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Lipid peroxidation in brain tumors

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ABSTRACT

There is a lot of evidence showing that lipid peroxidation plays very important role in development of various diseases, including neurodegenerative diseases and brain tumors. Lipid peroxidation is achieved by two main pathways, by enzymatic or by non-enzymatic oxidation, respectively. In this paper, we focus on non-enzymatic, self-catalyzed chain reaction of poly-unsaturated fatty acid (PUFA) peroxidation generating reactive aldehydes, notably 4-hydroxynonenal (4-HNE), which acts as second messenger of free radicals and as growth regulating factor. It might originate from astrocytes as well as from blood vessels, even within the blood-brain barrier (BBB), which is in case of brain tumors transformed into the blood-brain-tumor barrier (BBTB). The functionality of the BBB is strongly affected by 4-HNE because it forms relatively stable protein adducts thus allowing the persistence and the spread of lipid peroxidation, as revealed by immunohistochemical findings. Because 4-HNE can act as a regulator of vital functions of normal and of malignant cells acting in the cell type- and concentration-dependent manners, the bioactivities of this product of lipid peroxidation be should further studied to reveal if it acts as a co-factor of carcinogenesis or as natural factor of defense against primary brain tumors and metastatic cancer.

Abbreviations

2-HHE	2-hydroxyhexanal
4-HNE	4-hydroxynonenal
AA	arachidonic acid
AKR	aldo-keto reductases
ALA	alpha-linolenic acid
ALDH	aldehyde dehydrogenases
ATP	Adenosine triphosphate
BBB	blood-brain barrier
BBTB	blood-brain-tumor barrier
CAT	catalase
CNS	central nervous system
COX	cyclooxygenase
CYP450	cytochrome p450
DAB	3,3′-diaminobenzidine staining
DHA	docosahexaenoic acid
EGFR	Epidermal growth factor receptor
ERK	extracellular signal-regulated kinase
GPX	glutathione peroxidase
GSH	glutathione
GSSG	oxidized glutathione
HPODE	hydroperoxy octadecadienoates
L$^{\bullet}$	carbon-centered lipid radical
LA	linoleic acid
LL	lipid dimer
LO$^{\bullet}$	lipid alkoxyl radical
LOO$^{\bullet}$	lipid peroxyl radical
LOOH	lipid hydroperoxide
LOX	lipoxygenase
MDA	malondialdehyde
MMPs	matrix metalloproteinases
MRI	magnetic resonance imaging
NMDA	N-methyl-d-aspartate
NOX	nitric oxide system
NRF2	Nuclear Factor, Erythroid 2 Like 2
PUFA	poly-unsaturated fatty acid
ROS	reactive oxygen species

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SOD	superoxide dismutase
TBARS	thiobarbituric acid reactive substance
TIGAR	TP53 induced glycolysis regulatory phosphatase
TMZ	temozolomide

1. Introduction

The brain is a highly metabolically active organ, which requires about one fifth of total body oxygen consumption (Rink and Khanna, 2011). Consequently, oxidative metabolism of the brain results in continuous production of large amounts of reactive oxygen species (ROS), which are generated mostly by mitochondria. While ROS are needed for normal cognitive functions (Massaad and Klann, 2011), they are produced mostly by activated microglia and astrocytes (Lopez-Fabuel et al., 2016; Pawate et al., 2004). Hence, ROS are involved in numerous processes in the brain, modulating signal transduction and gene expression of neurons, defensive activities of the glial cells and communication between neurons and glia (Atkins and Sweatt, 1999).

Furthermore, ROS promote S-glutathionylation of ryanodine receptor, resulting in Ca^{2+} release and phosphorylation of the extracellular signal-regulated kinase (ERK) and the cAMP-response element-binding protein (CREB), thus contributing to hippocampal synaptic plasticity (Kemmerling et al., 2007). While ROS are involved in N-methyl-d-aspartate (NMDA) receptor signaling and function, excessive ROS are neurotoxic and may impair normal functions central nervous system (CNS), induce genetic alterations and promote brain tumorigenesis (Rinaldi et al., 2016). Under stressful conditions ROS upregulate NMDA receptor and may lead to glutamate induced blood-brain barrier (BBB) disruption (Betzen et al., 2009; Gao et al., 2007). In recent years, several excellent reviews on the roles of ROS in both physiology and pathology of the brain (Beckhauser et al., 2016; Salazar-Ramiro et al., 2016), including the chemistry of ROS have been published (Collin, 2019).

Delicate control of the redox homeostasis in the brain is regulated both by enzymatic and by non-enzymatic antioxidant defense systems (Ramírez-Expósito and Martínez-Martos, 2019). Among the most relevant endogenous antioxidants are glutathione (GSH) system, thioredoxin system, superoxide dismutase (SOD) and catalase (CAT), while NRF2 (Nuclear Factor, Erythroid 2 Like 2) is a considered to act as key regulator of antioxidants. In a recent review, the involvement of antioxidant defense mechanisms, in particular, NRF2, thioredoxin and GSH systems in tumorigenesis has been described in depth suggesting that altered antioxidant defenses and deregulated redox homeostasis are important hallmarks of cancer development (Jaganjac et al., 2020b).

For many years ROS have been considered as important factors of carcinogenesis, especially in the tumor initiation and promotion phases (Betteridge, 2000; Halliwell and Gutteridge, 1999; Perchellet and Perchellet, 1989). The relationship between cancer and oxidative stress is mostly based on the fact that cancer cells are usually exposed to higher levels of oxidative stress than normal cells (Pervaiz and Clément, 2004). However, in vivo studies on experimental tumor models have demonstrated that the process of tumor development can be reversed or at least decelerated by moderate levels of ROS, while high levels of ROS can be mutagenic and promote tumorigenesis (Jaganjac et al., 2008, 2010, 2012b; Zivkovic et al., 2005, 2007). In addition, inflammation generating inflammatory mediators in the tumor microenvironment can direct the course of tumor development (Landskron et al., 2014). While acute inflammation and excessive ROS released by inflammatory cells can lead to the destruction of malignant cells, continuous generation of ROS during chronic inflammation targeting non-malignant cells can eventually contribute to the tumorigenesis. Our earlier studies showed that rapid infiltration of granulocytes at the site of tumor transplantation, followed by their oxidative burst caused tumor regression (Jaganjac et al., 2008), while a continuous release of ROS by granulocytes was accompanied by tumor progression. During chronic inflammation elevated ROS are generated by inflammatory cells and epithelial cells and may cause accumulation of macromolecular impairments resulting in mutations, altered signaling pathways and enhanced release of other inflammatory mediators. Hence, oxidative stress, chronic inflammation and tumor development may be considered as particularly vicious circle that has been described in more depth in several excellent reviews (Aggarwal et al., 2019; Prasad et al., 2017; Reuter et al., 2010).

