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Antioxidant Adaptive Response of Malignant Glioma Related to Resistance to Antitumor Treatment

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1. Introduction

Glioblastomas are the most frequent and most malignant nervous system tumors [Stewart & Kleihues, 2003]. Despite technological advances in surgical treatment and new regimens of radiotherapy combined with chemotherapy, the median survival of patients with these tumors is approximately 1 year, and only 3% of patients survive more than 3 years [Stupp et al., 2005]. Glioblastomas have been traditionally defined as two clinically and cytogenetically distinct diseases: the primary or de novo glioblastomas and the secondary glioblastomas. The latter commonly appear in younger people (median age at onset ~45 years) as low-grade gliomas and possess aberrations in genes encoding platelet-derived growth factor receptor (*PDGFR*) and *TP53* [Stewart & Kleihues, 2003]. Primary glioblastomas occur more frequently (>80% of cases) and develop rapidly in older people (median age at onset ~60 years); survival of patients with such tumors is short, less than 3 months [Stewart & Kleihues, 2003]. The genetic profile of primary glioblastomas includes amplification and overexpression of the gene encoding epidermal growth factor receptor (*EGFR*), mutations of the phosphatase and tensin homolog (*PTEN*) gene, $p16^{INK4A}$ deletions, and loss of chromosome 10 [Stewart & Kleihues, 2003]. Several inhibitors that target *EGFR* or its downstream signaling cascade including Akt and mTOR have been evaluated for potential application in glioblastoma treatment [Krakstad & Chekenya, 2010]. Recent clinical trials of *EGFR* inhibitors, however, showed no therapeutic benefit [Prados et al., 2006; Rich et al., 2004].

Chemotherapy plays an important role in combined treatment of gliomas, whereas it appears to fail in a significant clinical outcome. This may be largely due to drug resistance of malignant gliomas developed [Lu & Shervington, 2008; Sarkaria, et al, 2008; Frosina, 2009; Bleau et al., 2009]. Multiple mechanisms may be involved in the development of drug resistance in gliomas, including DNA repair enzyme activities, particularly O^6-methylguanine methyltransferase for alkylating agents, overexpression of antiapoptotic proteins such as Bcl-2 or Bcl-X_L and ABC transporters that efflux anticancer drugs. Clarification of mechanisms for glioma drug resistance may provide us an important insight for the development of promising strategies for the treatment of gliomas.

A number of studies have suggested that heme oxygenase-1 (HO-1) expression occurs in various types of tumors, both animal models and human cancers including glioblastomas

[Fang et al., 2004a; Hara et al., 1996]. HO is a rate-limiting enzyme that catalyzes the initial step of heme degradation in which oxidative cleavage of the porphyrin ring results in generation of biliverdin, carbon monoxide (CO), and free iron [Maines, 1988; Schacter, 1988]. Cytosolic biliverdin reductase then reduces the biliverdin to form the potent antioxidant bilirubin. Three mammalian HO isoforms have been identified: HO-1, HO-2, and HO-3. Among them, HO-1 is a member (HSP-32) of the heat shock protein family, and HO-1 expression is triggered by various stress-inducing stimuli including hypoxia [Motterlini et al., 2000], heavy metals [Keyse & Tyrrell, 1989; Mitani et al., 1993], UV irradiation [Keyse & Tyrrell, 1989], and reactive oxygen species (ROS) and nitric oxide (NO) [Doi et al., 1999; Foresti et al., 1997]. Because of the antioxidant and cytoprotective nature of HO products, elevated HO-1 expression in glioblastomas may be a key component of cellular adaptation to oxidative stress and toxic insults induced by chemotherapeutic agents [Fang et al., 2004b]. The fact that HO-1 expression is related to resistance of glioma cells to oxidative stress and anticancer agents indicates that the pathways involved in regulating HO-1 expression in gliomas may be molecular targets for treatment. This chapter describes the mechanisms and regulation of HO-1 expression and the adaptive response of glioma cells. The chapter pays particular attention to the adaptive response signaling that is mediated by 8-nitroguanosine 3′,5′-cyclic monophosphate (8-nitro-cGMP), a newly discovered nitrated nucleotide that functions as an endogenous inducer of the response [Akaike et al., 2010; Fujii et al., 2010; Sawa et al., 2007; Zaki et al., 2009]. Also discussed is the potential application of HO inhibitors as a new class of chemotherapeutic and chemosensitizing agents.

