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The Impact of Redox Balance in Brain Tumors

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1. Introduction

In a normal cell, there exists a balance between the free radical generation and the antioxidant defense (Devi et al., 2000). It has long been documented that cancer cells are under increased and persistent oxidative stress due to increased reactive oxygen species. Oxidative stress describes the state of a cell whose antioxidant mechanisms can not manage its content of free radicals (Figure 1). As a consequence, cellular constituents are disrupted, and free radical reactions become less controllable since endogenous antioxidants are themselves injured by oxidative insults. Oxidative stress induces a cellular redox imbalance which has been found to be present in various cancer cells compared with normal cells; the redox imbalance thus may be related to oncogenic stimulation (Valko et al., 2006). Increased intrinsic reactive oxygen species (ROS) stress in cancer cells has been speculated to be due to a number of factors such as oncogenic stimulation, increased metabolic activity, and mitochondrial malfunction (Pelicano et al., 2004). The cellular redox state has important effects on the control of cell survival, apoptosis, and expression of tumor suppressor genes. A high cell redox state would encourage tumor formation by creating an enhanced cell proliferative environment. In opposition to this, a high cell redox state would also support increased apoptosis, which would inhibit tumor formation by eliminating partially transformed cells. In addition to ROS, various redox metals, due to their ability to generate free radicals, or non-redox metals, due to their ability to bind to critical thiols, have been implicated in the mechanisms of carcinogenesis. (Leonard et al., 2004; Valko et al., 2005). Cancer cells can generate large amounts of hydrogen peroxide and this, if it occurs in vivo, may contribute to their ability to mutate and damage normal tissues, and, moreover, facilitate tumour growth and invasion (Burdon, 1995). Indeed, it has been suggested that persistent oxidative stress in tumour cells could partly explain some important characteristics of cancer. A wide variety of normal and malignant cell types generate and release superoxide or hydrogen peroxide in vitro either in response to specific cytokine and growth factor stimulus or constitutively in the case of tumour cells (Szatrowski et al., 1991). Tumors of the nervous system are among the most common and pharmacologically intractable neoplastic disorders. Malignant peripheral nervous system tumors include neuroblastoma, the most common extracranial solid tumor. Because of the frequency with which neuroblastoma is metastatic or otherwise surgically incurable at the time of diagnosis, treatment of this tumor often involves chemotherapy. Malignant gliomas comprise the majority of primary brain tumors. (Louis et al., 2002). Of these, glioblastoma multiforme (GBM) is the most common and has the poorest prognosis. It is therefore apparent that a

more complete understanding of malignant gliomas and the pathophysiologic mechanisms responsible for tumor growth, invasion, and resistance to therapy is needed. Meningiomas are the most common types of the non gliomatous primary brain tumors, followed by schwannomas.