Due to its high lipid and iron contents, abundant oxygen consumption and consequential ROS production, the brain is very susceptible to ROS-induced damage. Depending on the type of ROS produced, their reactivity, diffusion distance and the site of generation, ROS can affect different macromolecules (Jaganjac et al., 2016). Among the usual ROS targets are polyunsaturated fatty acids (PUFAs) that are highly susceptible to ROS induced damage at the bis-allylic site. Increased iron content in the brain can further promote the chain reactions of lipid peroxidation and have additional role in tumorigenesis, alongside with the cellular growth support (Jaganjac et al., 2020c). Increased lipid peroxidation is considered to be mutagenic and carcinogenic (Zhang et al., 2002). The most abundant long-chain PUFAs in the brain are arachidonic acid (omega-6, AA) and docosahexaenoic acid (omega-3, DHA), while linoleic acid (omega-6 PUFA, LA) and alpha-linolenic acid (omega-3 PUFA, ALA) are the main precursors for the synthesis of long-chain PUFAs. Final products of non-enzymatic peroxidation of these PUFAs are reactive aldehydes, which have longer half-life and spread much further than ROS, especially if bound to the (extra)cellular proteins. Therefore, in this review, special attention is given to relevance of lipid peroxidation in the pathogenesis of the brain tumors.

2. Lipid oxidation: enzymatic vs. non-enzymatic, self-catalyzed peroxidation chain reaction

Lipid peroxidation is achieved by two main pathways, either by enzymatic or by non-enzymatic oxidation.

The enzymatic oxidation is mediated by the action of peroxidases such are cyclooxygenase (COX), lipoxygenase (LOX), phospholipase A2, and cytochrome p450 (CYP450). LOX catalyzes the oxidation of LA yielding hydroperoxy octadecadienoates (HPODEs), while AA can be oxidized by several distinct enzymatic pathways. Oxidation of AA, via LOX and COX pathway, results in the formation of prostaglandins, thromboxanes, leukotrienes, lipoxins and hydroperoxyl eicosatetraenoic acid, while oxidation with CYP450 yields epoxyeicosatrienoic acid and 20-hydroxyeicosatetraenoic acid (Hanna and Hafez, 2018).

The bis-allylic site of PUFAs is prone to free radical or nonradical species induced damage-triggering non-enzymatic oxidation of lipids (Fig. 1). The abstraction of allylic hydrogen from PUFA initiates lipid peroxidation forming the carbon-centered lipid radical ($L^{\bullet}$). In the propagation phase of the chain reaction, $L^{\bullet}$ rapidly reacts with molecular oxygen leading to the generation of lipid peroxyl radical ($LOO^{\bullet}$). The $LOO^{\bullet}$ further abstracts hydrogen from the other unsaturated lipids yielding new $L^{\bullet}$ and lipid hydroperoxides (LOOH). Lipid peroxidation is terminated when protective molecules, like lipid soluble antioxidants, donate a hydrogen atom to $LOO^{\bullet}$, thus causing formation of less reactive ROS and eventually stable molecules (Fig. 1).

Oxygen free radical-mediated lipid peroxidation of LA, similarly to enzymatic, will give rise to HPODEs, which are further reduced to hydroxyoctadecanoic acids by glutathione peroxidase (GPX). Due to the presence of three double bonds, AA is more sensitive to the free radical attack and produces F2-isoprostanes and isoflurane, while oxidation of DHA yields neuroprostane compounds similar to isoprostanes (Shichiri, 2014).

Major end-products of lipid peroxidation are reactive aldehydes, such are 4-hydroxyalkenals, 2-alkenals and ketoaldehydes and other similar α,β-unsaturated aldehydes, represented by well-studied short-

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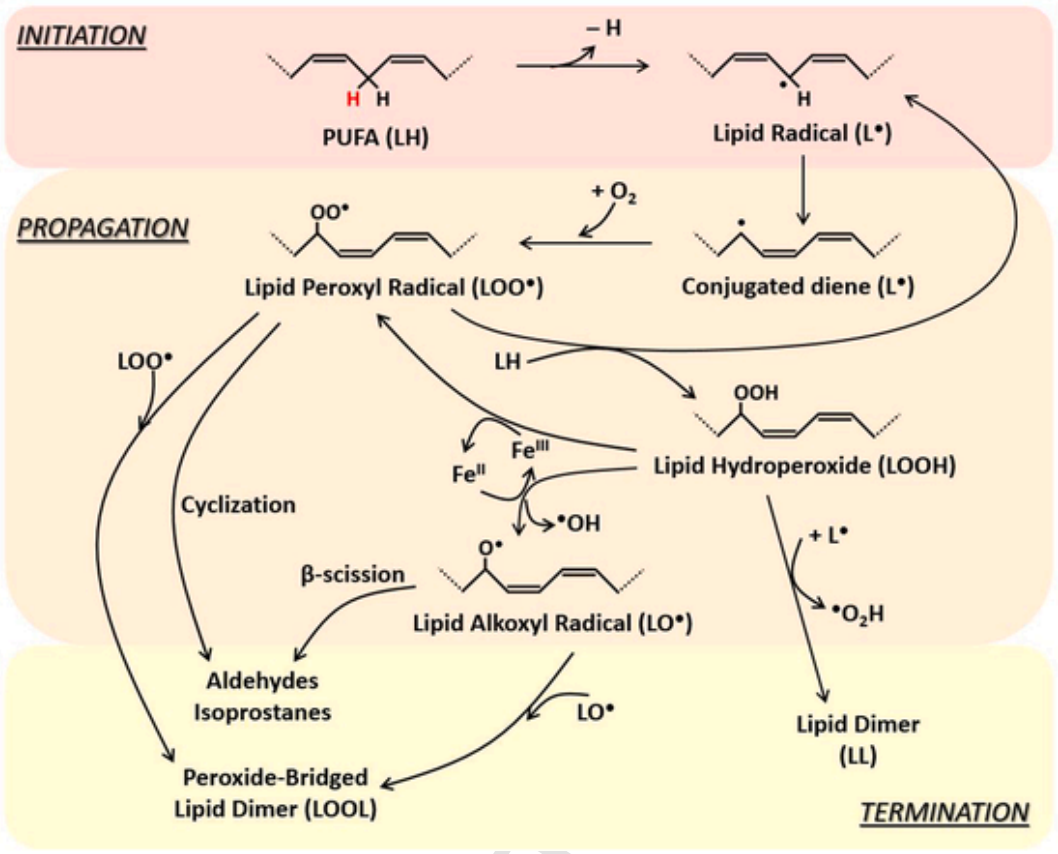

