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REVIEW

Perillyl alcohol, a pleiotropic natural compound suitable for brain tumor therapy, targets free radicals

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Abstract Monoterpenes such as limonene and perillyl alcohol (POH) are promising natural compounds with pro-oxidant properties partly due to endoplasmic reticulum (ER) stress-induced cytotoxicity, and antioxidant activity owing to their activity as free radical scavengers, inhibition of coenzyme Q synthesis, activation of antioxidant-responsive elements (inducing detoxification enzymes) and induction of apoptosis. Activation of ER-stress responses generates reactive oxygen species (ROS), which are highly reactive free radicals mainly produced during mitochondrial electron transfer for adenosine triphosphate (ATP) synthesis. When cells are subjected to oxidative stress conditions, there is an accumulation of ROS that can lead to irreversible cell injury caused primarily by lipid peroxidation, protein aggregation and/or DNA damage. Malignant tumors, such as glioblastoma multiforme, display elevated rates of oxygen consumption, necrosis and abnormal structural microvasculature. Alterations in the tumor microenvironment are tightly linked to tumor progression and occur as a result of activation of complex signaling networks involving inter-clonal cooperation, cell–matrix interactions and an ongoing inflammatory response leading to genetic and epigenetic alterations. This review will focus on the pro- and anti-oxidant activities of POH, which are greatly dependent on the respective ROS levels within the tumor microenvironment and involve the ER stress response system. As well, some critical aspects of tumor-associated metabolic changes and the consequences of endogenous ROS production for tumor progression will be discussed.

Keywords Reactive oxygen species · Hypoxia · Perillyl alcohol · Tumor microenvironment

Abbreviations

AKT	Protein kinase B
ARE	Antioxidant-responsive elements
ATP	Adenosine triphosphate
BMDCs	Bone marrow-derived cells
CAFs	Cancer-associated fibroblasts
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGFR	EGF receptor
EGFRvIII	EGFR variant III
ERK	Extracellular signal-regulated kinase
Gal-1	Galectin-1
GBM	Glioblastoma multiforme
HIF	Hypoxia-inducible factor
JNK	c-jun N-terminal kinase
K-Ras	Kirsten Ras
MAPK	Mitogen-activated protein kinase
MDR	Multidrug resistance
MMPs	Matrix metalloproteases
mRNA	Messenger RNA
mTOR	Mammalian target of rapamycin
NADPH	Nicotinamide adenine dinucleotide phosphate

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NF-κB	Nuclear factor kappa B
NKA	Na^+/K^+-ATPase
NOX	NADPH oxidase
PHD	Prolyl hydroxylase domain enzymes
PI3K	Phosphoinositide 3-kinase
POH	Perillyl alcohol
ROS	Reactive oxygen species
STAT5	Signal transducer and activator of transcription-5
TGF	Transforming growth factor
VEGF	Vascular endothelial growth factor

Introduction

In view of numerous health risks resulting from unbalanced reactive oxygen species (ROS) levels, research has focused on antioxidants as a potential therapy to restore the normal physiology under pro-oxidant conditions. Monoterpenes [e.g. limonene and perillyl alcohol (POH)] are promising natural compounds with antioxidant properties that can induce phase I and II enzymes such as glutathione-*S*-transferase, thus facilitating carcinogen detoxification (Belanger 1998; Crowell 1999). Production of ROS during cellular respiration or mediated by extra-mitochondrial enzymes such as nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase (NOX)) can threaten cell viability brought by a suitable aerobic environment required for homeostasis (Brieger et al. 2012). As a cellular defense mechanism, antioxidant systems driven by specific metalloenzymes located in both the cytosol and in the mitochondria control the oxidative reactions. Although potentially toxic to the cellular metabolism, moderate levels of ROS are required for biological signaling, biosynthetic reactions, chemical defense, and detoxification. In fact, this reflects the ROS paradox: though critical signaling molecules for cell proliferation and survival, their overproduction may lead to macromolecular damage and chronic pathological processes. During physiological conditions, a fine-tuned process controls the oxidative stress related to ROS production and degradation; however, when the antioxidant defenses are not sufficient to sustain the appropriate redox homeostasis, reversible or irreversible cellular damage often occurs (Brieger et al. 2012; Fimognari 2015; Zorov et al. 2014). In this illustrative review, we discuss the potential impact of endogenous ROS generation on hypoxic tumor microenvironment-driven brain parenchymal necrosis, and highlight the pleiotropic pro- and/or anti-oxidant effects of the dietary monoterpene POH in halting tumor progression.