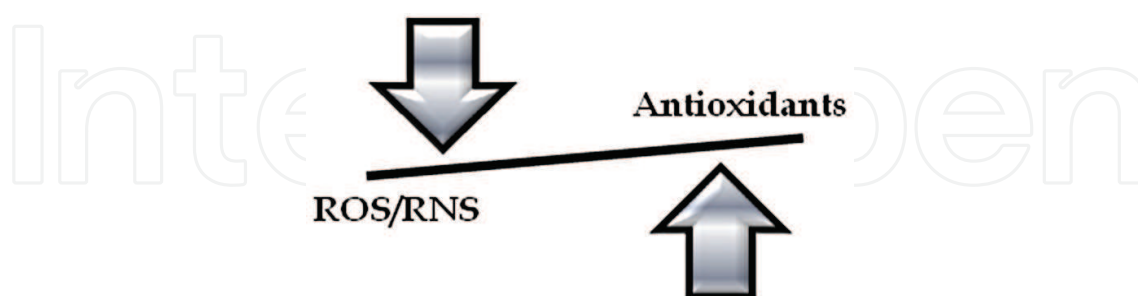


Fig. 1. Oxidative stress balance

2. Oxidative stress and neuronal redox countenance in the brain

Redox balance in neural tissue has an important role in the pathophysiology of neurotoxicity from free radical generation, but also in the pathophysiology of neurotoxicity from free radical generation. The concept of redox status includes both physiological and pathological effects of redox phenomena. ROS are particularly active in the brain and neuronal tissue and aggressive to glial cells and neurons. In-built endogenous antioxidant system plays its decisive role in prevention of any loss due to free radicals. However, imbalanced defense mechanism of antioxidants, overproduction or incorporation of free radicals from environment to living system leads to serious penalty and therefore to neuronal death (Halliwell, 2001). The brain has high content of peroxidizable unsaturated fatty acids, high oxygen consumption per unit weight, high content of iron which is a key in lipid peroxidation and a shortage of antioxidant defense systems (Floyd, 1999) so is more susceptible to oxidative stress compared to other tissues and is unique as a target organ for metastatic growth being surrounded by the blood-brain barrier. The generation of ROS, or free radicals, can exceed the scavenging ability of endogenous antioxidants, resulting in a shift of the redox state of the brain to the oxidative state.

The concentrations of free heavy metals are also tightly controlled in the nervous system by transport proteins such as ferritin (Sies, 1993), thus limiting the non-enzymatic catalysis of hydroxyl radical formation. The nervous system contains some antioxidant enzymes; including Cu/Zn- and Mn dependent superoxide dismutase (SOD), and glutathione peroxidase (GPx) which are expressed in higher quantities than catalase (Shivakumar et al., 1991; Hussain et al., 1995). This spectrum of enzymatic defences suggests that the brain may efficiently metabolize superoxide but may have difficulties in eliminating the hydrogen peroxide produced by the reaction. The accumulation of hydrogen peroxide is of major concern since the brain contains large quantities of iron and copper (Moos, 1995), which may catalyse the formation of the hydroxyl radical and induce lipid peroxidation (Oubidar et al., 1996)(Fig.1). Exogenous antioxidants are nowadays considered a promising therapeutic approach since they could play an important role in preventing and/or minimizing neuronal oxidative damage (Halliwell, 2001; Uttara et al., 2009).