2. Antioxidant adaptive response mediated by a nitrated cyclic nucleotide

The antioxidant adaptive response to oxidative stress is a critically important mechanism that allows aerobic organisms to maintain redox homeostasis. The Keap1 (Kelch-like ECH-associated protein 1)/Nrf2 (nuclear factor-erythroid 2-related factor 2) system plays a key role in adaptation to oxidative stress and toxic insults of electrophilic compounds (including many chemotherapeutic agents) by inducing antioxidant and cytoprotective enzymes such as HO-1.

2.1 The Keap1/Nrf2 system as a sensor of oxidants and electrophiles

Keap1 contains reactive cysteine residues that can serve as sensing moieties for oxidants and electrophiles [Dinkova-Kostova et al., 2005; Itoh et al., 2004; Sekhar et al., 2010]. Various electrophiles called Nrf2 inducers, both naturally occurring and synthetic, have reportedly reacted with Keap1 cysteine residues.

Keap1, which exists as dimers inside cells, comprises five distinct domains: (i) the N-terminal region (NTR, amino acids 1-60); (ii) the BTB (Bric-a-brac, Tramtrack, Broad-complex) domain (amino acids 61-178), which is an evolutionarily conserved protein-protein interaction motif that occurs in actin-binding proteins and zinc finger transcription factors and participates in binding to Rbx1-bound Cullin 3 (Cul3) [Dinkova-Kostova et al., 2005] and formation of homodimers [Zipper & Mulcahy, 2002]; (iii) the intervening region (IVR, amino acids 179-321), which is a central linker domain, especially rich in cysteine, that also takes part in binding toRbx1-bound Cul3 [A. Kobayashi et al., 2004]; (iv) the Kelch repeat domain (amino acids 322-608), which mediates binding to the Nef2 domain of Nrf2 [M.

Kobayashi et al., 2002]; and (v) the C-terminal region (CTR, amino acids 609-625). Site-directed mutagenesis assays have revealed that three cysteine residues, Cys151, Cys273, and Cys288, play critical roles in the Keap1-Nrf2 complex interaction [D.D. Zhang & Hannink, 2003]. Cys151, located in the BTB domain, is probably the major site that is directly alkylated by chemopreventive agents that work by activating the antioxidant response element (ARE) through Nrf2 [Eggler et al., 2007]. This modification of Cys151 leads to conformational changes in the BTB domain via perturbation of the homodimerization site and results in switching ubiquitination from Nrf2 to Keap1, thereby facilitating translocation of Nrf2 to the nucleus and its accumulation there [Eggler et al., 2005]. Cys273 and Cys288, which are located in the IVR domain of Keap1, are essential for stability of the Nrf2-Keap1 complex and maintenance of Nrf2 homeostasis [Wakabayashi et al., 2004]. ARE inducers, via conformational changes in Keap1—i.e., covalent modification or oxidation of cysteine thiol groups in the IVR region of Keap1—make Keap1 incapable of binding to Nrf2 and thereby facilitate nuclear translocation of Nrf2.

Nrf2, a member of the cap'n'collar family of basic region leucine zipper transcription factors, has a crucial role in regulating several stress-responsive genes, including HO-1 [Dinkova-Kostova et al., 2005; Bloom & Jaiswal, 2003; Itoh et al., 2004; Zhu et al., 2005]. Under basal conditions, transcriptional activity of Nrf2 is negatively regulated by the Nrf2-binding partner Keap1, a cysteine-rich cytoplasmic protein [Dinkova-Kostova et al., 2005; Sekhar et al., 2010; Surh et al., 2009; Zhao et al., 2010]. Keap1, serving as a substrate adaptor protein for a Cul3-dependent ubiquitin ligase complex, targets Nrf2 for ubiquitination and proteasomal degradation [Dinkova-Kostova et al., 2005; Sekhar et al., 2010; Surh et al., 2009; Zhao et al., 2010]. During oxidative stress, chemical modification of one or more cysteine residues of Keap1 facilitates Nrf2 dissociation, which leads to nuclear translocation of Nrf2. After migration to the nucleus, Nrf2 forms heterodimers with small musculoaponeurotic fibrosarcoma (sMaf) proteins and then binds to the cis-acting ARE [Motohashi & Yamamoto, 2007]. The result is transcriptional activation of a battery of genes that encode various phase II detoxifying or antioxidant enzymes, such as glutathione *S*-transferase (GST), NAD(P)H:quinone oxidoreductase (NQO1), and HO-1, as well as other cytoprotective proteins [Nguyen et al., 2003] .

