Chapter 23

The Stance of Antioxidants in Brain Tumors

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http://dx.doi.org/10.5772/54791

1. Introduction

The incidence of brain tumors and other types of cancer have been evidently increasing during the last few decades. Due to the well documented fact that the cancer cells are under high levels of oxidative stress, the relevance between oxidative stress and cancer has been the main topic of intense discourse (Powis & Baker, 1997; Pervaiz & Clement, 2004). Elevated levels of intrinsic oxidative stress has been emphasized in different types of tumors, possibly due to the clustering of factors such as enhanced metabolism, mitochondrial mutation, inflammation and cytokines (Mumper, 2009). Cellular damage on account of oxidative stress has been indicated in a range of disorders such as cancer (Floyd, 1990) diabetes mellitus (Dandona, et al.,1996), atherosclerosis (Valko, et al., 2007), neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (Jenner, 1997) autoimmune disorders such as arthritis and has also been indicated to be involved in aging (Ames & Shigenaga, 1992)

Oxidation is a natural process of cellular metabolism, but oxidation is what creates these destructive reactive oxygen species (ROS). ROS are constantly produced during oxidative metabolism and can have deleterious effects on cell function and viability due to their ability to induce damage to the cells. The formation of ROS is a consequence of aerobic metabolism (Castro, 2001). ROS are generated in many compartments and by numerous enzymes in cells (Fig. 1).

In normal conditions, the countenance in the intracellular ROS levels is maintained with the contribution of antioxidant scavenging systems and defense components. Yet, in some disorders such as cancer, the balance between the ROS and the antioxidant status falls off. Brain tissue also displays higher susceptibility to oxygen and glucose necessity, which are required to support normal function through glycolysis and oxidative phosphorylation thus the brain is particularly susceptible to oxidative damage since does not have much antioxidant storage. Additionally, the brain has a high amount of fatty acids. All these attributes lead to

brain cell damage. Thereby human brain encounters intense percentage of oxygen consumption, eventually generates an excessive amount of reactive oxygen species (ROS) when compared with other tissues.

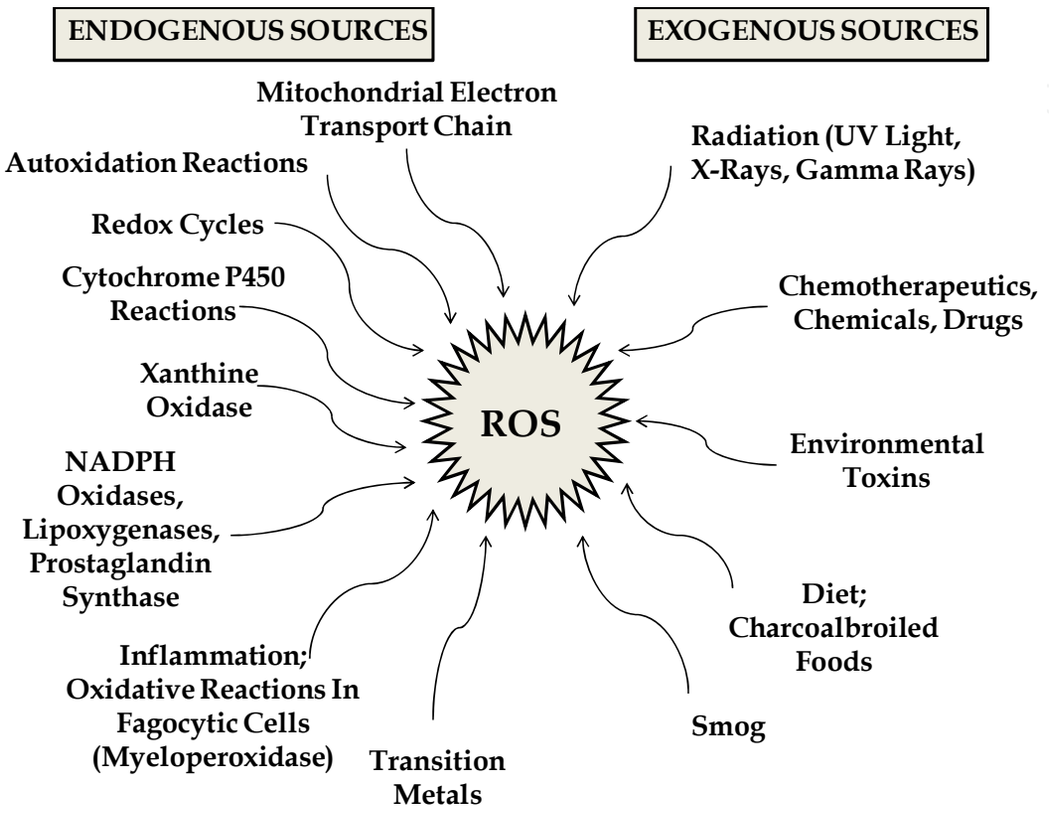

Figure 1. Sources of reactive oxygen species in the human body

Oxidative stress can be defined as the disturbance in the oxidant-antioxidant balance (Chandra, et al., 2000). The cancer cells exposed to oxidative stress tend to heavily interpret adaptation mechanisms and may deplete cellular antioxidant capacity. The generated excessive ROS cannot be neutralized by cellular antioxidants and oxidative stress endures (Pervaiz, 2006). The redox status related to the production of intracellular ROS in cancer cells has also been denoted to control the aggression of cancer cells. The reason of the induced oxidative stress in cancer cells is a result of the lower levels of antioxidant enzymes such as SOD, glutathione peroxidase, glutathione reductase, and catalase (Anshul, 2009). The reduced ROS combout is known in conjunction with tumor growth and metastasis.