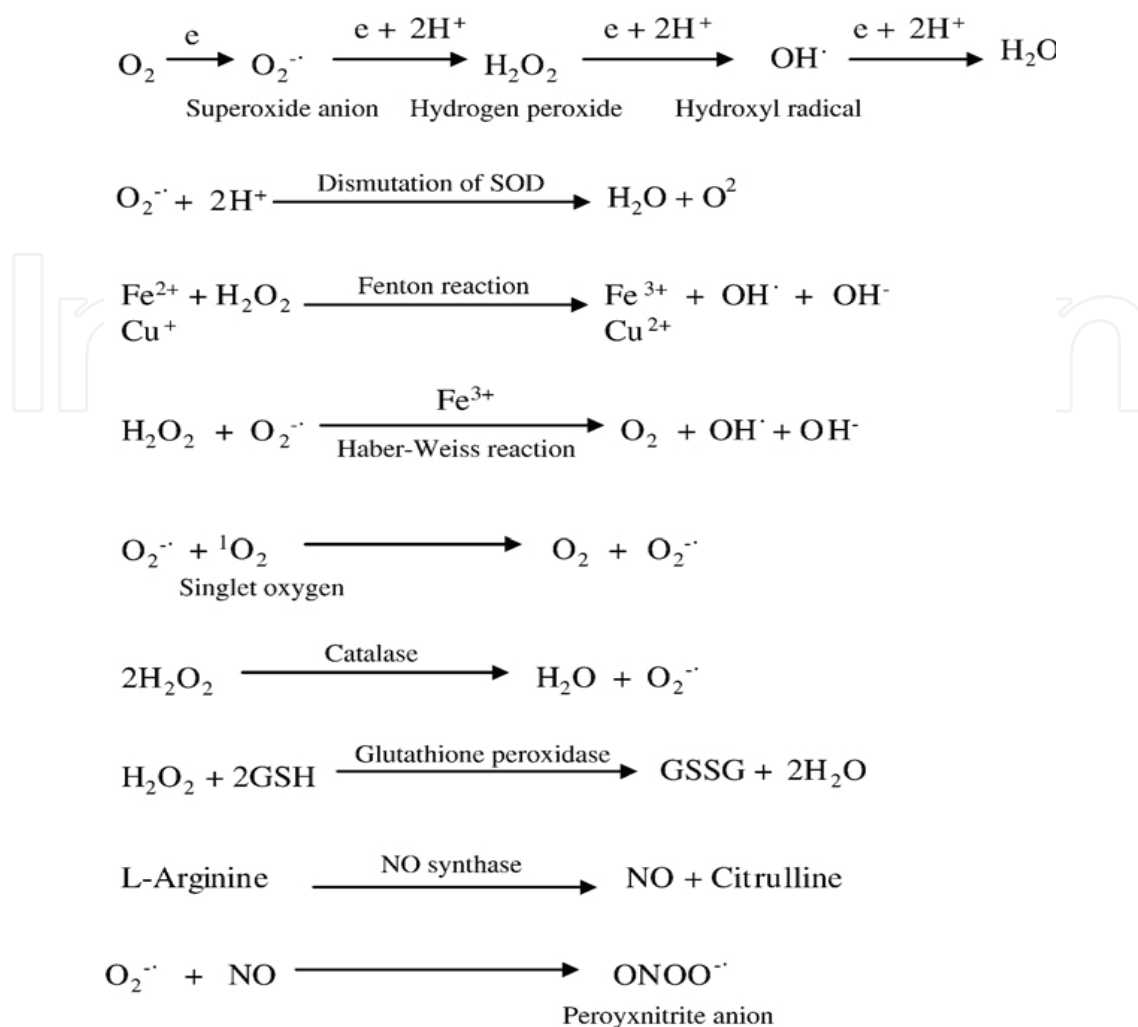


Fig. 2. Reactions of oxygen and nitrogen species

3. Reactive oxygen species (ROS) and reactive nitrogen species (RNS)

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are products of normal cellular metabolism. The interest in the role of oxygen-free radicals, more generally known as ROS and of RNS in experimental and clinical medicine is consequential (Halliwell, 1999). ROS/RNS are known to play a dual role since they can be either harmful or beneficial (Valko et al., 2004). Useful effects of ROS are having physiological roles in cellular responses to noxa and in the function of a number of cellular signalling systems. The harmful effects of ROS are balanced by the antioxidant action of nonenzymatic antioxidants in addition to antioxidant enzymes (Halliwell, 1996). ROS/RNS are known to act as secondary messengers controlling various normal physiological functions of the organism. In addition, ROS and RNS participate in various redox-regulatory mechanisms of cells in order to protect cells against oxidative stress and maintenance of cellular redox homeostasis. The cumulative production of ROS through either endogenous or exogenous insults is common for many types of cancer cell that are linked with altered redox regulation of cellular signaling pathways. ROS are not only toxicants to the cell, but also second messengers in intracellular signal transduction, and control the action of several signaling pathways. RNS include a series of metabolites which are nitric oxide, nitrite, peroxynitrite with functional implication

mainly in vascular stability. Overproduction of reactive nitrogen species is called nitrosative stress (Klatt & Lamas, 2000). This may occur when the generation of reactive nitrogen species in a system exceeds the system's ability to neutralise and eliminate them. Nitrosative stress may lead to nitrosylation reactions that can alter the structure of proteins and so inhibit their normal function and there has been much interest in the roles nitric oxide may play in the pathogenesis of GBM. When ROS/RNS levels exceed a certain threshold, deleterious effects are apparent and become dangerous for cell integrity (Panayiotidis et al., 1999; Barbouti et al., 2002). Oxidative stress can be defined as a deterioration of redox signaling and control (Jones, 2006). Overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS), a decreased antioxidant defense system, or both typically results in significant protein oxidation (Hensley et al., 1995; Stadtman & Berlett, 1997), lipid peroxidation (Markesbery & Lovell, 1998; Butterfield & Lauderback, 2002), and DNA/RNA oxidation (Butterfield et al., 2001). Increased formation of ROS and RNS in the cells can contribute to the process of carcinogenesis through either direct genotoxic effects or indirect via modification of signaling pathways that lead to altered expression of numerous genes. Modulations of cell signaling pathways can activate transcriptional factors, like AP-1, NF- κ B, HIF-1, and p53 among others (Arrigo, 1999; Bensaad, 2005). These transcriptional factors control the expression of genes the protein products of which participate in complex signal transduction pathways that can lead to cell transformation. The effect of reactive oxygen and nitrogen species is balanced by the antioxidant action of nonenzymatic antioxidants, as well as by antioxidant enzymes. Such antioxidant defences are extremely important as they represent the direct removal of free radicals, thus providing maximal protection for biological sites. As key mediators of cellular oxidative stress and redox state, ROS and RNS also provide plausible platforms for drug design. In fact, the efficacy of a number of established anticancer drugs.

