Abstract

All organisms maintain a strict redox environment, crucial for cell physiology, by preserving the pro-oxidant compounds generated during cell metabolism and from antioxidant system elements. In pathophysiological conditions, the redox environment is altered, causing oxidative stress, cell damage, and eventually cell death. In this chapter, we review the elements involved in the redox environment, including the oxidant, antioxidant, and glutathione systems. In addition, we summarize the physicochemical bases of the redox environment and the biological functions of the glutathione cycle. Finally, we propose a redox environment regulation model that considers some regulated variables that are actively involved in maintaining the redox environment: reactive oxygen species, reactive nitrogen species, and the redox couple GSH/GSSG.

Keywords: Redox environment, oxidant system, ROS, antioxidant system, glutathione

1. Introduction

All organisms maintain a strict redox environment, crucial for cell physiology, by preserving the pro-oxidant compounds generated during cell metabolism and from antioxidant system elements. In pathophysiological conditions, the redox environment can be altered, causing oxidative stress, cell damage, and eventually cell death. Two regulated variables are actively involved in maintaining the redox environment: the concentration of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and the redox couple GSH/GSSG.
2. Main body

2.1. The redox system

Oxidizing system elements are free radicals and reactive species of various atoms or compounds such as oxygen, nitrogen, iron, copper, and glutathione (GSH). With respect to free radicals, they are molecules or molecular fragments containing one or more unpaired electrons in their atomic or molecular orbitals, which cause the molecule to be very reactive [1]. However, not all reactive species are free radicals: at a pH of 7.4 ± 0.1 they may be electroneutral molecules, able to donate electrons to free radicals, and oxidize transition metals present in cells. Although several groups of compounds are considered oxidants, those considered to be the most important from the physiological point of view are those compounds derived from oxygen and nitrogen: ROS and RNS. Under physiological conditions, the presence of ROS and RNS is required for diverse signaling pathways [2,3]. Among the most important elements of the oxidizing system in living organisms are superoxide anion radicals (O$_2^-$), hydroxyl groups (•OH), hydrogen peroxide (H$_2$O$_2$), nitric oxide (NO), and peroxynitrite (ONOO$^-$) groups.

The presence of an electron in molecular oxygen (O$_2$) forms the free radical superoxide (O$_2^-$), which is considered to be a primary ROS that can interact with other molecules to generate secondary ROS or RNS [2,3]. Various metabolic pathways within the cell generate O$_2^-$, but the principal incomplete reduction route occurs in the mitochondrial respiratory chain: between 1 and 4% of O$_2^-$ is formed by the incomplete reduction of the total O$_2$ consumed in complex I (NADH: ubiquinone oxide-reductase) and III (cytochrome C oxide-reductase). The production of O$_2^-$ is also promoted by enzymatic complexes like xanthine oxidase (EC 1.1.3.22), cytochrome P450, nitric oxide synthase (NOS), or monoamine oxidase (EC 1.4.3.10).

Figure 1 shows how O$_2^-$ promotes the formation of H$_2$O$_2$, •OH, and ONOO$^-$ by various chemical pathways.

![Figure 1](image-url)

Figure 1. Reactive oxygen and nitrogen species formation from the superoxide anion radical. A) O$_2^-$ dismutation, which can be formed spontaneously or can be catalyzed by SOD. B) Haber-Weiss reaction. C) Fe$^{3+}$ to Fe$^{2+}$ reduction. D) Fenton reaction. E) Peroxynitrite (ONOO$^-$) formation.
In addition to forming ROS and RNS, O$_2^-$ can also inactivate enzymes involved in the antioxidant system, or in metabolic and signaling pathways such as catalase (EC 1.11.1.6), glutathione peroxidase (EC 1.11.1.19), glyceraldehyde-3-phosphate dehydrogenase (EC 1.2.1.12), ornithine decarboxylase (EC 2.1.3.3), and adenylyl cyclase (EC 4.6.1.1) [1,4]. For example, H$_2$O$_2$ is formed by spontaneous dismutation or catalyzation by superoxide dismutase (SOD, EC 1.15.1.1). Although this compound has practically no oxidative effect on biomolecules, it plays a major role in the oxidative stress process by generating ⋅OH groups. When H$_2$O$_2$ molecules pass through cell membranes, they reach compartments containing transition metals, such as Fe$^{2+}$ or Cu$^+$, which can oxidize them and induce the formation of ⋅OH radicals. Thus, ⋅OH radicals may be formed through pathways involving O$_2^-$ radicals or H$_2$O$_2$ [1,2,3,5].