Fig. 1. Scheme of non-enzymatic lipid peroxidation.
The abstraction of allylic hydrogen (red) from PUFA leads to the formation of lipid radicals (L$^{\bullet}$) and initiates a chain reaction of lipid peroxidation. This is followed by molecular rearrangement yielding conjugated dienes, more stable lipid reactive oxygen species. In the presence of molecular oxygen, conjugated dienes are transformed to lipid peroxyl radical (LOO$^{\bullet}$), which can abstract allylic hydrogen from another PUFA leading to the formation of lipid hydroperoxide (LOOH) and another L$^{\bullet}$. The presence of free iron FeII and FeIII will further catalyze transformation of LOOH to lipid alkoxyl radical (LO$^{\bullet}$) and LOO$^{\bullet}$, respectively. Lipid peroxidation is terminated when non-radical products are formed due to interaction with (lipid soluble) antioxidants (such as tocopherol). The reaction between two LOO$^{\bullet}$ or two LO$^{\bullet}$ will result in the formation of peroxide-bridged lipid dimer, while LOOH can react with L$^{\bullet}$ forming lipid dimer (LL). Finally, further decomposition of LOOH or LOO$^{\bullet}$ will give rise to isoprostanes and bioactive, reactive aldehydes, represented by 4-HNE, acting as "second messengers of free radicals".

chain aldehydes 4-hydroxynonenal (4-HNE), malondialdehyde (MDA) and acrolein, among which biological importance of 4-HNE is the best recognized. The important signaling role of 4-HNE in both physiology and pathology is well documented especially also for the brain cells (Jaganjac et al., 2020a; K. K. Zarkovic, 2003; N. N. Zarkovic, 2003, Rojo et a. 2014). Biological activities of 4-HNE depend on its concentration and the affected cell type. At low concentrations, 4-HNE can modulate cell proliferation, differentiation, and cellular antioxidant capacities. Opposite to that, at high concentrations 4-HNE can induce cell death, either through apoptosis or necrosis. Due to its three functional groups, 4-HNE is highly reactive and can interact with proteins altering their structure and function (Zarkovic et al., 2013). In addition, 4-HNE is also binding to DNA, thus leading to adduct formation, which can induce altered expression of numerous genes and elicit mutagenic effects (Jaganjac et al., 2012a). Only a limited number of studies have investigated the involvement of 4-HNE in the brain tumorigenesis, while its appearance in human astrocytic tumors in situ was shown to be proportional to the level of malignancy of these tumors (Zarkovic et al., 2005). The in vitro analysis of the brain tumor models found 4-HNE and ROS able to induce expression of aldo-keto reductases (AKR) AKR1C, AKR1A1 and AKR7A2 in human astrocytoma c1321N1 cells, protecting them from 4-HNE and ROS induced cytotoxicity (Li and Ellis, 2012). Moreover, human glioblastoma ADF cells seem to be more resistant to ROS-induced stress if compared to the counterpart normal cells (Peroni et al., 2020). These glioblastoma cells have higher level of the NADP^{+}-dependent dehydrogenase, which catalyzes 3-glutathionyl-4-hydroxynonanal oxidation, thus contributing to cell detoxification by removal of the main 4-HNE metabolite (Moschini et al., 2015). Therefore, relative resistance of malignant astrocytic cells against the cytotoxicity of 4-HNE, seems to be different from the other types of malignant tumors that are usually more sensitive to the cytotoxic effects of 4-HNE than are the respective counterpart non-malignant cells (Borovic et al., 2007; Milkovic et al., 2015). That is one of important reasons which make glial tumors difficult to treat by therapies relying on oxidative stress (radiotherapy, several types of chemotherapy, photodynamic treatments, etc.).

3. The blood-brain barrier in glioma

Medicamentous treatment of any brain disease is difficult especially due to the specialized protective brain shield, notably the selectively permeable membrane denoted the blood-brain barrier (BBB). This complex structure builds its physical, transport and metabolic properties on fine cooperation of their main structural components - endothelial cells and their basement blood vessel membrane with surrounding astrocytes, pericytes and microglia (Abbott et al., 2006). Brain endothelial cells differ in several structural elements from endothelial cells of the rest of the body – they have the continuous belt of tight junctions, increased numbers of mitochondria and low pinocytic activity, but do not have fenestrations (Cardoso et al., 2010). These differences, together with the local microenvironment, contribute to the low permeability of BBB for majority of molecules, including chemotherapeutics. The base-

ment membrane of endothelial cells together with *glia limitans* close up a perivascular space and serve as a complex supportive network for the glial soluble factors that regulate BBB properties (Persidsky et al., 2006). In case of glioma development impairment of the BBB occurs primarily due to functional changes of the BBB and its microenvironment (Zhao et al., 2017). The development of glioma is accompanied by newly formed tumor microvessels, which form the blood-brain-tumor barrier (BBTB). This barrier is characterized by formation of fenestrations and alterations of the tight junctions, together with an increase of perivascular space proportional with the tumor grading (Wolburg et al., 2012) (Fig. 2). Consequently, BBTB loses characteristics of BBB and becomes leaky, leading to brain edema as can be seen on magnetic resonance imaging (MRI) (Arvanitis et al., 2020). The contrast medium, which is not able to cross the functional BBB, accumulates proportionally with the tumor grade and BBB disruption leading to the edema formation (Pronin et al., 1997). Hence, a strong correlation between microvascular permeability and the tumor grade may be observed by neuroradiological examination using contrast enhanced MRI (Roberts et al., 2000). One of two possible explanations of BBB breakdown in malignant glioma implies the angiogenesis process during glioma development and formation of BBTB. The other explanation considers degradation of tight junctions and basement membrane due to glioma secretion of different mediators of tumor progression and invasion upon oxidative stress induction, including ROS and proteolytic enzymes (Schneider et al., 2004). Furthermore, brain edema formation is associated with the upregulation of aquaporin-4 (Warth et al., 2007) accompanied with redistribution of aquaporin-4 from endfeet membranes to entire cell surface due to the loss of ECM protein agrin (Warth et al., 2004). A study on human brain glioma tissues has revealed that aquaporin-4 expression in peritumoral edematous tissues positively correlates with the edema index, while no correlation was found for tumor tissue (Mou et al., 2010). In vitro studies on LN229 human glioblastoma cells suggested the potential role of aquaporin-4 in the migration and invasion of glioblastoma (Ding et al., 2011). However, the exact function of aquaporin-4 in gliomas remains to be better studied.

Hyperactive nitric oxide system (NOX) in glioma generates increased levels of NO and ONOO being even further aggravated by the activation of microglia (Rojo et al., 2014; Song et al., 2020). Under such oxidative stress conditions, ROS and RNS activate numerous signaling pathways (PI3K/AKT, MAPK, AMPK), but also a plethora of redox sensitive transcription factors (NfκB, Nrf2, HIFα), thus inducing lipid peroxidation and production of reactive aldehydes subsequently leading to impairment of the BBB (Rinaldi et al., 2016; Schieber and Chandel, 2014; Song et al., 2020). Namely, ROS directly activate protein tyrosine kinase causing phosphorylation of the tight junction proteins and the activation of matrix metalloproteinases (MMPs) both leading to an increase of the BBB permeability (Haorah et al., 2007; Staddon et al., 1995). The MMPs degrade proteins of the extracellular matrix. The MMP-2 and MMP-9 are secreted by proliferating glioma endothelial cells, while the MMP-12 is upregulated by glioma cells (Wolburg et al., 2012). Furthermore, MMP-9 (Chen et al., 2011), ROS (Boonstra and Post, 2004) and 4-HNE (Suc et al., 1998) can all activate epidermal growth factor receptor (EGFR), which is the receptor crucial for normal cell growth and differentiation, thus affecting the EGF-related downstream pathways. In the case of glioblastoma, EGFR activation possibly serves the growth enhancement and protection as it leads to *de novo* lipogenesis and replacement of PUFA with highly saturated fatty acids thus reducing cytotoxicity of lipid peroxidation (McKinney et al., 2019; Rysman et al., 2010) and, at the same time, stimulating glioma proliferation (Taïb et al., 2019).