Production of ROS and their consequences

ROS are highly reactive free radicals acting as electron acceptors or oxidizing agents that react with other molecules to achieve a stable configuration. ROS are often generated in response to tissue injuries caused by exposure to atmospheric pollution, chemical compounds, xenobiotics, and ionizing radiation. ROS are also produced during perturbations to metal metabolism caused by inflammatory cells (Fenton reaction in macrophages), and during respiratory and metabolic processes that include oxidative phosphorylation and NOX complex reactions in cell membranes (Brieger et al. 2012; Klaunig and Kamendulis 2004; Trachootham et al. 2009). Disparities between the speeds of ROS production versus elimination may result in oxidative or reductive stress, characterized by high or low ROS levels, respectively (Zorov et al. 2014). Nevertheless, cellular responses to reactive species depend upon the extent of ROS availability; wherein a limited increase of ROS can generate a transient cellular alteration, a moderate increase in ROS levels may promote cell proliferation and differentiation, while a severe increase generates irreversible oxidative damage (Trachootham et al. 2009).

As a by-product of oxygen metabolism, ROS are formed during electron transfer between respiratory chain complexes in steps that precede oxygen reduction to water for adenosine triphosphate (ATP) synthesis (Wardman and Candeias 1996). Physiologically, endogenous ROS generation and inactivation are mainly controlled by key antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase and peroxiredoxin (Klaunig and Kamendulis 2004; Zorov et al. 2014), and by non-enzymatic scavenger systems formed by antioxidant agents predominantly obtained from the diet, like vitamins A, C and E (Brieger et al. 2012; Costa et al. 2014; Klaunig and Kamendulis 2004).When cells are subjected to oxidative stress conditions, failure to engage antioxidant-scavenging enzymes results in ROS accumulation (Cook et al. 2004; Nathan and Cunningham-Bussel 2013; Zorov et al. 2014). Accumulation of ROS may result in metabolic alterations, lipid peroxidation affecting membrane structure and function, formation of insoluble protein aggregates, mutations and alterations in gene expression due to nucleic acid damage and interference in cell cycle control systems (growth, proliferation, arrest or senescence, apoptosis and necrosis) (Brieger et al. 2012; Trachootham et al. 2009; Zorov et al. 2014). In particular, the brain is greatly susceptible to oxidative damage due to the high rate of oxidative metabolism, increased presence of free iron/copper ions and haeme groups, elevated concentrations of polyunsaturated fatty acids and low to moderate levels of antioxidant enzymes (Dinocourt et al. 2015; Nathan and Cunningham-Bussel 2013; Zorov et al. 2014). Intracellular accumulation of

ROS also induces a positive feedback mechanism as a consequence of the opening of the mitochondrial permeability transition pore, a nonspecific pore in the mitochondrial inner membrane. This opening stimulates ROS-induced ROS release, amplifying ROS flow and signaling in the mitochondria itself and in neighboring mitochondria (Halestrap et al. 2004; Zorov et al. 2014). Hence, increased ROS levels induce chronic adaptive responses by activating signaling molecules and promoting oxidative modifications of cellular compounds, which may lead to degenerative conditions such as neurological disorders, atherosclerosis, and cancer (Brieger et al. 2012; Cook et al. 2004).

Production of ROS, warburg effect and cancer

Under physiological conditions, complete oxidation of glucose by aerobic respiration is responsible for efficient production of energy as ATP, whereas glucose fermentation is inhibited in the presence of oxygen—a process known as the "Pasteur Effect" (Costa et al. 2014; Klaunig and Kamendulis 2004). In contrast, tumor cells adapt to produce energy by glycolytic pathway into the pentose phosphate pathway to meet their metabolic and energetic demands, converting glucose to lactate instead of employing aerobic respiration in the mitochondria, even under normoxia a process called the Warburg effect (Bhalla et al. 2013; Crowell 1999; Elson and Yu 1994; Jahangir and Sultana 2007; Lee et al. 2014; Ray 2005). Although aerobic glycolysis is considered an inefficient process of energy generation (net yield of two ATP molecules per glucose molecule) in comparison to oxidative phosphorylation (about 38 ATP molecules), preferential use of glycolysis ensures robust cell growth and proliferation via upregulation of anabolic processes involved in the generation of biomass and nucleotide synthesis (Bhalla et al. 2013; Bhatia et al. 2008; Chen et al. 2015; de Cassia et al. 2013).