4. Redox status and apoptosis

The intracellular redox state which is directly related to the production of intracellular reactive oxygen species in cancer cells has also been indicated to control the aggressiveness of cancer cells. Cancer development represents a multistage process in which at least three distinct stages which are; initiation, promotion and progression are involved (Klaunig, 2004) and is characterized with increased cell growth and/or decreased capacity for apoptosis. Apoptosis is potentially a protective mechanism against both exogenous carcinogens and inflammatory states and is regulated in part by the cellular redox state. Since apoptosis is caused by elevated levels of free radicals, decreased concentrations of free radicals due to the excessive administration of antioxidants might actually stimulate survival of damaged cells and proliferation into neoplastic state and thus rather promote process of carcinogenesis than interrupt it. Mitochondrial driven apoptosis is most interesting when ROS mediated mechanisms are being considered. Typical features in apoptosis include permeabilization of the mitochondrial membrane in a process associated with ROS generation. Some of the physiological effects of free radicals may be mediated through their influence on redox sensitive transcription factors (Suzuki et al., 1997) and consequently modulation of gene expression (Cimino et al., 1997). Although care should be taken before concluding that free radicals are intracellular second messengers, there is growing agreement that they act as modulators of cell signaling and messenger systems. Therefore, it seems that the cellular redox status, defined as the balance between intracellular oxidants and antioxidants, is regulated so as to lie within an optimal range for cell survival. The

importance of cellular antioxidant capacity as the result of a complex cell program involves enhanced motility and a profound change in energy metabolism so avoiding oxidative damage and escaping excess ROS in the primary tumor site in cancer cells explain why redox signaling pathways are important.

5. Antioxidant defence

Cells have numerous protective mechanisms that maintain the concentrations of ROS within a range compatible with survival. The most efficient enzymatic antioxidants involve superoxide dismutase, catalase and glutathione peroxidase (Mates et al., 1999). Non enzymatic antioxidants involve vitamin C, vitamin E, carotenoids, thiol antioxidants (glutathione, thioredoxin and lipoic acid), natural flavonoids, melatonin and other compounds (McCall & Frei, 1999). Some antioxidants act in a hydrophilic environment, others in a hydrophobic environment, and some act in both environments of the cell. Glutathione (GSH), a thiol-containing tripeptide, is a major antioxidant and a cofactor of glutathione peroxidases (Meister, 1995); it is present in large quantities in the developing nervous system. It has been hypothesized that some trophic factors may upregulate neuronal antioxidant capacities (Mattson and Furukawa, 1996). If neuronal death involves an imbalance of the redox status towards oxidation, antioxidants should be protective.