2.2 Nitrated guanine nucleotide as an endogenous electrophile that activates the Keap1/Nrf2 system

Both NO and ROS are critically involved, via Nrf2-dependent mechanisms, as endogenous inducers of HO-1 expression in gliomas. 8-Nitro-cGMP is a nitrated nucleotide that was identified as a second messenger in NO and ROS signaling in induction of an adaptive response mediated by the Keap1/Nrf2 system [Akaike et al., 2010; Fujii et al., 2010; Ihara et al., 2011b; Sawa et al., 2007, 2011; Zaki et al., 2009]. 8-Nitro-cGMP also functions in extracellular signal-regulated kinase pathways in neurons [Kurauchi et al., 2011]. Formation of 8-nitro-cGMP can be triggered in rat C6 glioma cells by treatment with a chemical NO donor (*S*-nitroso-*N*-acetylpenicillamine or treatment with inflammatory stimuli (lipopolysaccharide plus pro-inflammatory cytokines) that activate endogenous NO production via expression of inducible NO synthase [Fujii et al., 2010]. Under these conditions, ROS production is also increased and depends on both NADPH oxidase and mitochondria [Ahmed et al., 2011a]. Pharmacological studies have suggested that 8-nitro-cGMP is formed from its precursor 8-nitroguanosine 5'-triphosphate by means of catalytic action of soluble guanylate cyclase [Fujii

et al., 2010; Ihara et al., 2011a]. So far, guanine nitration has been identified in various biological systems including lungs of mice suffering from viral pneumonia [Akaike et al., 2003], lungs of patients with idiopathic pulmonary fibrosis and lung cancer [Terasaki et al., 2006], and urine from cigarette smokers [Sawa et al., 2006].

Activation of the Keap1/Nrf2-mediated adaptive response by 8-nitro-cGMP involves a unique post-translational modification of the cysteine residues of Keap1 [Akaike et al., 2010; Fujii et al., 2010; Sawa et al., 2007; Zaki et al., 2009]. 8-Nitro-cGMP is the first known endogenously formed electrophilic nucleotide [Akaike et al., 2010; Fujii et al., 2010; Saito et al., 2008; Sawa et al., 2007; Zaki et al., 2009]. Because of its electrophilic characteristics, 8-nitro-cGMP reacts with cysteine residues in proteins, particularly residues with low pK_a values that facilitate deprotonation of those residues to form a cysteine thiolate anion [Ahmed et al., 2011b; Akaike et al., 2010; Sawa et al., 2010]. Reaction of 8-nitro-cGMP with the thiolate anion results in cGMP adduction to the cysteine residue, a process called "protein *S*-guanylation" (Fig. 1) [Sawa et al., 2007]. Keap1 was identified as a possible target during 8-nitro-cGMP-induced protein *S*-guanylation in cells [Fujii et al., 2010; Sawa et al., 2007; Zaki et al., 2009]. In fact, Keap1 *S*-guanylation was clearly demonstrated when rat C6 glioma cells were treated with lipopolysaccharide plus pro-inflammatory cytokines [Fujii et al., 2010]. Mass spectrometry revealed that Keap1 *S*-guanylation in rat C6 cells occurred predominantly at Cys434 [Fujii et al., 2010]. X-ray crystallographic analysis suggested that the Cys434 residue is located at blade 3 and is exposed to the outer surface of the β-propeller structure [Lo et al., 2006; Padmanabhan et al., 2006].

With regard to the mechanism of how *S*-guanylation of Cys434 causes Nrf2 activation, two possibilities present themselves. One is that *S*-guanylation of Cys434 may weaken Keap1 binding to the ETGE and DLG motifs of Nrf2, because Cys434 is located close to the Nrf2-binding region of the DC domain. The alternative possibility is that Cys434 modification may affect the integrity of the entire Keap1-Nrf2 complex. Fitting the atomic DC domain model into the overall Keap1 homodimer structure obtained via single-particle electron microscopy showed that the globular part of the Keap1 cherry-bob structure was bulkier than the DC domain, which suggests that the external DC domain surface is wrapped with the other part of Keap1, perhaps the IVR between the BTB and DC domains [Ogura et al., 2010]. Thus, *S*-guanylation may cause disruption of the globular structure incorporating the DC domain, which would disturb the entire structure and result in reduced ubiquitin ligase activity of the Cul3-Keap1 complex.