The enhanced oxidative stress can lead to modification of cellular targets and induce cell damage and death. Nuclear and mitochondrial DNA single strand breaks, mitochondrial inner membrane damage resulting with the loss of cellular ATP storage and initiation of lipid peroxidation in membrane phospholipids can be seen (Farber, et al., 1990). The cell damage and the following deficiency in cellular repair processes due to the constant oxidative damage are correlated with carcinogenesis(Behrend, et al., 2003; Federico, et al.,

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2007; Nair & Nair, 2007). Such as, guanine nucleotide base oxidation in DNA results in the formation of 8- hydroxy-2-deoxyguanosine (8-OHdG), which alters DNA and eventuates as mutagenesis and cause carcinogenesis (Gate, et al., 1999). ROS interaction with DNA results in fragmentation with the loss of bases and causes DNA strand breaks (Imlay, 1988; Farber, et al., 1990; Farber, 1994). When DNA strand breaks accumulates in cells, this can lead oncogenic transformation depending on the intensity of cellular repair processes (Federico, et al., 2007). At this level, cells exposed to excessive ROS stress either undergo apoptosis or in some cases the cells start to proliferate and thus are irreversibly turn into malignant cells (Fruehauf & Meyskens, 1997) and maintain excessive oxidative stress compared to normal cells. Thus the strategy of producing further ROS stress in malignant cells could be a successful anti-cancer strategy (Anshul, 2009).

On the other hand, ROS also subserve for the regulation of cellular functions and normal metabolism (Poli, et al., 2004). Adversely, low concentrations of ROS serve a variety of important cellular functions such as the activation and modulation of the signal transduction pathways (Monteino & Stern, 1996), modulation of the activities of the redox sensitive transcription factors (Li, et al., 1998; Oberley, 2002) regulation of apoptosis (Nulton-Persson, 2001; Fang & Iyer, 2007) and the regulation of mitochondrial enzyme activities (Nulton-Persson, 2001; Oberley, 2002). Increased ROS production is well displayed in transformed cells (Toyokuni, et al., 1995; Burdon, 1995; Storz, 2005; Kryston, et al., 2011) and growing evidence suggests that ROS act as second messengers in intracellular signaling pathways (Liou & Storz, 2010).

Recently, oxidative stress has been related with the etiology and the prospective treatment of cancer (Powis & Baker, 1997; Pervaiz & Clement, 2004). Cells have developed a number of antioxidant defense systems to confront the hazardous effects of endogenous ROS production and accumulation to protect against cellular oxidative damage. Antioxidants in the cells form a heterogeneous group including low molecular weight substances which are water or lipid soluble, being inclusive in the body through nutrition, also a number of endogenous metabolites own antioxidant activities.

Malignant gliomas account for the most diagnosed primary brain cancers (Behrend, et al., 2003). Despite of exquisite treatment approaches the prognosis remains poor. There is a well-documented association between increased consumption of antioxidants and decreased incidence of cancer. Antioxidant supplements are recommended as part of a cancer prevention diet. Even though cells have endogenous antioxidant enzymes, most human cancer cells have decreased antioxidant enzyme levels compared to their normal tissue counterparts. It is found that; cruciferous vegetables such as broccoli, horseradish, brussels, decreased the risk of anaplastic astrocytomas which is a type of aggressively growing brain tumor. One of the important functions of apoptosis is disposing of preneoplastic and neoplastic cells which appears when a damage or malfunction is recognized and signaling cascades are initiated so caspases and endonucleases that kill the cell are activated. In cell suicide, the signaling cascade avails ROS as messenger molecules. Thats why antioxidants are ascendant in the inhibition of apoptosis. So, the removal of antioxidants from the diet can be suggested as this may enhance apoptosis and inhibit tumor growth. The tumor cell survives in an ROS rich environment

depending on the overexpression of antioxidant enzymes and the excessive levels of nonenzymatic antioxidant scavengers. A range of complementary and alternative therapies can be inclusive for the treatment of brain cancer. Nutrients and herbs are believed to protect against side effects of conventional therapies, they may also enhance chemotherapy and support anticancer activities. At that, normal cells protect themselves when exposed to high doses of antioxidants while cancer cells can not adapt and they suffer damage caused by the antioxidants. Thus, high doses of antioxidants may be toxic to cancer cells but not to normal cells. Antioxidants which are active in the brain tissue, can cross the blood brain barrier and prevent oxidative damage, so this can also be taken into consideration as a good treatment and prevention strategy of brain cancer.