GSH is a major intracellular antioxidant present ubiquitously in the brain in millimolar amounts. GSH detoxifies intracellular H_2O_2 to H_2O and O_2 via oxidation to glutathione disulfide (GSSG) by the enzyme GPx. GSSG is recycled to GSH via glutathione reductase (GR). The GSH/GSSG ratio is critical to maintaining the intracellular redox balance (Smith et al., 1996). A decrease in total GSH levels, or an imbalance in the ratio of reduced to oxidized GSH may cause oxidative stress (Stadtman & Berlett, 1997) and lipid peroxidation (Markesbery & Lovell, 1998). So, the brain is heavily dependent on GSH as a primary endogenous neuroprotectant. It has been reported that elevation of intracellular GSH in tumour cells is associated with mitogenic stimulation (Shaw & Chou, 1986), that GSH controls the onset of tumour-cell proliferation by regulating protein kinase C activity and intracellular pH (Terradez et al., 1993). GSH and its dependent enzymes work in concert with other antioxidants and antioxidant enzymes to protect cells against reactive oxygen intermediates (Sies, 1986). So, it can be said that reduced GSH plays a role in the rescue of cells from apoptosis. GPx and GR decrease and protein oxidation increases in patients with glioblastoma multiforme and transitional meningioma and clear different oxidative status was found in the two kinds of tumors which represent specially one of the most malignant and most benign tumors respectively (Tanriverdi et al., 2007) and it was shown that there is a complex relationship between pro- and anti-apoptotic molecules in glioblastoma multiforme pathogenesis, thus targeting multiple pathways with advanced chemotherapeutic agents or radiotherapeutic regimens following total resections might be helpful in patients with glioblastoma multiforme (Atukeren et al., 2010). So the development of chemopreventive strategies would be desirably based on an association between a particular beneficial effect and a redox condition, as for example, with antioxidant protection against oxidative stress.

6. Mitochondrial redox status

One of the important sources for ROS generation is the mitochondria where some of the oxygen is reduced by single steps of one electron reduction, thus releasing superoxide

radical and other ROS (Giorgio et al., 2007). However, it is difficult to detect the occurrence of the superoxide radical in intact mitochondria, most probably in consequence of the presence of high SOD activity therein. Mitochondria have long been known to generate significant quantities of hydrogen peroxide as mitochondrial generation of superoxide to that of hydrogen peroxide is known. Since mitochondria are the major site of free radical generation, they are highly enriched with antioxidants including GSH and enzymes, such as SOD and GPx, which are present on both sides of their membranes in order to minimise oxidative stress in the organelle (Cadenas & Davies, 2000). Superoxide radicals are efficiently detoxified initially to hydrogen peroxide and then to water by Cu/ZnSOD and MnSOD. The redox components of the cell consists of interlinked mitochondrial redox indicators: glutathione (GSH/GSSG), thioredoxin (Trx/TrxR), glutaredoxin (Grx), peroxiredoxins (Prx), systems dependent solely on steady flux of NADPH generated through reduction of NADP^+ by NADH by the energetic component of mitochondria (Figure 3). Trx/TrxR system reverses protein disulfide linkages that occur in thiols of oxidized cysteine residues (Holmgren, 1985). Upregulation in the activity of the Trx/TrxR system seen in many tumors is thought to be a result of increased ROS production associated with oncogenic transformation and correlates with resistance to apoptosis and tumor cell proliferation (Baker et al., 1997; Lincoln et al., 2003). Disruption of the cellular redox state via inhibition of TrxR, either in the cytosol or the mitochondria has been shown to increase the ratio of oxidized/reduced Trx, increase ROS, modulate cell signaling, sensitize cancer cell lines to chemotherapeutic agents, and induce cell cycle arrest, senescence and apoptosis of cancer cells (Urig & Becker, 2006; Mukherjee & Martin, 2008) so decrease in mitochondrial bioenergetic capacity and altered redox status should be