Tumors usually grow under hypoxic environments that result from a combination of high oxygen consumption and inadequate blood supply. In response, tumor cells adapt their respiratory metabolism to support robust cellular proliferation under a situation of energetic stress. In addition, enhanced lactate secretion and ROS detoxification processes corroborate to promote extracellular acidification (da Fonseca et al. 2016; Loutrari et al. 2004). In highly glycolytic and metabolically reprogrammed tumor cells, reduction of extracellular pH by increased proton extrusion leads to the formation of a microenvironment conducive to immune tolerance to tumor-associated antigens (Cho et al. 2012; Garcia et al. 2010). Persistent activation of aerobic glycolysis further supports disease progression via recruitment of pro-tumorigenic immune cell subsets and increased secretion of inflammatory mediators such as vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGF/VEGFR2), which stimulates neoangiogenesis and supports an immunosuppressive tumor microenvironment (Gatenby and Gillies 2004; Shime et al. 2008). In addition, high concentrations of lactate, as an end-product of glycolysis metabolism are associated with increased metastatic potential and rapid cellular proliferation rate (Dang 2012; Devic 2016; Martinez-Outschoorn et al. 2010; Pedersen 2007; Sosa et al. 2013; Xu et al. 2005). Moreover, activation of phosphoinositide 3-kinase (PI3K) signaling pathway via protein kinase B (AKT) enhances glucose uptake via glucose transporter 1 (GLUT1) and stimulates phosphofructokinase activity, thereby increasing cell dependence on high glucose levels (Dang 2012; Sosa et al. 2013). The lower pH impacts important cell proliferation pathways via inhibition of signal transducer and activator of transcription-5 (STAT5) and extracellular signal-regulated kinase (ERK) (Costa et al. 2014). Alternatively, mitochondrial dysfunctions (e.g. due to fragmentation of cristae which possess the main enzymes to perform oxidative phosphorylation) are also responsible for supporting a glycolytic phenotype and aggressiveness of tumors, conferring resistance to therapeutics (Devic 2016). One hypothesis is that the highly invasive nature of malignant glioma, such as glioblastoma multiforme (GBM) is attributable to a hybrid tumorigenic population with mitochondrial alterations resulting from the merger between glioblastoma stem cells and macrophages/microglia (Ngo et al. 2015).

Pleiotropic responses to hypoxia

Hypoxic conditions induced by radiation leads to calcium overload, production of free radicals that render glioma stem cells resistant to treatment, and activate production of proangiogenic factors by both glial tumor and stromal cells. The hypoxia-inducible factor (HIF) is an oxygen-sensitive heterodimeric transcriptional complex responsible for regulating molecular responses to reduced O_2 availability, ensuring cellular adaptation and survival. HIF-1 is a complex composed of two basic helix-loop-helix proteins containing a Per-ARNT-Sim domain: a constitutively expressed and non-oxygen-responsive subunit (HIF-1β), and an oxygen-regulated subunit (HIF-1α) (Aykin-Burns et al. 2009; Devic 2016; Pedersen 2007). Under normoxia, the alpha subunit is continuously expressed, but quickly degraded by the ubiquitin–proteasome system via hydroxylation of prolyl residues within the oxygen-dependent degradation domain located at the protein core. These post-translational modifications performed by prolyl hydroxylase domain (PHD) enzymes maintain the stability and control the turnover of the HIF-1α subunit (Bhatt et al. 2015; Martinez-Outschoorn et al. 2010). In particular,

hydroxylation allows the interaction between von Hippel-Lindau tumor suppressor protein and HIF, forming a complex that targets HIF-1α for ubiquitin–proteasome degradation (Courtnay et al. 2015; Dang 2012; Shime et al. 2008).

Acidification of the tumor microenvironment induces the expression of HIF which is critical for HIF-1 stabilization and tumor cell adaptation to hypoxic conditions (Devic 2016; Ngo et al. 2015). Expression of HIF supports the glycolytic pathway by increasing the expression of glucose transporters GLUT1 and GLUT3, which are translocated to the cell surface to enhance glucose uptake thereby maintaining the energetic and biosynthetic demands for anabolic tumor growth (Pedersen 2007). Under hypoxic conditions and increased levels of ROS, the HIF-1α subunit is stabilized and its degradation inhibited. HIF-1α then forms a complex with the beta subunit and translocates to the nucleus. The heterodimer HIF-1α/β binds to a core pentanucleotide sequence (5′-RCGTG-3′) in the hypoxia-responsive elements located at the promoter region or in enhancer sequences, increasing expression of HIF1-target genes (Calcinotto et al. 2012; Shime et al. 2008).

HIF-1-target genes are involved in multiple cellular processes regulating cell survival, growth and differentiation (Bhatt et al. 2015; Calcinotto et al. 2012; Courtnay et al. 2015), invasion and metastasis, angiogenesis and vascular permeability, and iron metabolism (Hagen 2012; Huysentruyt et al. 2011; Weidemann and Johnson 2008). HIF-1 also targets genes involved in energy metabolism, including those whose protein products increase the supply of nutrients through enhanced glucose uptake and synthesis of glycolytic enzymes (Jones and Thompson 2009; Lee et al. 2004; Pakravan 2013; Richard et al. 2013; Weidemann and Johnson 2008). HIF-1α is also involved in mitochondrial respiration, modulating oxygen consumption by inducing the expression of pyruvate dehydrogenase kinase. Therefore, upregulation of HIF-1α optimizes glucose utilization to generate sufficient amounts of ATP under low oxygen availability, while inhibiting mitochondrial respiration and attenuating ROS generation (Ke et al. 2012; Pakravan 2013; Weidemann and Johnson 2008). Acute, intermittent, and cycling states of hypoxia are also associated with inadequate blood supply, whereas chronic hypoxia is the consequence of reduced oxygen diffusion resulting from tumor expansion. These hypoxic areas exert intensive selective pressure by evoking an adaptive response in surviving cells. Once transformed cells adapt to hypoxia, tumors become increasingly refractory to cancer therapy. Several potential mechanisms may be implicated in impairing the treatment response, including DNA over-replication, increased genetic instability and emergence of multidrug resistance (MDR). However, the actual contribution of different mechanisms triggered by cycling or chronic hypoxia leading to resistance to apoptosis remains unclear (Weidemann and Johnson 2008). Nevertheless, the establishment of hypoxic regions in solid tumors is directly associated with compromised respiratory metabolism and elevated aerobic glycolysis, which promotes the emergence of malignant clones by conferring a selective growth advantage that includes enhanced DNA damage repair capabilities and therapeutic resistance (Marin-Hernandez et al. 2009; Semenza 2010).