2. The redox status of the brain

Brain is considered enormously vulnerable to oxidative damage so is the target for oxidative stress damaging effects than the other tissues. One of the reasons is its having high oxygen consumption (Sah, et al., 2002) and this is around 20% of the total metabolic activity (Dal-Pizzol, et al., 2000). Also, the brain tissue contains much amounts of polyunsaturated fatty acids, which are particularly sensitive to free radical attacks and prooxidative transition metals such as high levels of iron which is a triggering factor in lipid peroxidation of the cell membranes and also the brain has a comparatively low antioxidant capacity (Sies, 1993; Bellissimo, et al. 2001; Freitas, et al., 2004) and glucose deprivation, which are needed to support normal metabolic functions through glycolysis and oxidative phosphorylation.

Massive neuronal death is the outcome of the secondary injury response, creating an excessive pool of ROS, which triggers a cascade of reactive oxygen chain reactions. The free metal concentrations are also controlled in the nervous system by transport proteins such as ferritin (Sies, 1993) and this limits the non-enzymatic catalysis of hydroxyl radical formation. The nervous system contains antioxidant enzymes; including Cu/Zn- and Mn dependent SOD and GPx which are expressed in higher quantities than CAT (Shivakumar et al., 1991; Hussain et al., 1995). It was shown that the zinc, iron and selenium concentrations were found significantly lower in cancer patients and the copper concentrations were found to be either elevated or significantly elevated, as 2-3 fold, when compared to age matched samples of normal tissues (Kuo, et al., 2002; Zuo, et al., 2006). It has been also shown that the Cu/Zn, Cu/Se and Cu/Fe ratios were found higher in cancer patients when compared to normal subjects.

Cancer cells display increased glycolysis rate combined with a reduced respiration rate (Spitz, 2000). The enhanced requirements for ATP; generates oxygen free radicals and this causes oxidative stress conditions to come out which eventually promotes cell death. Neurons and cancer cells consume glucose as energy source to respond this issue and glycolytic metabolism rules over in tumor cells. The release of cytochrome c couples with the pentose phosphate pathway and this initiates cytochrome c mediated apoptosis (Vaughn &Deshmukh, 2008). Caspase activation is initiated by cytochrome c when released from mitochondria during apoptosis. So, the cancer cells and neurons control apoptosis through

regulation of cytochrome c release, while utilizing glucose as a source of energy (Dajas, 2012). This marked changes in metabolism have been shown to be related with increased oxidative stress which is emphasized to be due to increased mitochondrial superoxide radical production (Oberley, et al., 1981). A more oxidizing redox status of the transforming cell occurs and this streamlines immortalization, increases cell proliferation and supports development of the malignant cell (Spitz, et al., 2000). In the initial steps of carcinogenesis, a relatively prooxidant intracellular environment is developed and entails the mutation of tumor suppression genes and the activation of the oncogenes. Thus, the loss of normal redox control in cell growth and development occurs (Blackburn, et al., 1999).

Oxidative stress in the brain is known to increase the glutamate release in the hippocampus, and this affects ionic homeostasis and neurotransmission (Costa, 2004). The glutamate receptors are activated subsequently so acidification occurs in neurons because of Ca^{2+} entry and this can be associated with the death of central neurons (Reynolds & Hastings, 1995; Bellisimo, et al., 2001). This countenance can be altered by increased ROS production or decreased intracellular antioxidant defense systems (Tejada, et al., 2006).

Studies have been done to evaluate antioxidant enzyme activities in different types of brain tumors. However, most studies have emphasized decreased levels of antioxidant enzymes and vitamins in diverse malignancies (Rao, et al., 2000; Manju, et al., 2002; Gromadzinska, et al., 2003) but still the results are inconsistent (Hennekens, et al., 1996).

2.1. Mitochondrial changes in tumor cells

Mitochondrial DNA is more vulnerable to mutation when compared with nuclear DNA. Conversely to nuclear DNA, mitochondrial DNA is in close proximity to the electron transport system where ROS are produced, and it doesn't have any protective histones and chromatin structure, also its repair capabilities are limited, and it doesn't have any introns (Copeland, et al., 2002). Many studies have established mitochondrial DNA changes in different cancer types related to these features (Lu, et al., 1992; Savre-Train, et al., 1992; Polyak, et al., 1998; Modica, et al., 2002; Modica, et al., 2007). Cancer specific mitochondrial DNA mutations have been identified. Recent studies, associating the alterations in mitochondrial DNA and cancer risk, suggest mitochondrial DNA changes during cancer development are more complicated than estimated (Ebner, et al., 2011; Lam, et al. 2012).

Mitochondria are highly prospered with antioxidants such as GSH and antioxidant enzymes such as superoxide dismutase and GPx, which exist on both sides of their membranes to minimise oxidative stress in the organelle because mitochondria are the major zone of free radical generation (Cadenas & Davies, 2000). Superoxide radicals are ascendantly detoxified into hydrogen peroxide and into water by Cu/ZnSOD and MnSOD. The redox components of the cell comprises mitochondrial redox indicators which are glutathione (GSH/GSSG), thioredoxin (Trx/TrxR), glutaredoxin (Grx) and peroxiredoxin (Prx) systems dependent merely on NADPH generation via reduction of $NADP^+$ by mitochondria.

In some apparent cases, when mitochondrial oxidative stress increases, over generation of the antioxidant defences above a certain threshold may lead to cell death. In normal cells, the same

process would take longer to happen as mitochondrial oxidative stress would be in basal levels and lower. Indeed, most of the anti tumor agents are known to act as prooxidant agents and they disturb the mitochondrial respiratory chain and this leads to an increase in mitochondrial oxidative stress levels (Chou, et al., 2004).