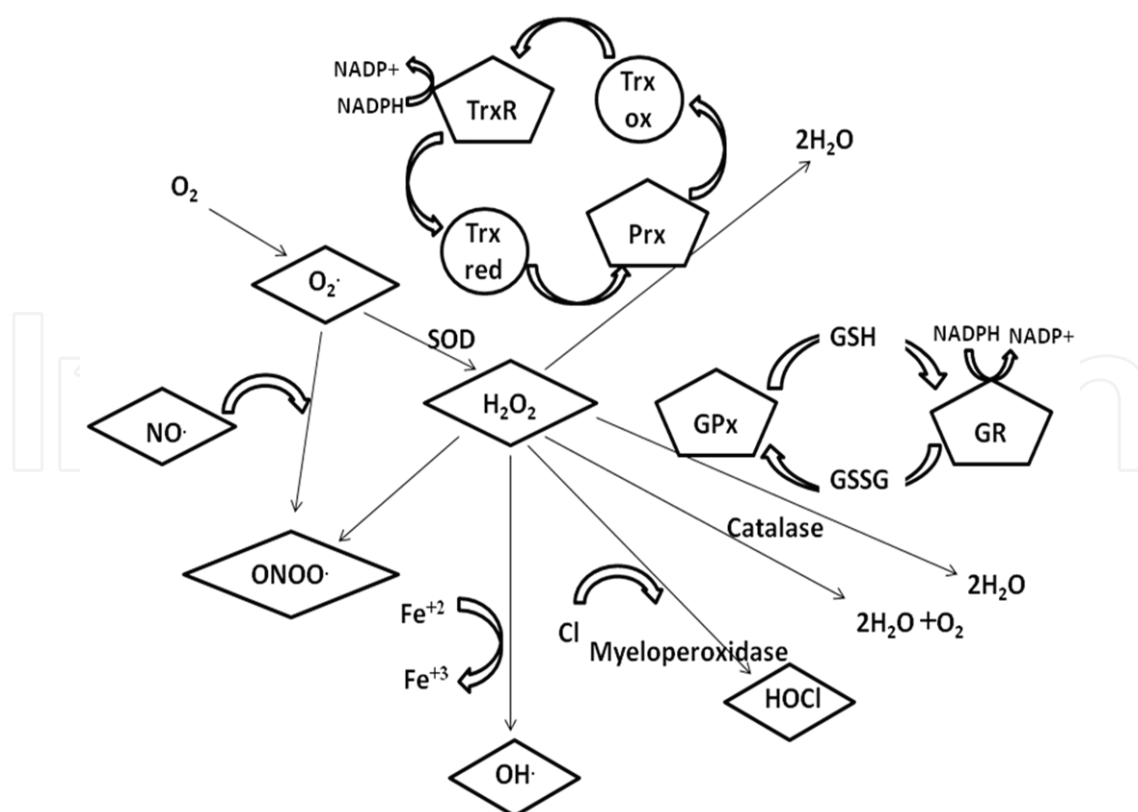


Fig. 3. Redox reactions

viewed as a concerted process. Prx are a family of proteins that function in antioxidant defense and in redox signaling cascades by reaction with peroxides. During their catalytic cycle, oxidized species of Prx are reduced and reactivated by thioredoxin or glutathione (Immenschuh & Baumgart-Vogt, 2005; Winterbourn & Hampton, 2008) and GSH is important for a wide range of cellular redox active proteins and pathways, including glutaredoxin (Grx), glutathione S-transferase (GST), glutathione peroxidase (GPx) and more (Meister & Anderson, 1983; Go et al., 2009).