HIF overexpression participates in the process of epithelial–mesenchymal transition by modulating the expression of transcription factors such as Snail, LOX and TWIST, and interactions of cancer stem cells with stromal cells, which induces a metastatic phenotype (Semenza 2010; Weidemann and Johnson 2008). The hypoxic microenvironment is advantageous for cancer stem cells because it maintains their clonogenic and tumorigenic potential, increasing resistance to therapy and possibly enabling cells to escape from low oxygen areas and migrate to specific distant organs (Pedersen 2007). However, when hypoxic cells cannot overcome the deleterious effect of severe or prolonged hypoxia or anoxia, a cascade of events ultimately leads to apoptotic cell death and necrosis. Therefore, the severity of oxygen deprivation determines whether the cell survives or undergoes apoptosis (Courtnay et al. 2015; Dang 2012; Devic 2016). Another cellular process affected by HIF upregulation is iron metabolism, which directly or indirectly impacts several vital biological processes (Jones and Thompson 2009). Iron is stored in small pools within the cytosol, in the mitochondrial matrix and in lysosomes (Hagen 2012; Ngo et al. 2015). It can be found in three different oxidation states: Fe(II), Fe(III), and Fe(IV) (Lee et al. 2004; Weidemann and Johnson 2008). Increased levels of HIF-2α were shown to up-regulate expression of a series of proteins involved in iron mobilization and transport (Chen et al. 2015; Lu et al. 2015). Iron oxidation–reduction reactions are closely related to ROS production. In its Fe(II) oxidative state, iron is soluble at physiological pH, but unstable in aqueous media, a characteristic that leads it to react with oxygen, forming Fe(III) and superoxide radicals, which can act as oxidizing or reducing agents (Bhatt et al. 2015; Gritsenko et al. 2012). Redox-active iron has the ability to directly catalyze damaging free radical formation via Fenton chemistry, where hydrogen peroxide generated by the interaction of the superoxide radical with hydrogen reacts with Fe(II) to give rise to hydroxyl, a very reactive and dangerous free radical (Pakravan 2013) capable of oxidizing a variety of organic substrates (Dang 2012). Superoxide dismutase is responsible for the conversion of superoxide into hydrogen peroxide, which inhibits PHD enzymes and triggers their degradation by ubiquitination (Jones and Thompson 2009).Besides redox-active iron, iron-dependent ROS-producing enzymes, such as xanthine oxidase or

NOX, contribute to production of ROS and ROS-dependent cell damage and death (Jomova and Valko 2011; Pakravan 2013).

Production of ROS and angiogenesis

Functional blood vessels maintain homeostasis and tissue growth through oxygen and nutrient supplementation and waste removal. In the case of tumors, the vascular network can facilitate metastasis by acting as a route for invasion into distant organs and tissues via pathways signaling Notch receptors, the ligand Delta-like-4, microRNA-132, and endoglin, a co-receptor for transforming growth factor (TGF)-β in endothelial cells (Dixon and Stockwell 2014; Kurz et al. 2011). In the early stages of the neoplastic process, formation of a tumor vasculature network is inefficient and precludes the adequate supply of blood and nutrients, restricting tumor growth and favoring cell death either by necrosis or apoptosis. However, upon initiation and establishment of adaptive responses within the hypoxic tumor microenvironment, the quiescent vasculature is activated to sprout and form new blood vessels (Dinocourt et al. 2015; Lee et al. 2004; Valko et al. 2005), which are characterized by tortuous, dilated and irregular forms. This abnormal structure is not yet able to efficiently support the demands of rapidly growing cells, leading to sustained tissue hypoxia and vasogenic edema (Kurz et al. 2011). ROS produced in response to hypoxia contribute to angiogenesis by acting as signaling molecules to stimulate endothelial cell proliferation and migration, leading to the formation of new vasculature partly through activation of the NOX complex by angiogenic stimuli, such as VEGF, angiopoietin-1 and the adipocytokine leptin (Valko et al. 2005). Exposure of cells to hypoxia/reoxygenation produces a sharp increase in oxidative stress, whereupon ROS modulate the expression of angiogenic-related genes, such as VEGF-A, angiopoietin, HIF-1, p53, epidermal growth factor (EGF), TGF-β, fibroblast growth factor and matrix metalloproteases (MMPs) (Kell 2009; Wardman and Candeias 1996). Signal transduction mediated by ROS further provides protection from apoptosis and anoikis (Winterbourn 2008) and supports a switch from oxidative phosphorylation to aerobic glycolysis, fueling a positive feedback for ROS/NOX production.