Relying on glycolysis other than oxidative phosphorylation for glucose oxidation and enhanced usage of glutamine as an energy source are the the two common metabolic reprogramming processes in cancer. Excessive upregulation in glutamine consumption is seen in tumor cells which is a second shift in energy metabolism (Barbosa, et al., 2012). Mitochondria are the the main energy producers via oxidative phosphorylation in normal cells and they produce various metabolic intermediates, and they mediate various apoptotic pathways (Weinberg & Chandel, 2009). Mitochondria exhibits same essential roles in cancer cells, too. Though, mitochondria undergo massive changes during oncogenesis, and this mostly result with a change in the energy metabolism, a resistance to apoptosis and enhanced ROS production.

Because the cancer cells have different metabolic and mitochondrial needs other than their normal counterparts, metabolic and mitochondrial changes in cancer cells may suggest an efficient and selective anti cancer therapy opportunity. This fact can be taken into consideration when targeting tumor mitochondria in terms of therapy.

3. Antioxidant defence systems

ROS are detoxified by exhaustive antioxidant defence systems. When the balance between ROS and antioxidant status is disturbed, cellular defences can be reeled causing an abnormal cell growth and this leads in turn to tumor cell forming (Wang, et al., 2011). Mammalian cells have developed a number of antioxidant defense systems to withstand the detrimental effects of ROS and they protect against cellular oxidative damage (Aoyama, et al., 2008). Antioxidants comprise of a highly heterogeneous group. They involve water or lipid soluble low molecular weight substances and enzymes such as CAT, SOD, GPx and GR. Also, a number of endogenous metabolites have antioxidant activities (Table 1).

Superoxide dismutase enzyme decomposes superoxide radicals into H_2O_2 and O_2. The most important H_2O_2 scavenging enzymes and concerned proteins having antioxidant capacity comprise CAT, GPx, GR enzymes associated with the synthesis of reduced GSH (Halliwell & Gutteridge, 1996) and a group of cysteine containing proteins known as thioredoxins, thioredoxin peroxidases (peroxiredoxins), and glutaredoxins (Kumar & Holmgren, 1999; Rhee, et al., 1999; Powis, et al., 2000; Holmgren, 2000). When ROS production is enhanced, the antioxidant scavenging capacity is disturbed and this results in the development of oxidative stress which leads to tissue injury and apoptosis activation (Todorova, et al., 2004).

GSH is a low molecular weight thiol and it has a key role in maintaining the intracellular redox balance. Cellular glutathione appears mainly in the reduced form as GSH, while some of the total GSH exists in its oxidized disulfide form as GSSG. Depletion of

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GSH and an eventual decrease in the GSH/GSSG ratio may be seen in oxidizing conditions, yet peroxidise coupled reactions can mediate its antioxidant activity. GSH also amends signaling pathways and some cellular events. In oxidative stress, GSH is depleted hereby the GSH pool is affected (Dickinson & Forman, 2002; Circu & Aw, 2008; Biswas & Rahman, 2009; Forman et al., 2009; Yuan & Kaplowitz, 2009).

ANTIOXIDANTS			
Enzymatic antioxidants			
Superoxide dismutase (SOD)			
Catalase (CAT)			
Glutathione peroxidase (GPx)			
Glutathione reductase (GR)			
Glutathione-S-transferase (GST)			
Non-enzymatic antioxidants			
Vitamin E	Flavonoids	Albumin	Haptoglobin
Vitamin C	Melatonin	Glutathione	Ceruloplasmin
Vitamin A	Uric acid	Ubiquinone	Transferrin
α-Lipoic acid	Bilirubin	Selenium	Lactoferrin

Table 1. Antioxidants

Vitamin E, vitamin C and carotenoids can be defined as traditional antioxidant nutrients when consumed with diet, also they have antioxidant and anti inflammatory properties along with multiple other bioactive phytochemicals. The phytochemicals that includes phenolic acids and their derivatives, flavonoids and different types of coumarins and tannins consist of a large and heterogeneous group (Liu, 2004).

The phenolic compounds have recently been attracting attention conversely to antioxidant vitamins and carotenoids (Gescher, et al., 2001) and still most have not been tested in placebo controlled cancer prevention strudies. Curcumin, a phenolic acid derivative obtained from the spice turmeric; resveratrol, a polyhydroxylated stilbene found in grapes ; and genistein, an isoflavone readily isolated from soy have been pointed out for future studies (Gullet, et al., 2010). These compounds are known to have antioxidant and anti inflammatory features (Djuric, et al., 2001; Leu, et al., 2006; Brisdelli, et al., 2009), and they are implied as promising in cancer prevention depending on in vitro and in vivo animal experiments (Sarkar, et al., 2006; Sarkar, et al., 2010; Kelkel, et al., 2010; Patel, et al., 2010; Slusarz, et al., 2010). Resveratrol; having a hydroxylated structure, is a well identified antioxidant. It can act both as free radical scavenger and as metal chelator. Moreover, it also amends many enzymes in the regulation of redox status which are CAT, SOD, GR, NADPH oxidase, xanthine oxidase and (Delmas et al., 2005; Pervaiz & Holme, 2009). Flavonoids are polyphenols and isoflavones and anthocyanidines as the subclasses of flavonoids. They have a strong antioxidant activity because of their

free radical scavenging and metal chelating features, also they can interact with enzymatic and non enzymatic mechanisms of the regulation of redox status (Heim et al., 2002; Laguerre et al., 2007; Aron & Kennedy, 2008) (Fig.2).