Among genes regulated by Nrf2, HO-1 has been regarded as conferring important protection against oxidative stress [T.J. Chen et al., 2006; Y.C. Chen et al., 2006; Konorev et al., 2002]. HO-1 may induce cytoprotective responses through various mechanisms including (i) reducing prooxidant levels (heme) [Jeney et al., 2002]; (ii) raising antioxidant levels (bilirubin) [Baranano et al., 2002]; (iii) generating the antiapoptotic CO [Brouard et al., 2000]; (iv) inducing ferritin, which detoxifies and removes free ferric ions [Balla et al., 1992]; and (v) blocking overstimulation of an immune response [Lee & Chau, 2002]. We found that 8-nitro-cGMP increased Nrf2 accumulation in the nucleus and HO-1 expression in rat C6 glioma cells (Fig. 2) [Fujii et al., 2010]. Treatment with 8-nitro-cGMP caused C6 cells to become resistant to cell death induced by oxidative stress related to hydrogen peroxide exposure [Fujii et al., 2010]. Therefore, 8-nitro-cGMP conceivably participates in an antioxidant signaling pathway involved in cytoprotection or adaptive responses to ROS and oxidative stress.

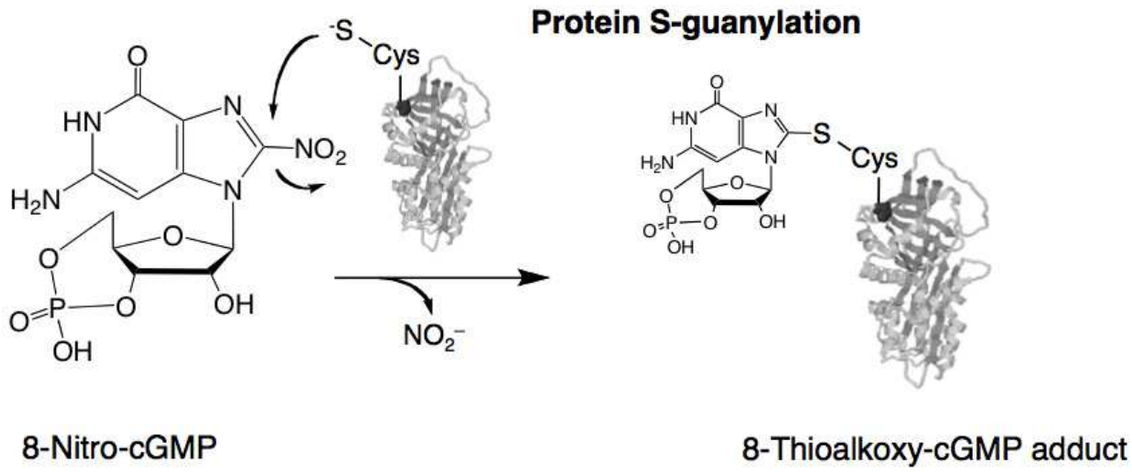


Fig. 1. Schematic representation of protein *S*-guanylation induced by 8-nitro-cGMP. The nucleophilic protein thiolate anions attack the C8 of 8-nitro-cGMP, which results in adduction of cGMP moieties to cysteine residues in proteins, with concomitant release of a nitrite anion.