Irradiation therapy induces hypoxia due to the deleterious effects of ionizing radiation in endothelial cells and generates a pro-thrombotic state that contributes to post-irradiation inflammation by increasing adhesion of inflammatory cells and diapedesis into the perivascular space (Hagen 2012). Tumor recurrence following radiotherapy is often associated with recruitment of bone marrow-derived cells (BMDCs) and activation of pericyte progenitor cells that restore the radiation-damaged vasculature and enable radioresistant tumor cells to undergo vigorous growth and proliferation (Dinocourt et al. 2015; Dixon and Stockwell 2014). Recruitment of BMDCs requires HIF-dependent up-regulation of stromal cell-derived factor-1 and interaction with its receptor C-X-C chemokine receptor-4 (CXCR4) on the BMDCs (Anderberg et al. 2013; Eilken and Adams 2010). Pharmacological inhibition of VEGF signaling is the only clinically approved anti-angiogenic strategy, but tumors acquire resistance shortly after treatment initiation by avoiding VEGF signaling requirements for angiogenesis (Goveia et al. 2014; Kranenburg et al. 2004; Tuettenberg et al. 2009). Therefore, to advance therapeutic strategies for malignant tumors, it might be worthwhile to consider a combinatorial approach that incorporates inhibitors of neovascularization and inflammation, to maximize tumor cell targeting, including refractory and residual cancer stem cells.

ROS light the fire on the tumor microenvironment

The tumor stroma elicits synergistic and reciprocal paracrine signals in tumor cells, which further promote somatic mutations, epigenetic modifications and neovascularization, that are key determinant for tumor progression and tissue remodeling (Albesiano et al. 2010; Carmeliet and Jain 2000). Tumor cells actively remodel the microenvironment by secreting molecules such as MMP, serine proteases, cysteine proteases, and ROS (Fiaschi and Chiarugi 2012; Ushio-Fukai and Nakamura 2008).

Tumor progression is a multistep process that involves cell–cell and cell–extracellular matrix (ECM) adhesion, invasion, migration, and angiogenesis. The ECM in the brain tissue is a complex network of glycoproteins and proteoglycans that fills the intercellular space and serves as scaffolding to provide a structural framework for the tissue and regulates the behavior of cells via signaling through specific integrin receptors (Barker et al. 2015; Fiaschi and Chiarugi 2012). The ECM is also a source of growth factors, providing survival and danger signals that activate pathways that influence the tissue microenvironment and play a proinvasive role in highly aggressive brain tumors (Kioi et al. 2010). The invasiveness of glioma cells, a feature that represents the major cause of mortality in patients with malignant brain tumors, is greatly shaped by the cellular microenvironment. Aberrant interactions between tumor cells and the ECM allow diffuse infiltration of single tumor cells into the compliant ECM brain parenchyma (Barker et al. 2015; Kioi et al. 2010).

Malignant glioma (grade IV) commonly presents amplification and overexpression of the EGF receptor (EGFR) and a constitutively active ligand-independent variant EGFRvIII, a tumor-specific receptor that activates multiple

mechanisms and pathways that confer enhanced tumorigenicity (Fiaschi and Chiarugi 2012; Goveia et al. 2014). Constitutive EGFRvIII signaling activity induces additional oncogenic receptors that contribute to cell cycle progression, angiogenesis, inhibition of apoptosis via activation of the PI3K/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway, activation of signal STAT3 and nuclear factor (NF)-κB, and stimulation of the rat sarcoma (Ras) mitogen-activated protein kinase (Ras/MAPK) pathway. Ras signaling is implicated in gliomagenesis, a process partly dependent on the dynamic interplay of the carboxy-terminal domain of the Ras proteins recognized by galectin (Gal)-1, Gal-3 and cGMP phosphodiesterase delta including a farnesyl isoprenoid group and palmitoyl groups in H/N-Ras isoforms (Costa et al. 2014; McAllister and Weinberg 2010). Ras and Ras-related C3 botulinum toxin substrate 1 (Rac1) GTPases, which are expressed in a variety of human cancers, form part of the NOX complex (Sosa et al. 2013) essential for Ras-mediated transformation (Gritsenko et al. 2012). Activation of GTPases results in increased levels of ROS (Fiaschi and Chiarugi 2012) which promote oncogenic Ras activation by distinct mechanisms, including point mutations, gene amplification and overexpression (Quirico-Santos et al. 2010). In turn, oncogenic Ras proteins stimulate a number of downstream effector pathways that culminate in increased stabilization of mRNAs encoding pro-angiogenic factors, thus contributing to tumor progression (Cha et al. 2016).