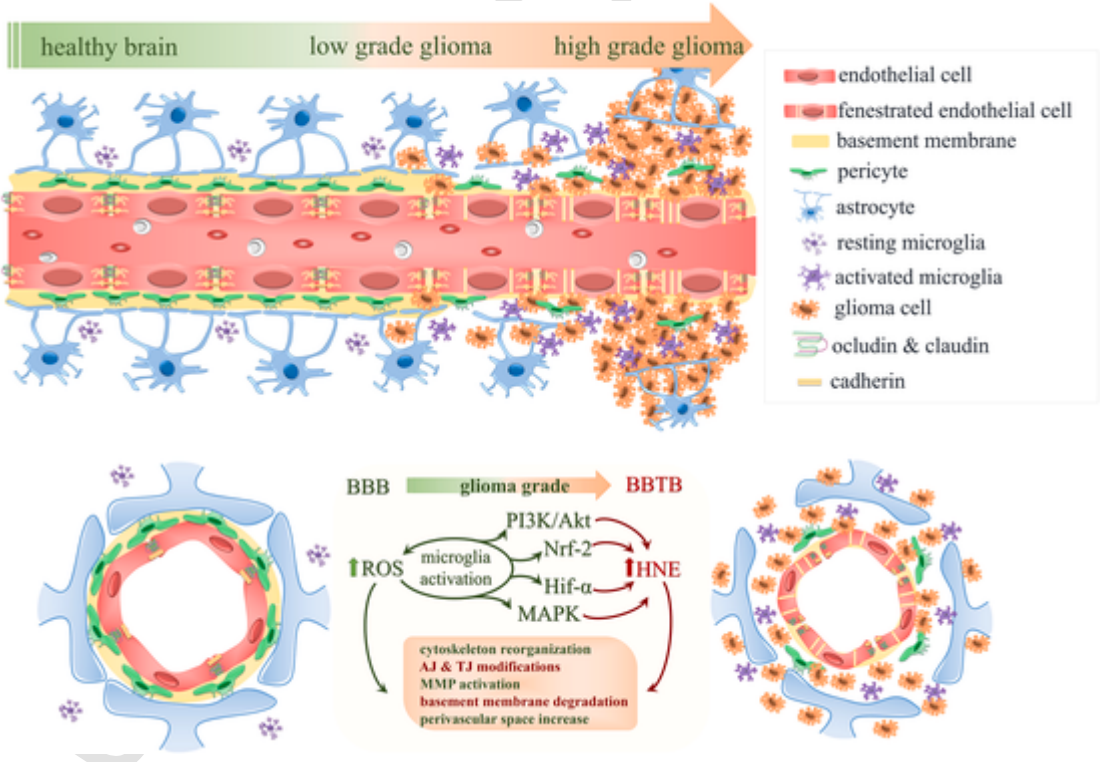

Fig. 2. Scheme of BBB and BBTB.
Transformation of the blood-brain barrier (BBB) to blood-brain tumor barrier (BBTB) correlates with tumor grading and includes alterations of tight and adherent junctions, formation of fenestrations, degradation of the basement membrane, perivascular space increase and detachment of glial end-feet. The VEGF induced angiogenesis in high grade gliomas results in leaky blood vessels and edema formation. Glioma induces ROS increase aggravated by microglia activation which further leads to activation of several signaling pathways (MAPK, PI3K/Akt) and redox sensitive transcription factors (Nrf-2, Hif-α). Consequently, lipid peroxidation increases and HNE accumulation together with ROS induce major structural changes that lead to BBB impairment. (AJ – adherent junctions; TJ – tight junctions; MMP – matrix metalloproteinases).

The presence of 4-HNE-protein adducts proportionally increasing with malignancy of astrocytoma was found both in tumor cells and in blood vessels suggesting their potential role in BBB regulation (Juric-Sekhar et al., 2009; Zarkovic et al., 2005). In favor of this assumption are several in vitro studies using different BBB models, which gave insights into possible 4-HNE roles in functionality of the BBB. Hence, 4-HNE was found first of all to act as a growth regulating factor and was detected immunohistochemically to be abundant within BBB under sepsis and ischemia of the brain, being even washed-out during reperfusion (Žarković et al., 1999). It was afterwards recognized as detrimental byproduct that increases the BBB permeability within several minutes after being used in vitro (Mertsch et al., 2001). The effects of 4-HNE on endothelial cells were recognized by later studies to vary from regulatory to devastating. As described by Chapple et al., 4-HNE can, by means of hormesis, modulate vascular functions (Chapple et al., 2013), thus maintaining redox balance targeting specific cellular pathways when present at physiological levels and provoking an adaptive response in case of high 4-HNE concentrations. In addition, low levels of 4-HNE can induce phosphorylation of p53 causing an increase in p53 protein (Sharma et al., 2008), which is a master regulator of numerous pathways including the cellular response to oxidative stress (Liu and Xu, 2011). The recent study demonstrated also that p53 has important role in supporting the BBB integrity by reducing oxidation of lipids (Akhter et al., 2019). However, too high levels of 4-HNE induce endothelial barrier dysfunction and activation of pro-inflammatory and pro-apoptotic signaling. Moreover, 4-HNE can inhibit endothelial cell proliferation, migration, and consequently angiogenesis in vitro through binding to proteins of extracellular matrix like fibronectin. Such 4-HNE-adducts can alter the expression of surface integrins (CD166, ICAM2, PECAM, integrin α5 and β1), of the adhesion molecules (cadherin-5, annexin A1) and of the growth factors/receptors (VEGFR, connective tissue growth factor, ephrin type-A receptor) (Xu et al., 2011). Furthermore, 4-HNE may affect endothelial barrier functions through activation of ERK, JNK and p38 proteins of MAPK signaling cascade. In such a way turn actin cytoskeleton rearrangement occurs (Usatyuk and Natarajan, 2004) that includes focal adhesion kinase, beta catenin, paxillin, VE-cadherin redistribution leading to formation of the intercellular disparities (Usatyuk et al., 2006). The formation of 4-HNE adducts with adherent and tight junction proteins, as well as integrins, contributes to the endothelial barrier dysfunction (Usatyuk et al., 2006). The 4-HNE also downregulates the expression of adhesion molecules ICAM-1, VCAM-1 and E-selectin (Pizzimenti et al., 2010). Additionally, through tyrosine kinase activation 4-HNE can stimulate phospholipase D (Natarajan et al., 1997), which is responsible for phospholipid signaling and reorganization of the cytoskeleton, membrane transport and signal transduction (Oliveira and Di Paolo, 2010). Even though all these studies emphasize 4-HNE role in BBB functioning, they have one major objection. Namely, they were done in vitro using models mainly build from only one type of cells, while complexity of the BBB and pluripotency of 4-HNE that can impact nucleic acids, proteins and lipids, require more complex model systems of the BBB or in vivo studies for more precise clarification of 4-HNE effects on the BBB.