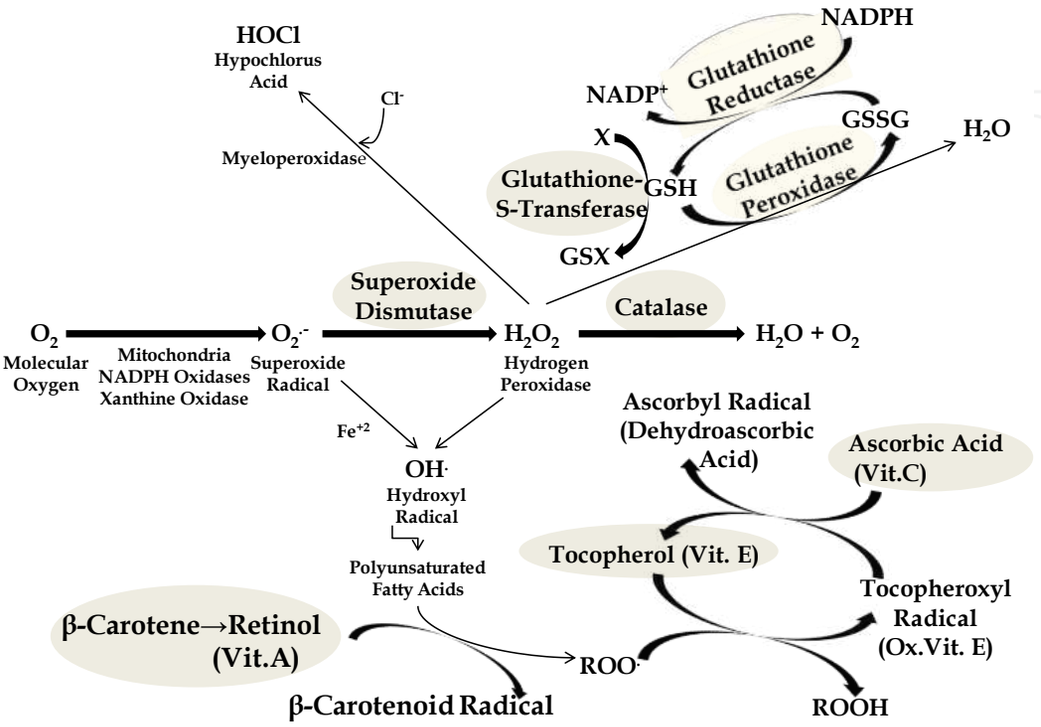

Figure 2. Antioxidant defence systems

Antioxidant molecules has been known as also beneficial in the induction of endogenous protective antioxidant enzymes and in the modulation of various of cellular signaling pathways (Valko et al., 2007). They can quickly oxidize spontaneously or induced by the biological microenvironment.

Antioxidant enzymes can antagonize initiation and promotion steps of carcinogenesis and they are reduced in cancer. Mitochondrial Mn-SOD is the most frequently decreasing enzyme and this suggests that MnSOD may be a new type of tumour suppressor gene. On the other hand, studies also suggest that the deficiency of the MnSOD enzyme activity depends on a defect in the expression of the related gene. Transition metal ions such as Mn and Fe have been found to be significantly lower in some tumours. It can be thought that, an impairment in the signal transduction may cause the defect in the MnSOD gene expression in the early stage of carcinogenesis (Mates, et al., 2000).

Studies are present implying low antioxidant status and enhanced oxidative stress in cancer patients, even before chemotherapy starts. Low activities of Cu, Zn-SOD, MnSOD, CAT, and GPx are shown in different types of tumor cells when compared with their normal counterparts (Sykes, et al., 1978). Some studies show that administration of antineoplastic agents during cancer therapy results in a higher level of oxidative stress rather than the stress induced by cancer it-

self (Conklin, 2000). Chemotherapeutic agents are thought to cause increase in ROS generation by affecting mitochondrial respiration chain (Carew, et al., 2003; Pelicano, et al., 2003).

In chemotherapy, an increase in lipid peroxidation products and a significant decrease in some plasma antioxidants such as Vitamin E, Vitamin C and carotenes are shown (Jeanne, et al., 2003). The increase in oxidative stress during chemotherapy may exceed the oxidative defense in cancer cells and this may initiate lipid peroxidation. Enhanced lipid peroxidation inhibits cancer cell proliferation and intervenes chemotherapy. Thus, the antioxidant status in cancer may play an important role in response to chemotherapy (Papageorgiou, et al., 2005).

3.1. Antioxidant status of the brain

Tumor cells frequently demonstrate a change in redox status. The alterations in the redox environment enhancing oxidation can induce some of the factors that cause cell proliferation and malignant transformation.