Expression of Kirsten Ras (K-Ras) and MAPK pathway activation lead to enhanced transcription of ECM proteins and cytoskeletal rearrangements that promote glioma invasion (Quirico-Santos et al. 2010; Ulrich et al. 2009). Gal-1 forms a complex with GTP-H-Ras via a high-affinity interaction with the farnesylated C-terminal hypervariable region of the Ras binding domain of Ras effectors (Salazar-Ramiro et al. 2016). In addition, K-Ras–GTP interaction with Gal-3 causes a conformational change in the molecule, which leads to the activation of rapidly accelerated fibrosarcoma protein (Raf) and PI3K pathways, but also causes inhibition of ERK signaling, resistance to apoptosis, loss of p53 functionality, and chemoresistance (Ashery et al. 2006; Cha et al. 2016; Qiu et al. 1995). Ras proto-oncogene products induce mitogenic signals through membrane GTPases and tyrosine kinase receptors, and their mutated forms are involved in the generation of mitochondrial ROS (Bedard and Krause 2007) which is essential for K-Ras-induced tumorigenesis (Qiu et al. 1995). Cells that constitute the connective tissue, such as fibroblasts and macrophages, directly influence the tumor microenvironment. Cancer-associated fibroblasts (CAFs) become activated by extrinsic or intrinsic oxidative stress which contributes to a proinflammatory microenvironment through secretory events and ROS generation (Arslan et al. 2007; Bedard and Krause 2007; Crowe 2004; Kranenburg et al. 2004; Lymbouridou et al. 2009). Moreover, metabolic reprogramming of CAFs generates the so-called "reverse Warburg effect" in which epithelial cancer cells are able to induce the Warburg effect in neighboring fibroblasts present on tumor stroma (Blaževitš et al. 2016; Ulrich et al. 2009). Hence, once ROS are detected by fibroblasts, they differentiate into myofibroblasts via TGF-β signaling, and then begin to secrete L-lactate and pyruvate, which are captured by cancer cells through their monocarboxylate transporters, thus establishing a link between the tumor-promoting effects of TGF-β signaling and the metabolic reprogramming of the tumor microenvironment (Ashery et al. 2006; Strano et al. 2007). In addition, oxidative stress activates fibroblast transcription factors, such as NF-κB and HIF-1α, which lead to angiogenesis, inflammation and autophagy (Ralph et al. 2010; Weinberg et al. 2010). As a consequence of autophagy events, nutrients released from this process are used by cancer cells in their oxidative mitochondrial metabolism to produce ATP, supporting cell survival (Fiaschi and Chiarugi 2012).

The monoterpene POH

While adequate ROS signaling is essential for maintaining homeostasis, macromolecular damage caused by inadequate ROS production may lead to malignant transformation when antioxidant systems fail to properly repair the damage (Bedard and Krause 2007; Salazar-Ramiro et al. 2016; Sosa et al. 2013; Toullec et al. 2010). Therefore, antioxidants may be conceived as potential therapy to restore the normal physiology under pro-oxidant conditions (Guido et al. 2012; Pavlides et al. 2009). Monoterpenes are hydrocarbons formed by junction of two isoprene units, which can be found in essential oils of citrus fruits and other plants, comprising volatile non-nutritive dietary components with chemopreventive properties (Guido et al. 2012; Krstic et al. 2015; Pavlides et al. 2009; Sosa et al. 2013). Monocyclic terpenes, such as POH (IUPAC name: [4-(prop-1en-2-yl) cyclohex-1-en-1-yl] methanol) and its precursor limonene are promising natural compounds with antioxidant properties derived from the mevalonate pathway in plants. In humans, POH is rapidly metabolized by liver microsomes via hydroxylation by cytochrome P450-type enzymes to perillyl aldehyde (perillaldehyde), perillic acid, and *cis* and *trans*-dihydroperillic acids with subsequent glucuronidation by UDP-glucuronyltransferase followed by excretion, primarily in the urine and to a lesser extent in bile (Chaudhary et al. 2009; Khan et al. 2011; Miguel 2010).

Monoterpenes were shown to modulate the expression levels of MDR P glycoprotein in tumor cells, to harbor

anti-mitotic, anti-inflammatory, anti-oxidant, anti-mutagenic and anti-angiogenic activities, as well as to enhance immune function and surveillance (de Cassia et al. 2013). POH is an amphipathic molecule with a high partition coefficient that packs along the lipid acyl tail disrupting the integrity and biophysical properties of the lipid bilayer (Fig. 1), increasing its permeability and facilitating drug transport and delivery, thereby overcoming drug resistance (Ruberto et al. 2000).

The effect of POH altering the membrane dipole potential boosts gradually depending on the concentration and physical interactions into the lipid–water interface (da Fonseca et al. 2016; Witzke et al. 2010). The hydrophobic part of the molecule interacts with lipid acyl tails and the –OH group interacts with the lipid head groups. Such configuration forms small clusters (Fig. 1) able to partition spontaneously into the membrane by increasing the enthalpy through stable hydrogen interactions with membrane phospholipid tails, further stabilizing and intensifying membrane stiffness (Bhalla et al. 2013; da Fonseca et al. 2013). In vivo, POH is rapidly metabolized into perillic acid and di-hydroperillic acid, which might represent the active components capable to mediate communication between extracellular and intracellular environment