4. Lipid peroxidation in primary brain tumors

The involvement of lipid peroxidation in primary brain tumors was first recognized more than 40 years ago. Since then, scientists are trying to elucidate its role in brain tumorigenesis. Studies, involving human samples are limited with the majority focusing on gliomas (Table 1). Based on the various types of glial cells from which glioma can originate, there are different types of gliomas, notably astrocytoma, oligodendroglioma and ependymoma. Until today, only a few studies investigated the involvement of lipid peroxidation in other primary brain tumors, like meningioma, craniopharyngioma and medulloblastoma, or in the secondary, metastatic brain tumors.

Table 1
Findings on involvement of lipid peroxidation in primary or metastatic brain tumors listed chronologically.

Author classification of tumor type (sample size)	Evidence of LPO and oxidative stress in human brain tumors	Reference
Astrocytoma, low-grade (8) Astrocytoma, high-grade (11) Glioblastoma (5) Astrocytoma, grade I-II (4) Astrocytoma, grade III and IV (30) Ependymoma (1) Meningioma (28) Acoustic neurinoma (17) Craniopharyngioma (7) Metastases (8) Lymphoma (3)	Low grade astrocytoma had higher GSH and TBARS compared to malignant lesions. This difference was particularly prominent at the tumor surface. Glioma, meningioma and acoustic neurinoma had elevated lipid peroxidation of erythrocytes as measured by TBARS assay, while only glioma had significantly increased levels of conjugated dienes in plasma compared to control and other tumor types. Erythrocyte TBARS and conjugated dienes did not significantly differ between benign and malignant brain tumors.	Louw et al. (1997) Rao et al. (2000)
Craniopharyngioma (55)	Lipid peroxidation and lactate accumulation is higher in craniopharyngiomas cyst fluid then in plasma.	Arefyeva et al. (2001)
Astrocytoma, high-grade (30) Glioma, low-grade (30) Nontumorous lesions (10) Healthy volunteers (28)	Patients with brain tumor have elevated MDA level in serum and tissue. The level of MDA correlated with the grade of tumor.	Cirak et al. (2003)
Brain tumor tissue (32) Normal tissue (19)	MDA and SOD levels were lower in tumor brain tissues compared to control tissue.	Popov et al. (2003)
Astrocytoma (45)	Presence of 4-HNE protein adducts in tumor cells correlated with the degree of tumor malignancy. The presence of 4-HNE protein adducts was lowest in diffuse astrocytoma and located mainly around blood vessels, compared to anaplastic astrocytoma and glioblastoma where 4-HNE protein adducts were diffusely distributed.	Zarkovic et al. (2005)
Glioma (21) Meningioma (14) Healthy volunteers (11)	MDA, catalase and GPX activity are elevated in serum of patients with brain tumors. No difference between tumor types was observed.	Yilmaz et al. (2006)
Astrocytoma (26)	The levels of 4-HNE, 2-HHE and histone H3 mRNA correlated with the pathological grade of astrocytoma. Poorer prognosis was observed for patients with high 4-HNE, 2-HHE and low n-hexanal.	Zajdel et al. (2007)
Glioblastoma (9) Astrocytoma (15) Healthy volunteers (20)	Patients with brain tumor have elevated activities of SOD and CAT in erythrocytes and elevated MDA in both plasma and erythrocytes compared to healthy volunteers. However, no differences were observed in respect to tumor type or surgery.	Woźniak et al. (2007)
Glioblastoma (29) Astrocytoma, high-grade (8) Astrocytoma, low-grade (8)	Carnitine levels increased with the grade of malignancy. Strong positive correlation between MDA and C20:4 carnitine levels was observed for glioblastoma samples.	Bayraktar et al. (2008)
Glioma, low-grade (42) Paired peritumoral region (22)	MDA and catalase levels are higher in peripheral zone of the tumor compared to central area of tumor. However, no significant differences are observed for SOD and GPX.	Lamari et al. (2008)

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Table 1 (*continued*)

Author classification of tumor type (sample size)	Evidence of LPO and oxidative stress in human brain tumors	Reference
Glioma, grade II-IV (6)	COX activity is decreased while GSH and MnSOD activity are increased in central region of gliomas compared to peripheral regions. TBARS, GSSG, GPX, GRd, SOD, protein carbonyls and level of oxidized mtDNA did not significantly differ between regions. In addition, peripheral mitochondria had greater H2O2 production capacity compared to central mitochondria.	Santandreu et al. (2008)
Glioblastoma (30) Astrocytoma, grade I-III (90) Ependymoma (30) Ependymoma, anaplastic (10)	Presence of 4-HNE protein adducts in tumor cells correlates with the degree of tumor malignancy. The highest expression of 4-HNE protein adducts is found in glioblastoma. Presence of 4-HNE protein adducts in microvessels of endothelium and walls of tumor cells correlated with the grade of malignancy.	Juric-Sekhar et al. (2009)
Astrocytoma (16) Meningioma (14) Metastases (11) Other brain tumor types (13)	Tumor tissues have decreased enzymatic and non-enzymatic antioxidants and increased LPO compared to peritumoral tissues. Higher grade tumors had higher LPO and GSH, GR and SOD were decreased compared to low grade tumors. The highest LPO levels were detected in astrocytoma, followed by metastatic tumor, meningioma and the lowest was recorded for other brain tumors.	Zengin et al. (2009)
Glioblastoma (25) Normal tissue (15)	SOD is decreased, while MPO, 3-nitrotyrosine and TBARS level is increased in tumor tissues compared to control.	Atukeren et al. (2010)
Anaplastic glioma (14) Benign astrocytoma (16) Metastases of breast cancer (15) Metastases of lung cancer (14) Metastases of kidney cancer (13) Metastases of skin melanoma (16)	SOD activity was elevated in malignant gliomas and metastases. Skin melanoma metastases showed approximately 60% higher SOD activity compared to malignant gliomas, while other brain metastases had SOD activity similar to malignant gliomas. MDA level was 2-fold increase in malignant gliomas and 3.5-fold increase in brain metastases.	Sidorenko et al. (2011)
Glioblastoma (30)	4-HNE protein adducts were detected in all samples. This study also demonstrated co-expression of 4-HNE and CD133.	Kolenc et al. (2011)
Meningioma (20) Glioma, low-grade (19) Glioma, high-grade (20) Normal tissue (15)	Advanced oxidation protein products and MDA were increased in tumor tissues while antioxidant capacity was decreased compared to control samples. In addition, high grade gliomas also had significantly increased levels of lipid hydroperoxides.	Atukeren et al. (2017)
Glioblastoma (51) Paired tumor samples after EGFR inhibitor therapy (21)	Aldehyde dehydrogenase ALDH1A1 is expressed in almost 70% of glioblastoma at initial diagnosis but at low level. EGFR inhibitor therapy induced ALDH1A1 levels in tumors with EGFR amplification.	McKinney et al. (2019)
Glioblastoma, primary resections (56) Glioblastoma, secondary resections (56)	Aldehyde dehydrogenase ALDH1A3 expression is elevated in the recurrent glioblastoma compared to expression of respective primary tumors. Higher ALDH1A3 expression correlates with poorer survival.	Wu et al. (2020)
Medulloblastoma (11) Teratoid rhabdoid (4) Ependymoma, grade II and III (4) Astrocytoma (10) Other brain tumors, grade I (5)	MDA was elevated in cerebrospinal fluid before mass debulking compared postoperative samples, however no correlations were noticed in respect to tumor type. MDA in plasma did not correlate with MDA levels in cerebrospinal fluid.	Piastra et al. (2020)