Elevated MnSOD levels were shown in the serum samples of neuroblastoma patients in a study (Kawamura, et al., 1992). In recent studies, MnSOD was found to be associated with loss of differentiation and increased clinical malignancy in neuroepithelial origined brain tumors (Landriscina, et al., 1996; Ria, et al., 2001). MnSOD was found significantly positive in Grade IV astrocytomas and medulloblastomas and negative in normal brain samples (Cobbs, et al., 1996). It can be said that MnSOD is overexpressed in most brain tumor types and enhanced MnSOD expression is related with a poor prognosis. MnSOD seems to be a tumor suppressor in the proliferative stage. When tumor progresses more aggressive, MnSOD is upregulated. MnSOD level positively correlates with increased metastasis so MnSOD has an oncogene role (Hempel, et al., 2011; Dhar, et al., 2011). Increase in MnSOD level was seen during the progression of different types of tumors, including brain, to the metastatic stage. Tumorigenesis and metastasis are dependent on the levels of ROS. A cell having low levels of MnSOD is vulnerable to oxidative stress then it may turn its progression to a tumor cell (Miriyala, et al., 2012). Oxidative gene polymorphism and brain tumor risk seems associated, the increased risk of glioma and meningioma type brain tumors were found to be related with variants in some antioxidant enzyme genes (Rajaraman et al., 2008) and in a study, MnSOD tissue expression is said to be a prognostic marker for glioblastoma (Park et al., 2009). SOD and GPx activities showed a clear decrease proportionally with tumor malignancy, decrease of SOD activity with the increasing grades of malignancy in brain tumors were implied.

The GSH redox cycle is one of the most important antioxidative systems (Arrick & Nathan, 1984; Mitchell, et al., 1989; Tedeschi, et al., 1990). GSH is a primary endogenous neuroprotectant for the brain. GSH protects neuron cells from lipid peroxidation and brain cells from peroxynitrite mediated oxidative damage (Mark et al., 1997; Koppal et al., 1999). GSH, also has roles in the activation of transcription factors, DNA repair, regulation of enzyme activity and many other metabolic processes (Meister, 1995). GSH synthesis, usage and export are the processes on which GSH homeostasis is dependent in glial and neuronal cells (Anderson, 1998). The main path for chemotherapy metabolism is through the conjugation of the xenobiotic with GSH. The removal of the GSH conjugates from the cell causes cellular GSH depletion and cellular redox balance disruption.

GSH content depends on the substrate availability in the brain and cysteine is the rate limiting substrate for neuronal GSH biosynthesis (Dringen, et al., 1999). Astrocytes provide neighbour cells the needed precursor amino acids for GSH synthesis (Hirrlinger, et al., 2010). GSSG levels and the GSH/GSSG ratios can be restored through the GR mediated pathway and flow of GSSG leaded by ATP dependent multi drug resistance-associated protein-1 (Mrp1) transporter in astrocytes and neurons (Hirrlinger, et al., 2001; Casagrande, et al., 2002; Minich, et al., 2006). Cultured astrocytes have high levels of reduced GSH (Dringen & Hamprecht, 1998) while oligodendrocyte precursors have high levels of iron but lower levels of cellular GSH when compared with astrocytes or neurons (Hussain & Juurlink, 1995; Thornburne & Juurlink, 1996), also oligodendrocyte precursors are more sensitive to oxidative stress induced death in relation to GSH depletion (Back, et al., 1998). The GSH neutralization system has been shown also in the chemoresistance of medulloblastoma (Colvin, et al., 1993). GSH and GST are prevalantly seen in brain tissue, thus highly expressed in various primary brain tumors (Bredel, 2001). GSH content and GST expression was shown to be related to tumor response to nitrogen mustard therapy in human brain neoplasms (Evans, 1993). Also in another study it was indicated that the cytotoxic effect of BCNU in human brain tumor cells seems associated with the GSH content (Ali-Osman, et al., 1989). When GST isoenzymes in neoplastic and non-neoplastic astroglia were compared, GST3 isoenzyme was seen to be significantly higher in tumors (Strange, et al., 1992). It is said that GST expression levels in brain tumors seems in association with the tumor histology as some tumor types express enhanced levels but some show only slight rise or decrease when compared to normal cells (Bredel, 2001). GST was found to be active in high levels in benign tumors such as meningioma but only two, three folds higher compared to normal tissue but it was slightly increased in astrocytoma (Matsumoto, et al., 1992). In glioblastomas, GSH levels were found significantly lowered compared to normal tissue and merely elevated in meningioma (Kudo, et al., 1990).

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). 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 radiotheraupetic regimens following total resections might be helpful in patients with glioblastoma multiforme (Atukeren et al., 2010).

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).

Serum β-carotene and α-tocopherol levels were found to be decreased in brain tumor patients when compared to healthy subjects and also more less in malign tumors than the benign types (Potishman, et al., 1991; Zheng, et al, 1993; Palan, et al., 1996). Few studies have been done to compare the levels of these antioxidants in various histological types of brain tumors. It was seen that β-carotene and α-tocopherol levels decreases when malignancy grade increases and the decrease was found significant for oligodendroglioma grade I-II, glioblastoma multiforme and medulloblastoma. The protective antioxidant effects of these two vitamins are suggested (Brigelius–Flohe, et al., 2002). The decreased antioxidant levels in brain tumor patients reflect the enhanced oxidative damage and increased cancer developing possibility, stating the role of antioxidants in cancer prevention and role of oxidative injury as the of cancer (Aggarwal, et al., 2006).

