Heme Oxygenase-1 in Central Nervous System Malignancies

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Central nervous system tumors are the most common pediatric solid tumors and account for 20–25% of all childhood malignancies. Several lines of evidence suggest that brain tumors show altered redox homeostasis that triggers the activation of various survival pathways, leading to disease progression and chemoresistance. Among these pathways, heme oxygenase-1 (HO-1) plays an important role. HO-1 catalyzes the enzymatic degradation of heme with the simultaneous release of carbon monoxide (CO), ferrous iron (Fe2+), and biliverdin. The biological effects of HO-1 in tumor cells have been shown to be cell-specific since, in some tumors, its upregulation promotes cell cycle arrest and cellular death, whereas, in other neoplasms, it is associated with tumor survival and progression. Since HO-1 overexpression is involved in the development and resistance of brain tumors to chemotherapy and radiotherapy, further researchers are needed to evaluate the possible use of HO-1 as a strategy to improve the outcome of well-established therapeutic regimens.

1. Introduction

Malignancies of the central nervous system (CNS) include neoplasia developing in the brain, spinal cord, and sellar region. Cancer cells display an altered metabolism, generally associated with an increase in reactive oxygen species (ROS) and altered redox balance resulting in cellular adaptation and proliferation. Resistance to oxidative stress is one of the major adaptive advantages, allowing cancer cells to increase their metabolic rate and proliferation and to survive free radical damage. Such an adaptive response to high doses of ROS is also linked to genetic modifications, which directly or indirectly modulate ROS. One of the master regulators of the antioxidant response is the nuclear factor erythroid 2 p45-related factor 2 (Nrf2). In general, the biochemical mechanism through which Nrf2 confers protection or resistance (in the case of cancer cells) provides that in response to toxic stimuli, Nrf2 is released from Keap1 in the cytosol and translocates to the nucleus where Nrf2 binds to antioxidant response elements (ARE). In this way, Nrf2 induces the expression of several antioxidant and detoxifying enzymes, i.e., γ-glutamate-cysteine ligase (γ-GCL), glutathione peroxidase (GPx), glutathione reductase (GR), NAD(P)H quinone dehydrogenase 1 (NQO1), and heme oxygenase-1 (HO-1)

HO-1 is significantly increased in various human tumors both in basal condition and during different anticancer therapies contributing, together with its by-products, to the development of a resistant phenotype. In this regard, it is important to take into due account the existence of a link among Nrf2, ROS, HO-1, and p53 as the main transcription factor playing a role during cell stress response, senescence, apoptosis, and carcinogenesis.

The aim of the present review is to summarize the role of the HO system and its related proteins in brain cancer, also evaluating how these proteins can improve cancer prognosis and therapies.

2. Biochemical Pathway of HO-1 in the Chemoresistance and Progression of Cancer

Several studies show that HO-1 plays a protective role in chemoresistance and tumor progression through the induction of endoplasmic reticulum stress (ER stress), autophagy, activation of MAPK kinases, and through the increase of macrophage infiltration. All these mechanisms offer the cell shelter from ROS damage and protein misfolding, making these cells much more resistant to damage. Although it has been demonstrated that HO-1 overexpression is opposed to the therapeutic strategies implemented by proteasome inhibitors (PI), several studies demonstrated that the inhibition of HO activity significantly improved the proapoptotic effect of PI and resulted in a significant reduction of the dose of PI. Indeed, the biological effect of HO-1 in cancer cells seemed to be involved both in cycle arrest and/or death and tumor survival and progression.

3. Embryonal Tumors
3.1. Neuroblastoma

Neuroblastoma (NB) is a pediatric solid cancer that often affects infants having an age between 0 to 4 years, with a median age of 23 months [39]. NBs present mass lesions in the neck, chest, abdomen, or pelvis and generally have a fatal prognosis [31][32]. In line with previous studies, our findings demonstrated that the silencing of HO-1 with a novel non-competitive inhibitor (LS1/71) makes SH-SYSY NB cells more sensitive to carbifilzomb (CFZ). Interestingly, CFZ treatment also induces the ERK and JNK signal transduction pathways, promoting cell proliferation and decreasing apoptosis rate. By contrast, LS1/71 was able to counteract these effects inhibiting ERK and JNK phosphorylation [24]. Furthermore, several studies demonstrated that miR-494, involved in HO-1 induction and cell responsive to oxidative stress, is expressed in NB cells [39]. Fest et al. tested the effect of HO-1 inhibition on NB progression in an in vivo model using A/J mice (H2-KK), which were treated with a sublethal subcutaneous dose of NXS2 cells and then ZnPPIX or sodium chloride were administered before surgery. HO-1 inhibition significantly reduced tumor growth, volume and liver metastasis, and induced apoptosis, decreasing Bcl2 and Bcl-Xl levels. Moreover, HO-1 inhibition stimulated immune cells to attack tumors promoting NXS2 cell lyse [38]. Conversely, several studies proposed HO-1 overexpression as a potential treatment for NB [39]. Accordingly, Hayama et al. demonstrated that through HO-1 induction, ferrearin-type neolignans cause apoptotic activity in human IMR-32, LA-N-1, NB-39, and SK-N- SH cell lines [49]. This effect is related to the CO produced by HO-1 that stimulates p38-MAPK and the JNK pathway, inducing BAX overexpression and apoptosis [41].