7. Prospects of antioxidant therapy

Several antioxidant defense mechanisms have evolved to protect cell components from the harmful effects of ROS and RNS. As is known two major groups of endogenous antioxidants are low molecular weight antioxidant compounds such as vitamin C and vitamin E, lipoic acid and ubiquinones and antioxidant enzymes (Gilgun-Sherki et al., 2001). Antioxidant enzymes activity and concentration of nonenzymatic antioxidants in human brain tumours were evaluated and significant increases in all enzyme activities and decreases in GSH and ascorbate levels were observed in brain tumors (Dudek et al., 2004) and consistent differences in the levels of antioxidants in different types of brain tumors were emphasized in different studies (Hanimoglu et al., 2007; Tanriverdi et al., 2007; Tuzgen et al., 2007; Zengin et al., 2009). The relationship between oxidative gene polymorphism and the risk of brain tumors is investigated and it was seen that; the increased risk of glioma and meningioma type brain tumors is related with variants in some antioxidant enzyme genes (Rajaraman et al., 2008) and in a study, tissue expression of MnSOD is suggested to be a prognostic marker for glioblastoma (Park et al., 2009). The importance of daily intake of antioxidants among people with malignant glioma was shown in various studies (Il'yasova et al., 2009; DeLorenze et al., 2010). Recently, exogenous antioxidants are considered a promising therapeutic approach in preventing or minimizing neuronal oxidative damage (Halliwell, 2001; Uttara et al., 2009). Recent interest has been focused on dietary phenolic antioxidants, such as carotenoids, cinnamic acids and flavonoids, as potentially useful agents (Fresco et al., 2006; Uttara et al., 2009). In a study, the effects of flavonoids which are natural polyphenolic antioxidant compounds in brain development, neuroprotection and glial tumor formation are discussed and suggested to develop new therapeutic approaches (Nones et al., 2010). Curcumin as a polyphenol gets attention in blocking brain tumor formation in a study. The chemopreventive and anticarcinogenic action of curcumin is shown and suggested as this might be due to its ability to inhibit proteins that initiate protective signals (Sudarshana et al., 2009). Also, *Gynostemma pentaphyllum* extract selectively shifted H₂O₂ concentration in glioma tumor cells to toxic levels due to increased SOD activity so can be suggested for cancer therapy (Schild et al., 2010) and the apoptotic effect of γ -Mangostin in *Garcinia mangostana* fruit was investigated and it was suggested as a potential in developing an anti brain tumor agent (Chang et al., 2010). In another study, the potential therapeutic effect of resveratrol being a dietary phytochemical antioxidant, is investigated in glioma type brain tumors (Gangliano et al., 2010). Also another study implies the importance of using nutritional antioxidants such as lycopene for their potential therapeutic benefit in the adjuvant management of high-grade gliomas (Puri et al., 2010). So antioxidants are incontestably implicated in brain cancer treatment and they may protect against side effects from conventional therapies, as well as enhance chemotherapy and support anticancer activities. Obviously, antioxidants must be chosen based on their ability

to treat a particular redox event or they must act contextually and evolve with the redox conditions to restore balance.

3. Conclusion

Various studies showed that not only oxidants but the redox status as a whole modulates mechanisms regulating neuronal fate. The deleterious effects of high concentrations of antioxidants and the protective actions of sublethal oxidative challenges suggest that neuronal survival depends on the maintenance of an adequate redox status between the two extremes of oxidative and reductive stress, respectively. In addition to its widespread consequences for our understanding of fundamental aspects of neuronal death, the concept of neuronal redox status as opposed to oxidative stress may have clinical implications. Neuronal survival thus seems to be associated with an optimal redox status; an imbalance towards oxidation leads to oxidative stress, whereas high doses of antioxidants may induce a reductive stress. Maintenance of intracellular redox state is critical to cellular homeostasis therefore tumor selectivity in targeting at the cellular and enzymatic levels are of great interest to the rational design of treating compounds. Targeting the mitochondrial apoptotic regulatory machinery is also a promising anticancer approach and in many studies thiol redox platforms were used to discover and develop drugs. Strategies for redox balance analysis rely on different assumption and this approach gives a dynamic idea of what is the general oxidative status in a given condition and evaluation of redox potential of molecules gives idea of what really happened in a period that is a function of half life of a given molecule so this maybe utilized in parallel to gain a more representative picture of a clinical conditioning evolution. Hence, chemotherapeutic outcomes are not compromised, administration of antioxidants capable of maintaining the antioxidant defense system in brain may protect cancer patients from the apparent cognitive rigors of chemotherapy and these redox manipulating compounds could be used in conjunction with existing treatments to beneficial effect. So, it can be said that, as a preliminary approach, to determine optimal doses of antioxidants in order to design treatment protocols respecting the redox homeostasis would be useful.

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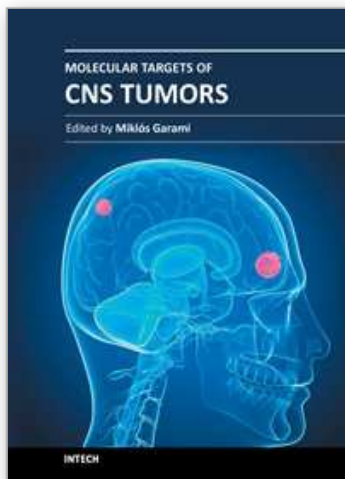
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