4. The potential therapy in brain tumors regarding antioxidants

Antioxidant consumption is appraised if it can be a pledging therapeutic approach in preventing or minimizing neuronal oxidative damage (Halliwell, 2001; Uttara et al., 2009). A relationship between excessive antioxidant consumption or high blood levels and a low cancer incidence was found in many studies (Comstock, et al., 1992; Van den Brant, et al., 1992). Also the importance of exogenous utilization of antioxidants with malignant glioma was shown in various studies (Il'yasova et al., 2009; DeLorenze et al., 2010) yet antioxidant supplementation by cancer patients during treatment is quite contentious. Indeed, a distinct declination or recommendation for the simultaneous use of antioxidants with chemotherapy has not been verified currently. The prospective antioxidant therapeutic approaches should involve either inhibiting the ROS generation or scavenging. Recently, new strategies for antioxidant consumption have been studied carefully in order to maximize the influence and safety by improving drug release and site specific targeting and to limit the adverse effects (Ratnam, et al., 2006). Cancer cells' having a a weak antioxidant defense system against oxidative stress brings about a theoretical basis for the use of ROS generating systems in treatment (Laurent, et al., 2005). Knowing that ROS have stimulating effects on tumor metastasis, the scavenging of ROS is also a reasonable strategy to inhibit metastasis (Nishikawa, et al., 2006). Main strategies as a potential treatment are the inhibition of the antioxidant enzymes and molecules in cancer cells and the production of ROS leading to apoptosis (Lopez-Lazaro, 2007; McCarty, et al., 2007). Recent studies involving ROS producing agents implied that their anti cancer and cytotoxic effects are limited to cancer cells and no toxicity was seen in the surrounding normal tissue (Yoshikawa, et al., 1995). The main mechanism of most chemotherapy drugs is via ROS formation, but also free radicals production during chemotherapy is a serious side effects (Block, et al., 2008). Interactions between chemotherapeutic compounds and antioxidants are quite complicated and also the dose, the localization and the metabolism of the drug have different effects. Furthermore, some antioxidants may act as oxidative molecules related with their relative concentration (Badajatia, et al., 2010).

The coexpression of catalase was shown to revert malignancy (Hempel, et al., 2011). The overexpression of catalase protected cancer cell from excessive peroxide production as a result of combined menadione/ascorbate anticancer treatment (Glorieux, et al., 2011). Also, the ability of ascorbate to radiosensitize primary human glioblastoma cells and mouse astrocytes and astrocytoma, was investigated and it was concluded that pharmacological concentrations of ascorbate radiosensitize glioblastoma primary cells more than astrocytes and this can be of clinical significance in therapeutic approach (Herst, et al., 2012). Besides, the activation of ferroptosis was shown to be resulted in the nonapoptotic destruction of some cancer cells and inhibiting this process by ferrostatin-1 seems to protect from neurodegeneration (Dixon, et al., 2012).

4.1. Targeting GSH pathway

GSH and the GSH related enzyme system might be a distinctive factor for the susceptibility of several brain tumors to different chemotherapeutic agents (Backos, et al., 2012). Studies have shown that drug resistance mediated by the GSH/GST system mediated drug resistance in brain tumors might be the outcome of a change in a GSH related enzyme system and increased GSH level (Ali-Osman, et al., 1989; Freidman, et al., 1992). Chemotherapeutics, thereby chemoresistance, were shown to be related with increased cellular GSH content in brain tumor cell lines (Ali-Osman, et al., 1989; Ali-Osman, et al., 1990). The increased GSH content is related with tumor drug resistantance so exhaustion of cellular GSH can restore the sensitivity to the cytotoxic effect of an anticancer agent (Barbosa, et al., 2012). So, it can be suggested that the depletion of GSH content may increase the sensitivity to different chemotherapeutics. The multidrug resistance-associated proteins (Mrp) can function as GSH, GSSG and GSH conjugate carrier (Jedlitschky, et al., 1994; Muller, et al., 1994). Expelling these drug metabolites conjugated with GSH ; changes the intracellular GSH levels distinctly. Mrps are considered to have a role in resistance development to chemotherapeutics in most human brain tumors (Bredel & Zentner, 2002). Mrp overexpression is associated with drug resistance in gliomas (Abe, et al., 1998) and conversely with clinical outcome in neuroblastoma (Norris, et al., 1996). Astrocytes have a potent GSH biosynthesis and antioxidant coupling is substantial in sustaining neuronal GSH status and conserving neurons from ROS (Dringen R & Hirrlinger, 2003). Even the concerned GST polymorphisms have been found to be associated with the survival (Kilburn, et al., 2010), decreased GSH levels seems to play an important role in the increased sensitivity of oligodendrogliomas to chemotherapy due to decreased GSH needed for detoxification. The elevated iron levels in these cells also makes them daintily exquisite to ROS generation based on chemotherapeutics (Yonezawa, et al., 1996). In a study, alantolactone which inhibits tumor growth and triggers apoptosis and GSH depletion in glioblastoma, is suggested as a potential lead compound for antiglioma therapy (Khan, et al., 2012).