The neutral form of the hydroxide ion (OH$^-$) is an ⋅OH group with high reactivity ($10^7$-$10^{10}$ M$^{-1}$ s$^{-1}$) and a very short half-life (10$^{-9}$ s) [6]. Thus, when ⋅OH groups are produced in vivo, they react near their site of formation and are very toxic to biomolecules such as DNA, proteins, and membrane phospholipids.

Many investigators consider NO to be radical because it contains an unpaired electron in its 2π orbital. When NOS (EC 1.14.13.39) metabolizes the conversion of L-arginine to L-citrulline, NO radicals are formed [7]. Under physiological conditions, NO is involved in processes such as neurotransmission, blood pressure regulation, defense mechanisms against pathogens, and immune response regulation [2]. In aqueous media, NO has a short half-life but in a hypoxic environment it presents greater stability with a half-life of more than 15 s [8]. The toxic effect of NO is in fact closely related to the formation of the secondary RNS ONOO$, which occurs when NO is overproduced. ONOO$ has a very high reaction constant ($7 \times 10^9$ M$^{-1}$ s$^{-1}$), making it a powerful membrane-oxidizing agent that produces lipid peroxidation [2]. In fact, the reaction between ONOO$ and carbon radicals (⋅CO$_2$) produces the secondary RNS, a nitrite radical (⋅NO$_2$). These radicals mediate protein nitrotyrosilation by reacting with the hydroxyl group of the tyrosine amino acid (TyrOH) to produce the tyrosyl free radical (Tyro$^.$), which can then be neutralized by another ⋅NO$_2$ [9].

2.2. Antioxidant system

In aerobic organisms, various processes such as growth, cell differentiation, apoptosis, and immune response require low concentrations of oxidants such that an increase generates a state of oxidative stress that causes cellular malfunction and even death. Therefore, an antioxidant system capable of neutralizing ROS and RNS is essential to the optimal function of many cellular operations.

The antioxidant system is divided into two subsystems: enzymatic and non-enzymatic. Within the non-enzymatic antioxidant system are organic compounds such as ascorbic acid, α-tocopherol, carotenoids, flavonoids, and reduced GSH. While enzymes such as catalase (EC 1.11.1.6), glutathione peroxidase (GPX, EC 1.11.1.19), and SOD are considered the first line of enzymatic antioxidant defense, other enzymes, such as glutathione reductase (GR, EC 1.6.4.2), glutathione S-transferase (GST, EC 2.5.1.18), and thioredoxin reductase (EC 1.6.4.5) [1,2,5,10], also contribute to defense. Thus, maintaining the oxidation concentration of an organism at
homeostasis is complex and must be executed within narrow limits. Figure 2 shows an overview of the interactions between the oxidant and the antioxidant system.

![Diagram of LIPID PEROXIDATION PROCESS]

**Figure 2.** Reduced glutathione (GSH) role and the participation of other antioxidants (lipoic acid, vitamins C and E) in the ROS formation and lipid peroxidation. Reaction 1: O$_2^-$ is formatted from the O$_2$ reduction process mediated by the NAD(P)H oxidase and xanthine oxidase complex or produced by no enzymatic pathways such as those involving semi-ubiquinone in the mitochondrial respiratory chain. Reaction 2: O$_2^-$ is dismutated by superoxide dismutase (SOD) to H$_2$O$_2$. Reaction 3: H$_2$O$_2$ is neutralized by glutathione peroxidase (GPX) using GSH as cofactor. Reaction 4: Oxidized glutathione (GSSG) is reduced to GSH by reductase glutathione (GR) using NADPH.

### 2.3. Non-enzymatic antioxidant system

Inside the cell, several nucleophilic organic compounds, such as vitamin A, vitamin E, ascorbic acid, and dihydro lipoic acid, function to neutralize reactive species. For example, α-tocopherol, commonly known as vitamin E, is the most active of tocopherols [11]. It has a chroman ring, which is responsible for its antioxidant activity, while the carbon phytyl side chain of vitamin E remains anchored to the cell membrane (Figure 3). Furthermore, α-tocopherol is the lipid antioxidant that most potently inhibits *in vitro* lipid peroxidation propagation, and it is the dominant tocopherol found in the bloodstream.