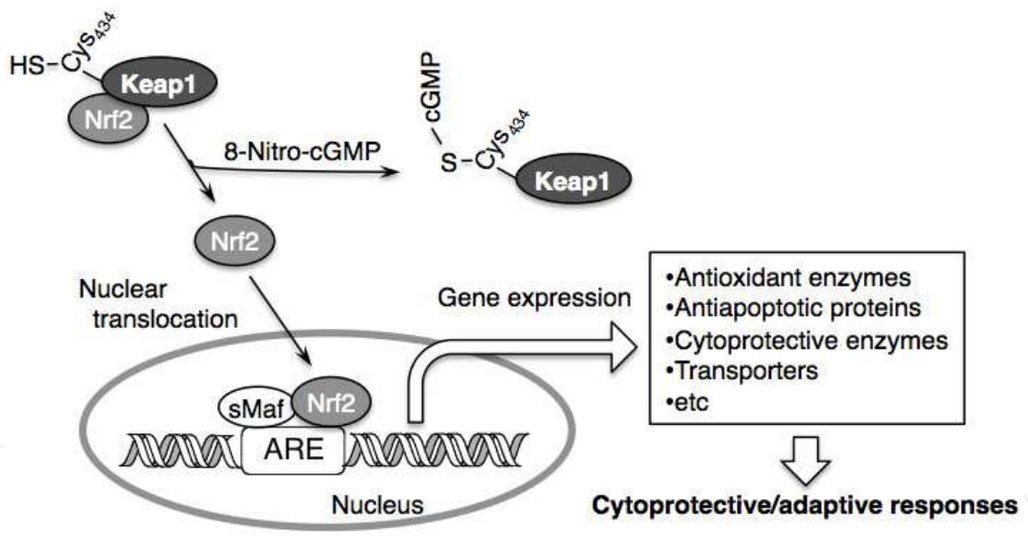


Fig. 2. 8-Nitro-cGMP-mediated cytoprotection as a result of *S*-guanylation of Keap1. *S*-Guanylation of Keap1 facilitates dissociation of Nrf2 from Keap1 and leads to translocation of Nrf2 to the nucleus. In the nucleus, Nrf2 forms a heterodimer with sMaf proteins, thereby inducing expression of various cytoprotective enzymes.

3. Genetic regulation of the Keap1/Nrf2 system in cancer cells

Hypermethylation of the promoter CpG island is an epigenetic mechanism that leads to gene silencing [Warnecke & Bestor, 2000]. Quite recently, promoter methylation of the *KEAP1* gene was found in malignant gliomas [Muscarella et al., 2011]. A strong inverse correlation was discovered between methylation levels and *KEAP1* mRNA transcript in tumor tissue [Muscarella et al., 2011], which suggests the occurrence of *KEAP1* gene

silencing in gliomas. The reduction in *KEAP1* expression caused by promoter methylation may contribute to constitutive Nrf2 stabilization and subsequent activation of an antioxidant response in gliomas, as seen in certain cancer cells such as those in the lung [Wang et al., 2008] and prostate [P. Zhang et al., 2010]. Inactivation of Keap1 functions by somatic mutations causing amino acid substitutions has been found in cancer cells in the breast, lung, gallbladder, and liver [Shibata et al., 2008a; Singh et al., 2006; Taguchi et al., 2011]. Also, mutations in the *NRF2* gene that are related to the reduction in Keap1-Nrf2 interaction were identified in human cancers of the lung, head and neck, and esophagus [Shibata et al., 2008b; Taguchi et al., 2011]. Such mutations in the *KEAP1* and *NRF2* genes, however, have not yet been found in gliomas and hence warrant further investigation.

4. HO-1 as a target for chemosensitization: The therapeutic potential of HO inhibitors

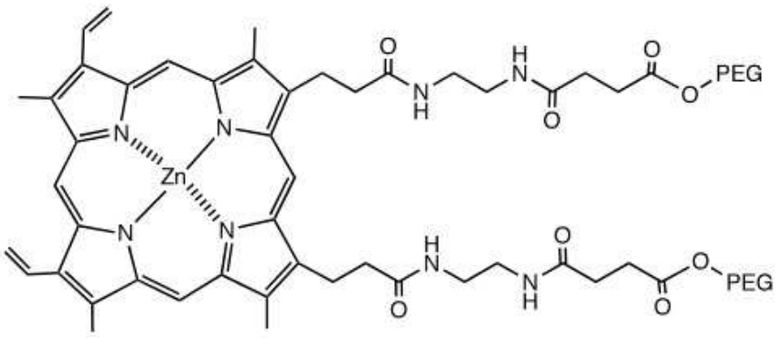
Many antitumor agents, such as cisplatin, doxorubicin, mitomycin C, vinblastine, and arsenic trioxide, produce cytotoxic effects via generation of ROS and/or electrophilic actions, which lead to oxidative stress [Dilda & Hogg, 2007; Fang et al., 2007; Simizu et al., 1998]. Hence, those antitumor agents activate Nrf2-dependent HO-1 induction, either by direct actions or by indirect means, i.e., by augmenting the intrinsic signaling cascade mediated by endogenous inducers including 8-nitro-cGMP, as mentioned above. Tumor cells subsequently become resistant to treatment with those antitumor agents. That the HO-1-dependent antioxidant system would be a potential target for chemosensitization is therefore conceivable. The following discussion will cover the effects of disrupting the HO-1-dependent antioxidant system on chemosensitivity, with particular attention to HO inhibitors as new chemosensitizers.