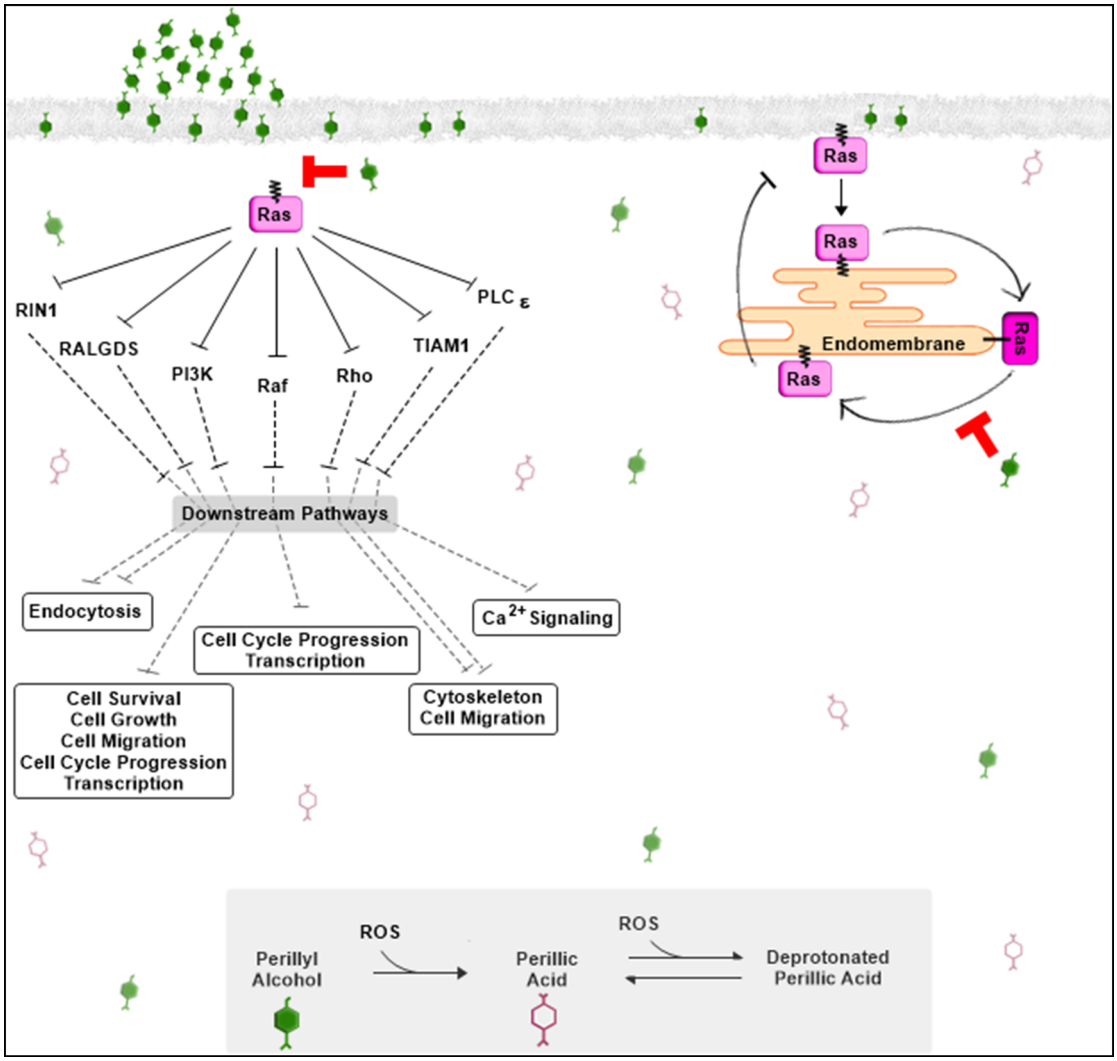

Fig. 1 Perillyl alcohol (POH) in aqueous phase forms clusters and interacts with membrane phospholipids, thereby modifying plasma membrane structure and dynamics, which further prevents anchorage and stabilization of isoprenylated Ras proteins. Reduction of membrane-bound Ras protein affects downstream signal transduction pathways related to endocytosis (RIN1 and RALGDS); cell survival and growth (PI3K); cell cycle transcription and progression (PI3K, Raf); cell migration (PI3K, Rho, TIAM1); cytoskeleton organization (Rho, TIAM1); and calcium signaling (PLCγ). POH exerts a direct action on HMG-CoA reductase in the mevalonate/isoprenoid/cholesterol pathway by competitive inhibition of both farnesyl and geranylgeranyl transferases, and reduction of coenzyme Q synthesis. Perillic acid and di-hydroperillic acid are major scavengers of free radicals. Chemical structure of POH depicted completely painted and perillic acid structure depicted with white center

by activating several signal transduction pathways (Teiten et al. 2012).

POH cellular targets and mechanisms of action

POH is a monoterpene that exerts remarkably diverse biological properties mostly mediated by modifying structure and dynamics of the plasma membrane bilayer (da Fonseca et al. 2016; Witzke et al. 2010) (Figs. 1, 2). POH acts as molecular glue in the aqueous phase forming clusters consisting of ~20 molecules (Witzke et al. 2010), continuously diffusing across the membrane and eventually binding to an intracellular structure (Witzke et al. 2010).