Vitamin C or ascorbic acid is essential for the synthesis of various proteins such as collagen, oxytocin, and vasopressin. Its antioxidant capacity lies in the tocopheryl radical reduction that is anchored to cell membranes (reactions 8 to 12 of Figure 2). In addition, ascorbic acid can reduce nitrites and inhibit the formation of nitrosamines [12].
Dihydrolipoic acid (DHLA) or 6,8-dimercapto-octanoic acid is an organic compound that acts as a cofactor for some enzymes. The high electron density in the two SH groups gives the molecule characteristics of a nucleophile, which favors the 1,2-dithiolane-ring formation of the α-lipoic acid (LA) (chemical name: dithiolane-3-pentanoic acid), when it interacts with reactive species. LA and DHLA exhibit direct free radical scavenging properties, and as a redox couple, with a low redox potential of −0.32 V, is a strong reductant [13]. At a concentration of 0.05–1 nM, DHLA neutralizes the species ⋅OH, LOO⋅, ONOO−, and hypochlorous acid; furthermore it can form stable complexes with Mn2+, Cu2+, Zn2+, and Fe2+, preventing oxidative interactions between these transition metals and biomolecules. Finally, LA/DHLA also functions as an antioxidant by regenerating ascorbic acid when it reduces dihydroascorbate and the semidihydroascorbic radicals [12].

Now we move on to GSH, one of the most important antioxidant organic compounds because of its dependence on the cell redox environment.

### 2.4. The reduced glutathione-oxidized glutathione (GSH/GSSG) ratio and the reduction–oxidation (redox) environment

#### 2.4.1. The physicochemical basis of the redox environment

Cellular processes in aerobic organisms depend on oxidation processes, which promote the mobilization of electrons from organic molecules to oxygen; this produces the energy required to maintain cellular processes. In general, the presence of redox couples controls electron flow, but a reducing environment is also necessary: the redox environment is the sum of all the redox states of the reduction–oxidation couple that are inside the cell (intracellular redox environment) or in the extracellular fluid (extracellular redox environment).

Historically, the term redox state has been used to define the redox environment; however, based on physicochemical studies, Schafer and Buettner defined the redox state as the reduction potential of a redox couple [14]. Figure 4 shows the half-cell reduction potential ($E_{PC1/2}$) change of the redox pair involved in maintaining the redox environment, which involves the transfer of two electrons.

The next redox couple is involved in maintaining the redox environment because the curves generated show a third-order model. The $pK_a$ group is over the physiological pH and the reduced oxidized ratio is 1:100, 1:1000, or greater:
1. NADPH/NADP⁺ system considering a 0.1-mM concentration.
2. Reduced thioredoxin/oxidized thioredoxin (TrxSH₂/TrxSS) system considering a 15-μM concentration.
3. GSH²/GSSG system considering a 3-mM concentration.

Furthermore, although all three intracellular buffer systems contribute to maintaining the redox environment, the most influential couple appears to be GSH²/GSSG: it had the highest concentration, indicating that it better buffered the potential changes in the range between −300 and −100 mV. Interestingly, varying the reduced pair concentration caused changes in the EPC₁/₂ that are perfectly associated with various processes like cell proliferation, differentiation, apoptosis, and necrosis [14–19].

2.5. The GSH cycle and biological functions

The synthesis of reduced GSH (γ-L-glutamyl-cysteinyl-glycine) occurs in the cell cytoplasm and involves two ATP-dependent enzymatic steps (Figure 5).

GSH synthesis begins when amino acids (e.g., glutamate, cysteine, and glycine) enter the cell. While glutamate and glycine may enter the cell by secondary active transport, cysteine enters by a neutral amino acid transport mechanism. (Some glutamate transporters can also transport cysteine.) In fact, cysteine is considered the limiting amino acid for GSH synthesis because it is present at a lower concentration in the plasma and has a lower Km [20].

Once amino acids have entered the cell, γ-glutamylcysteine synthetase (γ-GCL, EC 6.3.2.2) produces γ-glutamylcysteine. This formation process involves two steps: the interaction
between glutamate and ATP in the presence of Mg\textsuperscript{2+} to form γ-glutamylphosphate (intermediate) and the intermediate interaction with cysteine and ADP release [21]. The first step is the most important in the formation of GSH because γ-GCL is the GSH synthesis-limiting enzyme. γ-GCL is a heterodimeric enzyme composed of a catalytic subunit called a heavy subunit (γ-GCL\textsubscript{H} Mr ≈ 73 kDa) and a regulatory subunit or light subunit (γ-GCL\textsubscript{L} Mr ≈ 31 kDa). The activity of γ-GCL depends primarily on the substrates and is inhibited by GSH. Specifically, the activity of γ-GCL\textsubscript{L} is controlled by kinases such as protein kinase A (PKA) and protein kinase C (PKC) [22].