Knockdown of HO-1 or its master regulator Nrf2 is a straightforward approach to disrupting the HO-1 antioxidant system. We found that knockdown of HO-1 by means of small interfering RNA (siRNA) resulted in the induction of apoptosis in SW480 human colon cancer cells in culture [Fang et al., 2003]. Liu et al. [2011] reported that Nrf2 knockdown effectively led to suppressed HO-1 expression and enhanced sensitization to arsenic trioxide-induced apoptosis in cultured human glioma cells U251MG and A172. Quite recently, HO-1 expression was found to be regulated post-transcriptionally by microRNA (miRNA). Beckman et al. [2011], by using an HO-1 reporter assay, found that a combination of two miRNAs (miR-377 and miR-217) markedly reduced HO-1 expression. Mature miRNAs are ~21-22 nucleotides long and affect post-translational expression of genes by interacting with complementary target sites in the 3′-untranslated region of the mRNA [Jackson & Standart, 2007]. The exact molecular mechanisms used by miRNAs to mediate translational repression are still being studied intensively; however, modulation of HO-1 activity by miRNAs may be an alternative strategy for sensitizing tumor cells to chemotherapy.

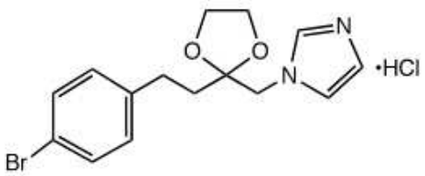
Direct inhibition of HO-1 enzyme activity may be an alternative approach for disruption of the HO-1-mediated antioxidant system in tumor cells. Metalloporphyrins are a class of compounds in which various metals such as cobalt, zinc, manganese, chromium, or tin replace the central iron in heme [Drummond, 1987]. These metalloporphyrins can act as competitive inhibitors of the HO reaction because they bind inefficiently to molecular oxygen, so HO is prevented from degrading the metalloporphyrins [Drummond, 1987].

Antitumor and chemosensitizing effects of metalloporphyrin-type HO inhibitors such as zinc protoporphyrin (ZnPP) and cobalt protoporphyrin have been demonstrated in cultured tumor cells and in animal models [Doi et al., 1999; Fang et al., 2003, 2004b; Liu et al., 2011; Tanaka et al., 2003]. Combining chemotherapeutic agents such as camptothecin, doxorubicin, arsenic trioxide, gemcitabine, and imatinib, as well as irradiation, with ZnPP or related inhibitors may lead to improved antitumor treatment [Fang et al., 2004b; Gleixner et al., 2009; Liu et al., 2011; Mayerhofer et al., 2008; Miyake et al., 2010].

Polyethylene glycol-conjugated ZnPP (PEG-ZnPP) is a water-soluble derivative of ZnPP (Fig. 3) [Sahoo et al., 2002]. PEG-ZnPP accumulates in solid tumor tissues after intravenous injection because of its unique ability to form micelles in aqueous media [Fang et al., 2003; Sahoo et al., 2002]. As evidenced by accumulation of PEG-ZnPP in tumors, tumor-targeted inhibition of HO activity may be achieved by using PEG-ZnPP, which induces apoptosis in solid tumors via induction of oxidative stress [Fang et al., 2003]. Potent synergistic activity was also observed when PEG-ZnPP was combined with antitumor agents [Fang et al., 2004b]. This combined treatment was tolerated well, with no evident signs of severe toxicity and no dose-limiting toxicity so far. These observations point to new applications of PEG-ZnPP in combination therapy with various anticancer agents as well as irradiation.



PEG-ZnPP (metalloporphyrin-type inhibitor)



2-[2-(4-Bromophenyl)ethyl]-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolane hydrochloride (imidazole-dioxolane-type inhibitor)

Fig. 3. Chemical structures of HO inhibitors used in combination with anticancer agents to treat tumors.