3.2. Medulloblastoma

Medulloblastoma is characterized by a significant burden of adverse outcomes in survivors [43]. Traditional genetic analysis suggests that isochromosome 17q, which results in the loss of 17p and the gain of 17q, represents the most common aberration in medulloblastomas [44][45][46]. Therapeutic strategies for medulloblastoma include a combination of surgery, radiotherapy, and chemotherapy [45][47]. Although HO-1 and HO-2 expression also showed no significant association with the different medulloblastoma subtypes, patients with high HO-1 and low HO-2 expression have better survival [48]. Moreover, HO-1 induction played a cytoprotective role against oxidative stress in DAOY cells exposed to the CO donor, suggesting HO-1 as a pharmacological target to enhance the efficacy of radiotherapy or chemotherapy [49][50].

3.3. Meningiomas

Meningioma is a common tumor of the central nervous system affecting the meninges, classified as Grade I, Grade II or “atypical”, and Grade III or “anaplastic” [51][52]. Genetic alterations, such as mutation or loss of the tumor suppressor gene neurofibromatosis 2 (NF2) on chromosome 22, constitute a leading cause of about 50% of meningiomas [53][54]. Current guidelines suggested surgery followed by radiotherapy as treatment of choice for intracranial meningiomas [55][56]. A study conducted by Takahashi et al. showed that HO-1 induction in rat KMY-J cells treated with TS-PDT (photodynamic therapy using talaporfin sodium) may contribute to resistance in meningioma cells, also attenuating its therapeutic effect. In particular, the mRNA expression level of Hmox1 was significantly increased, and this effect was counteracted when a study conducted by Takahashi et al. showed that HO-1 induction, ferrearin-type neolignans cause apoptotic activity in human IMR-32, LA-N-1, NB-39, and SK-N- SH cell lines [49]. This effect is related to the CO produced by HO-1 that stimulates p38-MAPK and the JNK pathway, inducing BAX overexpression and apoptosis [41].

4. Diffuse Astrocytic and Oligodendroglial Tumors

Gliomas, the most common group of primary brain tumors, include astrocytoma, oligodendroglioma, ependymoma and glioblastoma multiforme [15].

4.1. Astocytoma

Astrocytomas are most frequently caused by several chromosomal alterations, such as trisomy or polysomy of chromosome 7 [59][59]. Several lines of evidence suggested that HO-1 expression was involved in a worse prognosis of patients with Grades II and III astrocytomas, suggesting a pro-tumoral role of HO-1 in glioma progression [61].

4.2. Oligodendroglioma

Oligodendroglial tumors- oligodendrogliomas and oligoastrocytomases- are caused by the loss of heterozygosity (LOH) for chromosome arms 1p and 19q, which, in turn, derive from a non-balanced translocation t (1:19) (q10: p10) [62][63][64]. In high-grade gliomas, HO-1-expressing macrophages are higher in areas of solid tumor growth and decrease with
increasing tumor distance, suggesting HO-1 accumulation as an indicator of neoangiogenesis in hypoxic areas. Furthermore, HO-mediated heme degradation is involved in cellular CO production, inducing angiogenesis and neoplastic growth.

### 4.3. Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is the most aggressive glioma grade which is divided into primary and secondary subgroups according to clinical characteristics, most frequently caused by the amplifications of the EGFR gene on chromosome 7, or mutations in the TP53 or in the retinoblastoma (RB1) pathways. Both in vitro and in vivo studies have reported the role of Nrf2 in blocking the proliferation of human glioma, confirming its role in maintaining self-renewal in GSCs. Moreover, HO-1 could be considered a potential target to counteract both initial and metastatic grade tumor growth. In fact, when HO-1 is not expressed, the GBM cell invasion is inhibited. The expression of HO-1 was also directly correlated with FoxP3, a marker of regulatory T-cells (Treg), and tumor growth. Indeed, Treg progressively infiltrates gliomas with an increase in brain tumor grade, determining an immunosuppressive environment. Furthermore, GBM cells display a hypoxia-dependent differential modulation of biliverdin reductase (hBVR), increasing its expression and promoting cell survival under hypoxic states.