Thermodynamically, two processes can occur once the γ-GCL is formed: it may form GSH when it combines with glycine, acting as GSH synthetase (GS, EC 6.3.2.3), or it may interact with the γ-glutamyl cycle transferase to form 5-oxo-L-proline and L-cysteine. The prevailing way depends on the \( K_m \) of each enzyme; under physiological conditions, the \( K_m \) of GS is 12 times higher than that of γ-glutamyl cycle transferase. Thus, more than 95% of the time, GSH formation is promoted [23].

**Figure 5.** Reduced glutathione (GSH) cycle. Glutathione reductase (GR), glutathione S-transferase (GST), and oxidized glutathione (GSSG).
Once GSH is synthesized, there are several processes in which it participates:

1. **Hydrolyse plasma GSH hydrolysis for cell GSH* in novo synthesis; for example, when hepatocytes secrete GSH, another cell can hydrolyze it in its precursors (cysteinyl-glycine and glutamate) by γ-glutamyl-transpeptidase (γ-GT, EC 2.3.2.2) that are expressed on the outer plasma membrane. Compounds, such as cysteinyl-glycine or its S-conjugates, may be subject to peptidases, causing them to form free amino acids that can be introduced into the cell and initiate GSH formation [23,24].**

2. **Detoxify electrophiles to conjugate electrophiles with α and β unsaturated carbonyls by glutathione S-transferase (GST, EC. 2.5.1.18). This reaction results in electrophile removal and glutathione S-conjugate metabolism by the γ-GT enzyme and cysteinyl-glycine peptidase [24]. However, this process is not always beneficial for the cell because sometimes more toxic species can be produced, as we will discuss later.**

3. **Detoxify hydrogen peroxide by glutathione peroxidase (GPX, EC 1.11.1.19) [25].**

4. **Maintain ascorbic acid and vitamin E levels [11,12].**

5. **Communicate intracellular processes as internal modulator of several signaling pathways [26].**

6. **Modulate NMDA receptors in the central nervous system [27].**

7. **Transport metals (e.g., Cu^{2+}, Hg^{2+}, Pb^{2+}, and Zn^{2+}) [28].**

GSH mitochondrial concentration is approximately 11–15 mM. Entry of GSH into the mitochondria is dependent on electroneutrality conveyors such as tricarboxylic or dicarboxylic acids [28]. In general, the GSH/GSSG ratio is greater than 10 for cells and organelles like mitochondria and nuclei, whereas the endoplasmic reticulum has a lower GSH/GSSG ratio between 1 and 3 [14].

### 2.6. Redox system regulation model

For several years, physiologists have sought to establish a simple model for studying physiological variables in comparison with cybernetic models [30].

The generalities of the model are presented in Figure 6. To be regulated, any physiological variable requires the following characteristics:

1. **A value that fluctuates over a narrow range.**

2. **A sensor that reports to a comparator, which compares the variable value to a set point.**

3. **An integrator center that sends information loops to the input (feedback) or output (feed forward) elements so that these loops will activate variables that are generally controlled to keep the regulated variable within a narrow range.**

Although this model is generalized for all physiological variables, it may be adapted for use with intracellular variables.
In particular, our research group considers the intracellular redox environment as a regulated variable since it has the elements described above. In Figure 7, we present the proposed model.

Figure 6. Control systems general model. Modified from [30].

Figure 7. Redox environment regulation model proposed. Our model considers the GSH and ROS as regulated variables, which are sensed by intracellular proteins. Both act as receptors and integrators. In turn is produced a response to compensate the $E_{PC1/2}$ reduction or to increase ROS production to maintain the redox environment.

In particular, our research group considers the intracellular redox environment as a regulated variable since it has the elements described above. In Figure 7, we present the proposed model.
In our model we consider two actively regulated variables involved in maintaining the redox environment: ROS and RNS concentrations, and the couple GSH\(^2\)/GSSG \(E_{PC1/2}\) redox.

ROS and RNS are sensed in microorganisms predominantly by proteins like oxyR, sosRS, Hsp33, PRXI, PrXII, and the Yap1-GPX3 complex. These proteins not only act as receptors, they also modulate signaling pathways. The final function of intracellular communications is to reduce the reactive species generation and/or neutralize them by stimulating the expression of antioxidant enzymes. Furthermore, it has been proposed that these routes activate cell survival pathways to prevent death, although in extreme oxidative stress apoptosis is favored even above necrosis.