In addition to the metalloporphyrin-type HO inhibitors, non-porphyrin-based HO inhibitors have been developed (Fig. 3). Azalanstat, an imidazole-dioxolane compound, was produced as such an HO inhibitor [Vlahakis et al., 2005]. With azalanstat as the lead compound, so far

more than 100 imidazole-based compounds have been synthesized and their HO inhibitory activities evaluated [Kinobe et al., 2006; Roman et al., 2007; Vlahakis et al., 2005]. Some of these compounds are quite selective for HO-1, with selectivity indices greater than 300 relative to HO-2, a constitutive isoform of HO [Kinobe et al., 2008]. One recent study showed that the imidazole-based compound OB-24 exhibited potent antitumor activity in a hormone-refractory prostate cancer model, especially in combination with paclitaxel [Alaoui-Jamali et al., 2009], which suggests that additional investigations of this type of HO inhibitor and possible uses for tumor chemosensitization are warranted.

Chapter summary

- Drug resistance is a major cause of treatment failure in patients with malignant gliomas.
- Multiple mechanisms may be involved in the development of drug resistance in gliomas, including augmented DNA repair enzyme activities, overexpression of antiapoptotic proteins and ABC transporters, whereas detailed mechanisms remain unknown.
- Heme oxygenase-1 (HO-1), a rate-limiting enzyme for heme degradation, may contribute to the development of chemoresistance in gliomas, via inducing gene expression of antioxidant, antiapoptotic, cytoprotective enzymes and drug transporters.
- Nitric oxide, reactive oxygen species, and their down stream electrophilic second messengers such as nitrated cyclic nucleotide play crucial roles in HO-1 expression via activation of redox-sensitive transcriptional factor (Nrf2).
- HO inhibitors exhibit potential to sensitize tumor cells against chemotherapy.

5. Conclusion

This chapter describes induction mechanisms of the antioxidant adaptive response in gliomas. Nrf2 stabilization may be induced by post-translational cysteine modification of Keap1, which is a repressor of Nrf2, under conditions of excess production of NO and ROS. 8-Nitro-cGMP is a newly discovered second messenger for NO and ROS signaling that can induce *S*-guanylation of Keap1 in glioma cells. *KEAP1* gene silencing via promoter methylation is an alternative mechanism that may contribute to constitutive Nrf2 stabilization. Activation of Nrf2 signaling leads to the expression of genes encoding phase II detoxifying or antioxidant enzymes as well as other cytoprotective proteins. Among these enzymes, HO-1 is known as a strong antioxidant and antiapoptotic enzyme that protects cells from oxidative stress-related injury. Many studies have shown that inhibition of HO-1 activity, by using either siRNA or HO-1 inhibitors, is a promising strategy for chemosensitization of cancer cells. In addition to direct antioxidant actions of HO-1, which support cancer cell growth as discussed in this chapter, HO-1 expression may contribute to the growth of gliomas by facilitating neovascularization via a vascular endothelial growth factor-dependent mechanism [Morita et al., 2009; Nishie et al., 1999]. HO-1 expression is also correlated with progression of gliomas, possibly through FoxP3-mediated T cell immune suppression [Deininger et al., 2000; El Andaloussi & Lesniak, 2007]. Improved understanding of the mechanisms mediating the Keap1/Nrf2-HO-1 antioxidant response and regulation by 8-nitro-cGMP and its downstream signaling cascade is necessary for development of chemotherapeutic drugs that will target malignant gliomas.

6. Acknowledgment

We thank J.B. Gandy for excellent editing of the manuscript.

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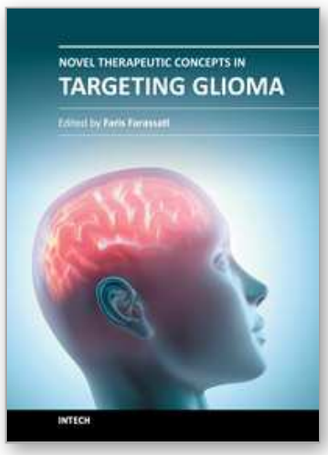
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Edited by Prof. Faris Farassati

ISBN 978-953-51-0491-9
Hard cover, 306 pages
Publisher InTech
Published online 04, April, 2012
Published in print edition April, 2012

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Tomohiro Sawa and Takaaki Akaike (2012). Antioxidant Adaptive Response of Malignant Glioma Related to Resistance to Antitumor Treatment, Novel Therapeutic Concepts in Targeting Glioma, Prof. Faris Farassati (Ed.), ISBN: 978-953-51-0491-9, InTech, Available from: http://www.intechopen.com/books/novel-therapeutic-concepts-in-targeting-glioma/antioxidant-adaptive-response-of-malignant-glioma-related-to-resistance-to-antitumor-treatment

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