Although some earlier studies reported controversial findings on lipid peroxidation in tumor tissues when compared to the normal brain tissues (Louw et al., 1997; Popov et al., 2003), nowadays most of the studies agree that the presence of lipid peroxidation correlates with the histopathological grade of brain tumor and that incidence of lipid peroxidation is accompanied by altered antioxidant defense systems. Amid the lipid peroxidation markers investigated in brain tumors or biological fluids of brain tumor patients the major are 4-HNE, MDA, 2-hydroxyhexanal (2-HHE) and conjugated dienes (Table 1).

Studies done by our group and others have shown that 4-HNE level is increased in brain tumors (Fig. 3), proportional with the grade of tumor malignancy and is, therefore, associated with poorer prognosis (Juric-Sekhar et al., 2009; Zajdel et al., 2007; Zarkovic et al., 2005). We revealed the presence of 4-HNE-protein conjugates in the endothelium of microvessels within the brain tumors that also correlates with the tumor malignancy, as does the appearance of 4-HNE in the tumor cells themselves (Juric-Sekhar et al., 2009). Moreover, we found co-expression of 4-HNE and CD133 in glioblastomas (Kolenc et al., 2011), suggesting possible importance of 4-HNE for the growth of malignant stem cells of the brain tumors, for which CD133, denoted also as prominin-1, was identified as a surface marker (Singh et al., 2003). The above studies on the 4-HNE in primary brain tumors and the fact that 4-HNE is a pluripotent bioactive molecule, as described above, suggests its important role in the brain tumorigenesis. That is further stressed by the most recent findings showing that the aldehyde dehydrogenases (ALDH), which are enzymes involved in 4-HNE metabolism, are elevated in recurrent glioblastoma (Wu et al., 2020) and glioblastoma with EGFR amplification occurring after EGFR inhibitor therapy (McKinney et al., 2019).

These findings could be of clinical relevance because ALDH1A3-positive cells are less sensitive to temozolomide (TMZ) treatment, while patients suffering from glioblastoma with high ALDH expression have worse survival duration (Wu et al., 2020). Depletion of ALDH1A3 in human glioblastoma LN229, U87MG and T98G cells leads to increased autophagy after TMZ treatment and promotes lipid peroxidation, while the addition of N-acetylcysteine neutralizes these effects (Wu et al., 2020). The results of the same study also revealed close co-localization of ADLH1A3, p62 and 4-HNE-modified proteins, supporting assumed interactions of 4-HNE and ALDH1A3 in autophagy. Moreover, if present at low concentrations 4-HNE can reversibly inhibit the ALDH enzymes, while at high concentrations 4-HNE irreversibly inhibits ALDH enzymes thus reducing its own cleavage and the metabolism of reactive aldehydes in general (Doorn et al., 2006).

The TP53-induced glycolysis and apoptosis regulator (TIGAR) is another enzyme found to be upregulated in glioblastoma that closely correlates with poor survival of patients (Tang and He, 2019). It was shown experimentally that the TIGAR knock-down leads to decreased NADPH and consequently decreased reduction of the oxidized glutathione (GSSG) to GSH, leading to increased ROS production and lipid peroxidation. The TIGAR also induces AKT activation, inhibits apoptosis, promotes proliferation and metastasis in U-87MG cells, which could together with its role in maintaining oxidation resistance promote tumorigenesis of glioblastoma (Tang and He, 2019). Furthermore, α-synuclein is a protein commonly present in various brain tumors (Kawashima et al., 2000), which can be present in oligomeric form that induces ROS formation, oxidizes ATP synthase altering the efficiency of ATP production and also promotes lipid oxidation (Ludtmann et al., 2018). Eventually, it should be mentioned that depending on the concentration of 4-HNE and duration of the cellular exposure to it, 4-HNE can modulate mitochondrial metabolism leading even to the mitochondrial leakage and severe oxidative stress (Al-Menhali et al., 2020).

Another well-known aldehyde in primary brain tumors is MDA, frequently assessed by measuring thiobarbituric acid reactive substance (TBARS). Similar to 4-HNE, MDA was also found to be elevated in tumor tissues and to correlate with the histopathological grade of the tumor (Cirak et al., 2003; Zengin et al., 2009). The presence of MDA appeared as more prominent at tumor peripheral zones than in the central tumor area (Lamari et al., 2008), while MDA was also shown to be present at high levels in brain metastases of various tumors (Sidorenko et al., 2011; Zengin et al., 2009). Complementary to that, the incidence of MDA seems to be lower in peritumoral tissues, whereas both enzymatic