This representation using the basis of a cybernetic model is new, and it allows the correlation of the effects of all systems, especially the GSH cycle to maintain homeostasis of the redox environment.

Finally, we can conclude that the redox environment is an essential variable to the entire system: maintaining a good immune response [31] and suitable neurogenic events [32], controlling growth, behavior, propagation, and differentiation of tumor cells [33], and most of all ensuring the correct function of organelles like the endoplasmic reticulum [34]; however, the redox environment has also been related with some undesirable events such as drug resistance in certain tumor cells [35]. Therefore, continued study of the redox environment is important to uncovering its role in signal transduction, disease, and health.

Acknowledgements

This study was partially supported by SIP 20140748 and 20150798. E.C-E, M.F-C., and R.O-B are fellows of EDI, COFAA, and SNI. V.B-V is a fellow of SNI. Carolyn Unck edited the language of this manuscript. We thank Instituto Politecnico Nacional for supporting this manuscript.

Author details

Edgar Cano-Europa\(^1\), Vanessa Blas-Valdivia\(^2\), Margarita Franco-Colin\(^1\) and Rocio Ortiz-Butron\(^2\)*

*Address all correspondence to: rocipn@yahoo.com.mx

1 Metabolism Laboratory of Physiology Department, National School of Biological Sciences, National Polytechnic Institute, Mexico City, Mexico

2 Neurobiology Laboratory of Physiology Department, National School of Biological Sciences, National Polytechnic Institute, Mexico City, Mexico
References

[1] Halliwell B, Gutteridge JMC. Free radicals in biology and medicine, Oxford University Press, 1999.

[2] Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007; 39: 44–84. DOI: 10.1016/j.biocel.2006.07.001

[3] Buettner GR, Wagner BA, Rodgers VG. Quantitative redox biology: an approach to understand the role of reactive species in defining the cellular redox environment. Cell Biochem Biophys 2013; 67(2): 477–483.

[4] Gutteridge J, Halliwell B. Free radicals and antioxidants in the year 2000: A historical look to the future. Ann New York Acad Sci 2000; 899: 136–147. DOI: 10.1111/j.1749-6632.2000.tb06182.x

[5] Wlodek L. Beneficial and harmful effects of thiols. Pol J Pharmacol 2002; 54: 215–223.

[6] Pastor N, Weinstein H, Jamison E, Brenowitz M. A detailed interpretation of OH radical footprints in a TBP-DNA complex reveals the role of dynamics in the mechanism of sequence-specific binding. J Mol Biol 2000; 304: 55–68. DOI: 10.1006/jmbi.2000.4173

[7] Brett DS, Snyder SH. Isolation of nitric oxide synthetase, a calmodulin-requiring enzyme. Proc Nat Acad Sci 1990; 87: 682–685.

[8] Chiueh CC. Neuroprotective properties of nitric oxide. Ann New York Acad Sci 1999; 890: 301–311. DOI: 10.1111/j.1749-6632.1999.tb08007.x

[9] Winterbourn CC, Kettle A J. Radical-radical reactions of superoxide: a potential route to toxicity. Biochem Biophys Res Commun 2003; 305: 729–736. DOI: 10.1016/S0006-291X(03)00810-6

[10] Dorado-Martínez C, Rugerio-Vargas C, Rivas-Aranciba S. Estrés oxidativo y neurodegeneración. Rev Fac Med UNAM 2003; 46: 229–237.

[11] Van Acker SABE, Koymans LMC, Bast A. Molecular pharmacology of vitamin E: structural aspects of antioxidant activity. Free Rad Biol Med 1993; 15: 311–328.

[12] Fang YZ, Yang S, Wu G. Free radicals, antioxidants, and nutrition. Nutrition 2002; 18: 872–879. DOI: 10.1016/S0899-9007(02)00916-4

[13] Moini H, Packer L, Saris NE. Antioxidant and prooxidant activities of alpha-lipoic acid and dihydrolipoic acid. Toxicol Appl Pharmacol 2002; 182: 84–90. DOI:10.1006/taap.2002.9437

[14] Schafer FQ, Buettner GR. Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple. Free Rad Biol Med 2001; 30: 1191–1212. doi:10.1016/S0891-5849(01)00480-4
[15] Cai J, Jones DP. Superoxide in Apoptosis. Mitochondrial generation triggered by cytochrome c loss. J Biol Chem 1998; 273: 11401–11404. DOI: 10.1074/jbc.273.19.11401