### 5. HO-1 Inhibitors and Their Potential Use in the Treatment of CNS Malignancies

The promising ways of HO-1 inhibition are founded on the genetic inhibition of HMOX1 by silencing RNA, on the use of metalloporphyrins (zinc protoporphyrin-ZnPPIX, tin protoporphyrin -SnPPIX, or chromium protoporphyrin-CrPPIX) and on the use of imidazole-based compounds. Many of the inhibitors used in medical research, in addition to having a competitive interaction with HO-1, are non-specific because they also inhibit HO-2, the constitutive isoform. Moreover, imidazole-based compounds - also used in combination with other chemotherapeutic drugs - are characterized by a non-competitive binding mode showing high selectivity enzymatic activity inhibition of HO-1 with respect to HO-2.

### 6. Conclusion

Table 1 reported a list of CNS tumors in which HO-1 is associated with an arrest in cell cycle division and subsequent cellular death or tumor survival and progression. In order to confirm the role of HO-1 as a possible molecular target for brain cancer, further research should be performed. In conclusion, understanding the mechanisms related to the HO-1 system may offer an additional target for future therapies and ameliorate oncological patients’ outcomes.

### Table 1. List of studies carried out in CNS tumors in which HO-1 expression was analyzed. The table shows tissues or cell lines, HO-1 expression, treatments, and outcomes with relevant references.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Cell line</th>
<th>HO-1 Expression</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NB</td>
<td>HTLA-230</td>
<td>↓</td>
<td>BTZ</td>
<td>Apoptosis</td>
<td>[33][34]</td>
</tr>
<tr>
<td>NB</td>
<td>GI-ME-M</td>
<td>↓</td>
<td>Etoposide</td>
<td>Apoptosis</td>
<td>[35]</td>
</tr>
<tr>
<td>NB</td>
<td>SH-SY5Y</td>
<td>↓</td>
<td>CFZ</td>
<td>Apoptosis</td>
<td>[36]</td>
</tr>
<tr>
<td>NB</td>
<td>SH-SY5Y; SK-N-BE</td>
<td>↓</td>
<td>H_{2}O_{2}</td>
<td>↓ Viability</td>
<td>[35][37]</td>
</tr>
<tr>
<td>Cell Line</td>
<td>Treatment</td>
<td>Effect</td>
<td>Molecular Mechanism</td>
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<tr>
<td>A/J Mice (H&lt;sup&gt;2&lt;/sup&gt;-K&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>↓ NXS2</td>
<td>↓ Tumor growth, volume, and metastasis</td>
<td><a href="#">38</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMR-32; SK-H-SH</td>
<td>↑↑↑ WA</td>
<td>Ferroptosis</td>
<td><a href="#">39</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMR-32; LA-N-1; NB-39; SK-N-SH</td>
<td>↑ Ferrearin-type neolignans</td>
<td>Apoptosis</td>
<td><a href="#">40</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMR-32; LA-N-1</td>
<td>↑ VK3-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>G2/M cell cycle arrest, apoptosis</td>
<td><a href="#">41</a></td>
<td></td>
<td></td>
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<tr>
<td>Resected specimens</td>
<td>↑</td>
<td>Protect tumor cells</td>
<td><a href="#">42</a></td>
<td></td>
<td></td>
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<tr>
<td>DAOY</td>
<td>↑ ROS</td>
<td>↑ Viability</td>
<td><a href="#">43</a></td>
<td></td>
<td></td>
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<tr>
<td>KMY-J</td>
<td>↓ TS-PDT</td>
<td>↓ Viability</td>
<td><a href="#">44</a></td>
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<td></td>
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<tr>
<td>Sample from Biorepository</td>
<td>↑</td>
<td>Worse prognosis</td>
<td><a href="#">45</a></td>
<td></td>
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<tr>
<td>rat intracranially transplanted C6 gliomas and Resected specimens</td>
<td>↑</td>
<td>Macrophage infiltration, tumor growth and angiogenesis</td>
<td><a href="#">46</a></td>
<td></td>
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<tr>
<td>Primary GBM cell</td>
<td>↓</td>
<td>Inhibits GBM cell invasion</td>
<td><a href="#">47</a></td>
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<tr>
<td>U251</td>
<td>↓</td>
<td>Apoptosis</td>
<td><a href="#">48</a></td>
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<tr>
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<td>↓ ATO</td>
<td>Apoptosis</td>
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<tr>
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<td>↑ Treg infiltration</td>
<td><a href="#">50</a></td>
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<tr>
<td>U87MG</td>
<td>↑ 35G8</td>
<td>Autophagy and ferroptosis</td>
<td><a href="#">51</a></td>
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References


**Keywords**

Brain cancer; Oxidative stress; Heme oxygenase-1

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