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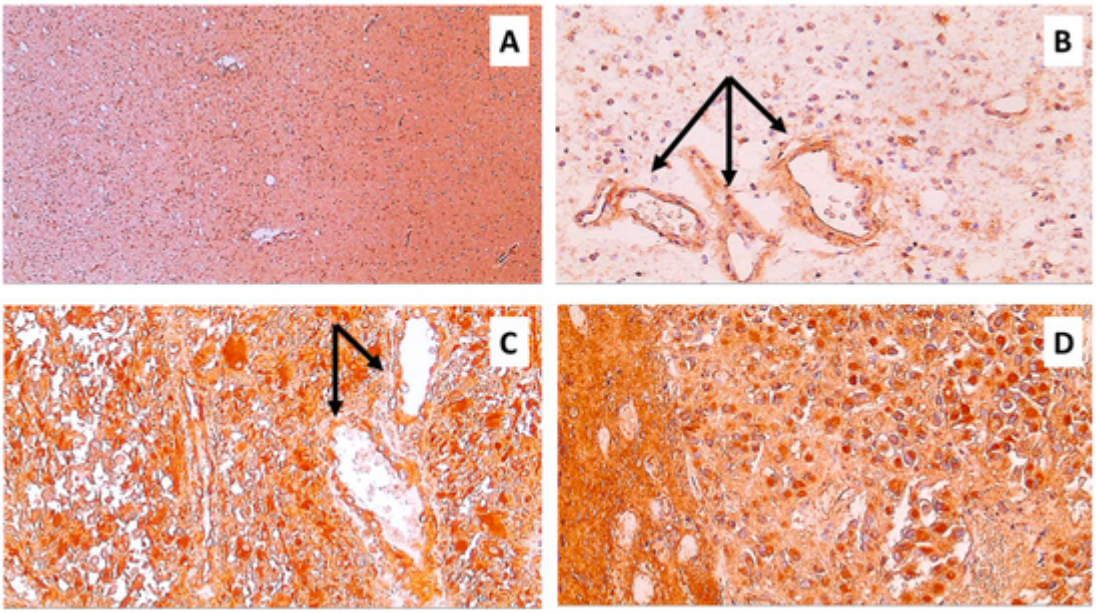

Fig. 3. Immunohistochemical findings of 4-HNE-protein adducts in human brain tumors.
Genuine monoclonal antibodies (courtesy of Prof. Georg Waeg, KF University, Graz, Austria), specific for 4-HNE-histidine adducts were used on formalin-fixed, paraffin embedded tissue specimens, as described before (Zarkovic et al., 2017). Immunopositivity was visualized using brown-colored 3,3′-diaminobenzidine staining (DAB), with blue hematoxylin contrast-staining.A - The infiltration zone of a low-grade diffuse astrocytoma (G II, left side) into surrounding brain tissue (right side). The 4-HNE immunoreactivity appears stronger in the affected brain tissue, than in the tumor itself (magnification 100×).B - Low to mild 4-HNE immunoreactivity in tumor cells of the low-grade diffuse astrocytoma (G II), with more pronounced moderate immunostaining of the tumor's blood vessels, indicated by arrows (magnification 400×).C - Strong 4-HNE immunopositivity of tumor cells and vascular endothelium (indicated by arrows) in glioblastoma multiforme (G IV) (magnification 400×).D - Strong 4-HNE immunopositivity in tumor cells of metastatic renal carcinoma (right side, note strongly 4-HNE-immunopositive nuclei of carcinoma cells) and even more pronounced in surrounding brain tissue (left side) (magnification 400×).

and non-enzymatic antioxidants seem to be increased. In addition, the amount of MDA was found to correlate with the amount of C20:4 carnitine in glioblastoma patients (Bayraktar et al., 2008).

However, although patients suffering from brain tumors have usually increased levels of the lipid peroxidation markers in the blood (Cirak et al., 2003; Woźniak et al., 2007; Yilmaz et al., 2006) the correlation of systemic lipid peroxidation with the type of primary brain tumors or the degree of their malignancy was not reported.

5. Lipid peroxidation in brain metastases

The metastases of cancer to CNS, notably to the brain, are among the most difficult clinical problems and a cause of deep human suffering. Despite recent therapeutic breakthroughs estimated survival time of patients with brain metastases is still less than one year (Lowery and Yu, 2017). Alongside with melanoma, primary cancers that most frequently metastasize to the brain originate from lungs, breast, colon and kidney, although any type of cancer, including hematological malignancies, can disseminate to the brain (Nayak et al., 2012; Patchell, 2003). Cancer metastases to the brain develop through hematogenous seeding from a primary tumor penetrating the brain microvasculature.

The brain metastases can often be the first presenting symptoms of malignant disease in patients with undiagnosed advanced-stage cancer. It is estimated that about 20% of patients with cancer will develop eventually brain metastases (Hall et al., 2000; Nayak et al., 2012). The true incidence of brain metastasis is likely even higher because guidelines for majority of solid tumors do not recommend routine brain MRI screening in patients who do not have any prominent neurological deficit. Hence, autopsy studies have suggested higher incidence (up to 40%) of brain metastases in patients with cancer (Posner and Chernik, 1978; Tsukada et al., 1983). In advanced primary disease, the risk of developing brain metastases is even higher and increasing (Steeg et al., 2011). In patients without brain metastases detected at the time of initial diagnosis, the median time from initial cancer diagnosis to the development of brain metastases is related to the primary cancer type (Nieder et al., 2011). In one study the median time for patients with breast carcinoma to develop brain metastases was 44 months, while it was only 11 months for patients suffering from primary lung cancer (Berghoff et al., 2016). Such differences may be due to variations in screening and the staging of the disease but also in respect to biological differences between different tumor types.

Tumor growth involves complex microenvironmental tumor:host interactions, neuroinflammatory cascades and neovascularization. Aiming to spread from the site of origin, tumor cells leave from the primary tumor and invade the surrounding tissues, venules, capillaries, and lymphatic system to further interact with immune cells thus promoting cell motility through extracellular matrix. When cancer cells get into the circulation, they begin the process of metastatic extravasation from the vasculature. The brain metastases tend to occur mostly at the junction between grey and white matter and watershed areas between vascular territories where tumor cells benefit from extended time of blood flow. Thus, tumor cells have more time to extravasate from the vasculature and overcome the BBB (Achrol et al., 2019). At the time when diagnosis of a primary tumor is done, more than 80% of patients already have multiple brain metastases, disallowing surgery as a therapeutic option (Ammannagari et al., 2013; Patchell et al., 1998).

The protective features of the brain include neuronal support cells and BBB aiming to restrict the chemical and nutrient content of the CNS and defend it against invading cells. These brain characteristics represent on one hand the barrier preventing cancer cells to enter the brain, but on the other they provide safe surrounding for cancer cells able to metastasize to the brain. Brain metastases have to adapt to the brain environment and avoid anti-cancer defense of the astrocytes and eventually to develop resistance to therapies applied (Lowery and Yu, 2017).

Therefore, to successfully form the brain metastases cancer cells spread through blood must complete the following these steps: 1) migration across BBB, 2) survival in the brain microenvironment and 3) malignant cell growth (Zou et al., 2019). In these crucial stages of the

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brain metastases development astrocytes may have different functions. When activated they are considered to act as effective cancer-killing defense factor in the brain microenvironment (Valiente et al., 2014). Opposite to that, some studies found that astrocytes could have a pro-metastatic function and facilitate brain metastases by increasing their formation and survival, migration of cancer cells through the BBB and stemness of the invading cancer cells, even modulating the immune response within the brain metastatic lesions (Priego et al., 2018; Valiente et al., 2014).

