the global proteome profile of the lung, brain, heart, and muscles. Changes in proteomic profile have been discussed in another chapter in more detail, here we would limit ourselves to perturbations in proteome ROS in terms of their modifications. Proteins, in their native conformations, have side chains of various types that can be exposed to extrinsic factors and become vulnerable to wandering reactive oxygen species and thus show reactivity with them and get modified. Some of the common redox modifications of proteins include nitrosylation, nitration, carbonylation, sulfhydration, etc. In different types of modifications, different residues are involved, most often tyrosine, cysteine, and serine. An elaborate discussion effect of potential post-translational modification (PTMs) have been recently studied by the author and others. We reported the cross-talk between the protein nitrosylation and carbonylation in hypoxic cell culture systems and later observed several PTMs in human subjects. Authors investigated the direct and indirect interactions between nitrosylation and carbonylation especially involving two protein networks associated with coagulation and inflammation pathways, found to be interlinked with redox signalling, suggesting the role of redox PTMs in hypoxia signalling favouring tolerance and survival (Gangwar et al. 2021).

5.6 Conclusion

The involvement of redox biology in high altitude physiology and pathological conditions is highly complex and a lot more is remaining to be explored, especially the downstream effectors of ROS involving several regulatory proteins, membrane lipids, and hormones. A deeper insight of these aspects in future is likely to enlighten the accomplishment of clinical success in quick identification of hypoxic susceptibility testing and management of post-hypoxic pathological conditions.

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