[16] Cai J, Wallace DC, Zhivotovsky B, Jones DP. Separation of cytochrome c-dependent caspase activation from thiol-disulfide redox change in cells lacking mitochondrial DNA. Free Rad Biol Med 2000; 29: 334–342. DOI: 10.1016/S0891-5849(00)00312-9

[17] Hwang C, Sinskey AJ, Lodish HF. Oxidized redox state of glutathione in the endoplasmic reticulum. Science 1992; 257: 1496–1502. DOI: 10.1126/science.1523409

[18] Jones DP, Maellaro E, Jiang S, Slater AF, Orrenius S. Effects of N-acetyl-L-cysteine on T-cell apoptosis are not mediated by increased cellular glutathione. Immunol Lett 1995; 45: 205–209. DOI: 10.1016/0165-2478(95)00004-O

[19] Kirlin WG, Cai J, Thompson SA, Diaz D, Kavanagh TJ, Jones DP. Glutathione redox potential in response to differentiation and enzyme inducers. Free Rad Biol Med 1999; 27: 1208–1218. DOI: 10.1016/S0891-5849(99)00145-8

[20] Aoyama K, Watabe M, Nakaki T. Regulation of neuronal glutathione synthesis. J Pharmacol Sci 2008; 108: 227–238. DOI: 10.1254/jphs.08R01CR

[21] Griffith OW, Mulcahy RT. The enzymes of glutathione synthesis: gamma-glutamylcysteine synthetase. Adv Enzymol Relat Areas Mol Biol 1999; 73: 209–267.

[22] Griffith OW. Biologic and pharmacologic regulation of mammalian glutathione synthesis. Free Rad Biol Med 1999; 27: 922–935. doi:10.1016/S0891-5849(99)00176-8

[23] Weber GF. Final common pathways in neurodegenerative diseases: regulatory role of the glutathione cycle. Neurosci Biobehav Rev 1999; 23: 1079–1086. DOI: 10.1016/S0149-7634(99)00041-X

[24] Konigsberg-Fainstein M, Aguilar-Maldonado B. Radicales libres y estrés oxidativo. Aplicaciones médicas, Manual Moderno, México, 2008. ISBN 9707293217, 9789707293212.

[25] Beckett GJ, Arthur J R. Selenium and endocrine systems. J Endocrinol 2005; 184: 455–465. DOI: 10.1677/joe.1.05971

[26] Kenneth H, Kent AR, Prasad Gabbita S, Scott S, Floyd RA. Reactive oxygen species, cell signaling, and cell injury. Free Rad Biol Med 2000; 28: 1456–1462. DOI: 10.1016/S0891-5849(00)00252-5

[27] Oja SS, Janaky R, Varga V, Saransaari P. Modulation of glutamate receptor functions by glutathione. Neurochem Int 2000; 37: 299–306. DOI: 10.1016/S0099-1963(00)00253-0

[28] Filomeni G, Rotilio G, Ciriolo MR. Cell signaling and the glutathione redox system. Biochem Pharmacol 2002; 64: 1057–1064. DOI: 10.1016/S0006-2952(02)01176-0
[29] Lash LH. Mitochondrial glutathione transport: physiological, pathological and toxicological implications. Chem Biol Interact 2006; 163: 54–67. DOI: 10.1016/j.cbi.2006.03.001

[30] Russek M, Cabanac M. Regulación y control en Biología, CECSA, México DF, 1983.

[31] Trujillo JA, Croft NP, Dudek NL, Channappanavar R, Theodossis A, Webb AI, Pursell AW. The cellular redox environment alters antigen presentation. J Biol Chem 2014; 289(40): 27979–27991.

[32] Ostrakhovitch EA, Semenikhin OA. The role of redox environment in neurogenic development. Arch Biochem Biophys 2013; 534(1), 44–54.

[33] Ostrakhovitch EA. Redox environment and its meaning for breast cancer cells fate. Curr Cancer Drug Targets 2011; 11(4): 479–495.

[34] Margittai É, Enyedi B, Csala M, Geiszt M, Bánhegyi G. Composition of the redox environment of the endoplasmic reticulum and sources of hydrogen peroxide. Free Rad Biol Med 2015; 83: 331-340.

[35] Espey MG. Redox physical oncology: intersections between redox and the physical environment in cancer. Free Rad Biol Med 2015; 79: 251–252.