4.2. Targeting mitochondria

Cancer cells have distinct metabolic and mitochondrial needs from their normal counterparts so mitochondrial alterations in the context of metabolic reprogramming are an appealing target for different therapeutic approaches. Most anti tumor agents act as prooxidants and they

disturb mitochondrial respiratory chain and enhance mitochondrial oxidative stress (Chou, et al., 2004). Considering that ROS have a role in activating signaling pathways thereby guiding to metabolic remodeling; mitochondrial oriented antioxidants involving MitoQ may donate to normalizing the metabolic phenotype in cancer cells. This antioxidant molecule has already been indicated to diminish the hypoxic stimulation of ROS and to impair HIF-1alpha protein by decreasing its transcriptional activity (Sanjuan-Pla, et al., 2005).

Occasionally, overloading the antioxidant system by increasing mitochondrial oxidative stress over a certain threshold can be encountered leading to cell death. The same process would take longer to come up in normal cells because the basal mitochondrial oxidative stress would be lower. In a recent study, sulforaphane, having antioxidant and anti tumor features is suggested to provide antitumor activity in malignant glioma cells via mitochondria and caspase dependent pathways (Huang, et al., 2012).

4.3. Therapy via natural antioxidants

A great number of plants are good sources of phytochemical antioxidants and which have been estimated having cancer fighting ability (Wang, et al., 2011). There is a reasonable scientific and commercial interest in espialling new anti cancer molecules from natural sources, involving secondary plant metabolites (Kinghorn, et al., 2003). Phytochemical antioxidants existing in foods exhibit their anticancer properties via reducing ROS induced oxidative damage by either scavenging or by increasing endogenous antioxidants (Du, et al., 2007). Natural antioxidants have the ability to modulate signal transduction pathways by the activating or inhibiting multiple redox sensitive transcription factors which is asserted as their potential use as chemopreventive agents for therapy. They can act a part in initiation, promotion and progression stages of carcinogenesis to prevent cancer progress (Sporn, 1991).

Recently potential chemopreventive activities of dietary polyphenols was shown in most studies (Thomasset, et al., 2007). The effects of flavonoids being natural polyphenolic antioxidant compounds in brain development, neuroprotection and glial tumor formation are mentioned and developing new therapeutic approaches was discussed (Nones et al.; 2010). Epigallocatechin-3-gallate (EGCG) from green tea, curcumin from turmeric, and resveratrol from grapes are some examples of polyphenols.

Resveratrol has the ability to block the activation of carcinogens and induce their detoxification, thus to prevent ROS damage and alleviate inflammatory responses and to reduce the proliferation of cancer cells which reflect its chemopreventive property (Aggarwal, et al., 2004; Shankar, et al., 2007). The chemotherapeutic potential of resveratrol is refered to its blocking angiogenic and metastatic processes of tumor progression and relieving chemotherapy resistance (Aggarwal, et al., 2004; Fulda & Debatin, 2006). The potential therapeutic effect of resveratrol being a dietary phytochemical antioxidant, is investigated in glioma type brain tumors (Gangliano et al., 2010) and glioblastoma multiforme cells exhibited variable responses to resveratrol depending on the brain associated sulfonation activity of the cells and resveratrol seemed to have value in glioblastoma treatment (Sun, et al., 2012). Also the combination of resveratrol with alkylating agent temozolomide was shown to improve the efficacy of chemotherapy for brain tumors (Herst, et al., 2012). EGCG also

exhibited the same effect with temozolomide like as resveratrol in another study, in brain tumor therapy (Chen, et al., 2011). 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 (Purkayastha, et al., 2009).

Different studies implied the importance of using nutritional antioxidants. Lycopene, present in tomato, was shown for its potential therapeutic benefit in the adjuvant management of high grade gliomas (Puri et al., 2010). Gynostemma pentaphyllum extract selectively shifted H_2O_2 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 shown and it was suggested as a prospective anti brain tumor agent (Chang et al., 2010).

5. Conclusion

The incidence of brain tumors is obviously increasing recently. The occurance of ROS are the inevitable outcome of the metabolism and they have important roles in many biochemical processes but they must be precisely kept under control. Antioxidant molecules are that delay, prevent, or remove the existing oxidative damage to a target molecule. The brain is quite vulnerable to ROS damage because of its low antioxidant levels. To get over ROS damage, the brain needs a sufficient supply of antioxidants and it seems convinent that working up with ROS signaling pathways would provide a great neuroprotective effect. The development of the suitable antioxidant compounds seems a challenging and pledging strategy for brain tumor treatment but plenty of work has to be done to emphasize the exact role of antioxidants for therapy in clinical use.

Adjusting the antioxidant dose and scheduling of the administration or combining different antioxidants and exploring a more potent and specific antioxidant should be the main theme. Also the preventive and therapeutic molecule should target multiple biochemical pathways comprising the processes entailing malignancy and restrain the unwanted side effects and toxicity in the normal tissue counterparts. In the same time should attend a beneficial task in stimulating the therapeutic effect of chemotherapy and diminishing certain side effects. It is clear that there is a deficient evidence concerning the prospective antioxidant therapies in brain tumors. Regarding to the fact that there is little knowledge concerning complementary therapy with antioxidant molecules and their effects or side effects, there is a crucial need for further research of these treatment strategies.

Acknowledgements

We would like to dedicate this chapter to brain cancer patients.

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