Astrocytes are a major source of fatty acid synthesis in the brain, which are used by neurons to support synapse formation and function (Mauch et al., 2001; van Deijk et al., 2017). In the recent study, Zou and colleagues (Zou et al., 2019) found that once migrated across the BBB to the brain parenchyma, cancer cells take advantage of this high fatty acid microenvironment to support their proliferation. This is the ultimate step for metastatic cancer cells to form macrometastases, for which inflammation-activated astrocytes serve as a source of production of polyunsaturated fatty acids utilized by proliferating cancer cells to build their membranes (Aizawa et al., 2016).

Zengin et al. studied the level of MDA, measured by TBARS, and antioxidant activities (GSH, SOD and GR) in different types of primary and metastatic brain tumors and their surrounding healthy tissues (Zengin et al., 2009). They demonstrated that the extent of lipid peroxidation is increased in all primary and metastatic brain tumors when compared with their surrounding tissues, while primary astrocytoma showed even higher MDA levels in comparison with brain metastases. Furthermore, in all tumor types analyzed, MDA levels showed a negative correlation with SOD and GR activity, and with GSH levels. In metastatic tumors, GSH levels and GR activity showed a significant positive correlation and SOD activity, also showing a significant correlation with GSH levels (Zengin et al., 2009). A significant reduction of GSH in metastatic and other brain tumors, in comparison with peritumoral tissues, was also found in the study by Navarro (Navarro et al., 1999).

Therefore, increased levels of lipid peroxidation products in brain metastases and primary tumors of the brain support the assumption that the malignant tumor cells produce large quantities of free radicals, thus supporting carcinogenesis.

6. The appearance of 4-HNE in the brain tumors

As can be seen on Figs. 1 and 3, a self-catalyzed chain reaction of lipid peroxidation generates 4-HNE that forms relatively stable protein adducts and maintain its bioactivities acting as a second messenger of free radicals. That could not only result in the spread and accumulation of 4-HNE within the affected tissues, but also its regulatory as well as cytotoxic effects could be manifested in the cell-type and concentration-dependent manners. Our immunohistochemical findings obtained by the genuine monoclonal antibody specific for the 4-HNE-histidine adducts, have shown that the development of astrocytoma is associated not only with production of 4-HNE (Fig. 3A) within the tumor tissue but even more in the surrounding non-malignant brain cells. This finding resembles similar findings described before for oropharyngeal malignancies, liver cancer and lung cancer (primary and metastatic). Even more, higher presence of 4-HNE in normal tissue of the brain surrounding astrocytoma also resembles previously described levels of 4-HNE in non-malignant cells near cancer (Gęgotek et al., 2016; Zhong et al., 2017; Jakovčević et al., 2020). This is opposite to the findings on MDA in normal peritumoral brain tissue (Zengin et al., 2009), so we assume that cancer growth induces 4-HNE due to persistent lipid peroxidation on one hand, but on the other non-malignant cells could produce 4-HNE also as defense mechanism against invading cancer (Gęgotek et al., 2016; Zhong et al., 2017; Jakovčević et al., 2020). In favor of this hypothesis are also findings on concentration-dependent anticancer effects of 4-HNE, which might be produced by non-malignant cells in the vicinity of cancer thus blocking the cancer-specific membrane-associated catalase (Bauer and Zarkovic, 2015). Similar findings of increased lipid peroxidation in peritumoral non-malignant tissues were found before also for colon carcinoma both in the case of 4-HNE and acrolein (Biasi et al, 2002, 2006; Zarkovic et al., 2006).

The source of 4-HNE within non-malignant brain tissue could be not only glial cells but also BBB itself, especially because arterial smooth-muscle cells can accumulate 4-HNE in an age-dependent manner (Zarkovic et al., 2015). Therefore, it is not surprising that in the case of low-grade astrocytoma (Grade II), 4-HNE is mostly prominent in blood vessels (Fig. 3B) being less pronounced in tumor cells, while in the most malignant astrocytic tumor, glioblastoma multiforme (Grade IV), 4-HNE is abundant in blood vessels and in tumor cells (Fig. 3C). Finally, in case of brain metastases, as presented on Figure 3D, 4-HNE can be found strongly pronounced in cancer cells (even in their nuclei, which is exceptional), and even more in surrounding brain tissue. That is again raising the question if so much 4-HNE present in the normal tissue affected by cancer development is due to its decay caused by lipid peroxidation or due to an attempt of normal cells to defend the normal tissue from invading cancer. While findings of more pronounced 4-HNE in normal brain in the vicinity of metastatic cancer is again opposite to findings on MDA, which was found lower in metastatic than in primary brain tumors and peritumoral tissue, the highest levels of 4-HNE found in the brain near metastatic cancer are very well in agreement with findings of higher 4-HNE levels in normal lung tissue surrounding lung metastasis of remote, mostly colon cancer) (Piskač Živković et al., 2017). This topic deserves further research and could help better understanding not only of the origin of 4-HNE in brain tumors, but also of its biological activities relevant for the tumor:host relationship.

7. Conclusions and future perspectives

There is enough evidence showing that lipid peroxidation is associated with the development of various CNS diseases including primary and metastatic brain tumors. Major sources of lipid peroxidation in the brain might be astrocytes and the blood vessels, also within the BBB, which is in case of brain tumors modified into the BBTB. The final product of non-enzymatic lipid peroxidation, reactive aldehyde 4-HNE, which forms relatively stable protein adducts, might be responsible for the persistence and the spread of lipid peroxidation and oxidative stress, acting as the second messenger of free radicals.

Immunohistochemical findings on the presence of 4-HNE in primary brain tumors suggest positive relationship between lipid peroxidation with malignancy of astrocytic tumors and the tumor progression. In case of cancer metastases in the brain, the levels of 4-HNE seem to be even higher, peaking at the maximum of immunohistochemical positivity revealed in the peritumoral brain tissues. Because 4-HNE can act in cell-type and concentration-dependent manners, either as cytotoxic product of PUFA peroxidation or as a regulator of vital functions of normal and of malignant cells, bioactivities of this reactive aldehyde should further be studied to reveal if it serves as a co-factor of carcinogenesis or/and as a factor of the host's defense against cancer.

Finally, since 4-HNE increases permeability of the BBB, it is likely that 4-HNE might be in the future used as a potential humoral biomarker of various CNS diseases, including brain tumors, or even as biological inducer of the BBB permeability that could enhance penetration of the medicinal remedies into the brain.

Author statement

Herewith, on behalf of all co-authors, I declare that contribution of the co-authors of the manuscript “Lipid peroxidation in brain tumors”, which was prepared upon your invitation for the SI denoted “The oxidative/nitrosative stress in brain tumors”, for which you act as guest editors was: Morana Jaganjac – Conceptualization; Data curation; Visual-

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ization; Roles/Writing - original Marina Cindrić - Visualization; Roles/Writing - original. Antonia Jakovčević - Roles/Writing - original. Kamelija Žarković - Data curation; Validation; Visualization; Roles/Writing - original. Neven Žarković - Conceptualization; Data curation; Formal analysis; Project administration; Supervision; Validation; Visualization; Roles/Writing - original. Sincerely yours,

Declaration of competing interest

There is no conflict of interest.

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