Ras is synthesized and modified in the cytosol before it is anchored at the membrane, which is essential for the signaling of lipid-anchored GTPase proteins (Amos et al. 2006). Moreover, a three-stage post-translational modification alters membrane affinities via lipidation of a hydrophobic CAAX motif, allowing insertion into the membrane and unidirectional vesicular transport (Abankwa et al. 2007; Afshordel et al. 2015). Although the amount of Ras membrane-associated nanoclusters is crucial for effective signaling, Ras continuously seeps from the plasma membrane, exchanging constantly with internal membranes into the vast endomembrane system including the Golgi, endoplasmic reticulum, and endosomes (Abankwa et al. 2007) (Fig. 1). Lipid post-translational modifications (farnesylation and/or palmitoylation) are required for transforming activity of Ras oncogenic proteins (H-Ras, N-Ras, K-Ras4A and K-Ras4B), each with a specific post-translational modification, membrane affinity and with ability to mediate tumor cell survival, growth, proliferation, migration, and metastasis (Berndt et al. 2011). POH inhibits HMG-CoA reductase, a rate-limiting enzyme of the mevalonate/isoprenoid/cholesterol pathway, and exerts a competitive inhibition of both farnesyl and geranylgeranyl transferases required for Ras- and Rho-proteins membrane anchorage and oncogenic function related to stimulation of the Ras-Raf-MEK-ERK pathway (Afshordel et al. 2015; Berndt et al. 2011; Schmick et al. 2015). In addition, interaction of POH with membrane phospholipids induces structural modifications that prevent the anchorage and stabilization of already isoprenylated, but not yet anchored Ras proteins, decreasing expression of membrane-bound Ras protein and increasing its presence in the cytosol, thus indicating a direct involvement inhibiting downstream signal transduction pathways to the nucleus (Fig. 1). This further prevents activation of effector pathways related to various cellular functions such as: endocytosis (RIN1 and RALGDS); cell survival and growth (PI3K); cell cycle transcription and progression (PI3K, Raf); cell migration (PI3K, Rho, TIAM1); cytoskeleton organization (Rho, TIAM1), and calcium signaling (PLCγ) (Berndt et al. 2011) (Fig. 1).

POH diffusion within the membrane bilayer alters the functionality of Na^+/K^+-ATPase (NKA) phase I cycle, causing a sharp increase in intracellular Na^+, Cl^-, Ca^{2+}, and a decrease in K^+ availability (Garcia et al. 2010). Imbalance of ion transport homeostasis activates voltage-dependent Ca^{2+} channels and the Na^+/Ca^{2+} exchanger that increase intracellular Ca^{2+} content and activate cell death pathways due to mitochondria bioenergetics failure (Heo et al. 2005). In concert with this, POH upregulates expression of aquaporins, integral membrane proteins that provide specific transcellular water and ion (K^+ and Cl^-) transport for maintenance of brain osmotic homeostasis and decreased vasogenic edema (Papadopoulos and Verkman 2013) (Fig. 2). Hence, there is a straight correlation of AQP4 expression in glioma cells with the extent of brain edema, especially in astrocytoma and glioblastoma multiforme, and also further evidence of a direct role for AQP facilitating tumor invasiveness (Papadopoulos and Verkman 2013). Moreover, it is conceivable that POH treatment stimulates dissociation of Nrf2 from its repressor Keap1. Nrf2 is stabilized and translocated to the nucleus, where it binds with high affinity to ARE (antioxidant responsive element) in the promoter region of target genes implicated in detoxifying ROS (Fig. 2). In this context, POH may indirectly exert an antioxidant effect via AQP4-Ca^{2+}/Na^+ exchanger downstream transcriptional pathway activation.

Distinct from its function as an ion pump, the NKA also acts as a signal transducer, interacting with a set of membrane proteins in the caveolae (signalosome), and independently of changes in intracellular Na^+ and K^+ concentrations further influences gene expression and cell growth (Xie and Askari 2002). Among the downstream consequences of POH interaction with Na^+, K^+-ATPase is Src kinase activation, which is responsible for the transactivation of the EGFR and activation of membrane-anchored proteins, including Ras and p42/44 MAPKs, leading to JNK phosphorylation and apoptosis (Garcia et al. 2010). Likewise, concomitant increase of intracellular Ca^{2+} activates NF-κB, AP-1 and transcriptional regulation of early response genes (*c-fos, c-jun*).

Free radicals contribute to the oxidative balance, but trigger molecular cell death pathways by increasing brain vascular permeability and dysfunction of ion transporters in the cell membrane, which contribute to cytotoxic edema, defined as cellular swelling, in addition to cellular metabolic disturbances (Heo et al. 2005). Chemopreventive and anticarcinogenic actions of POH are also related to the induction of detoxifying enzymes and as free radical scavenger, preventing inhibition of plasma membrane ion transport systems

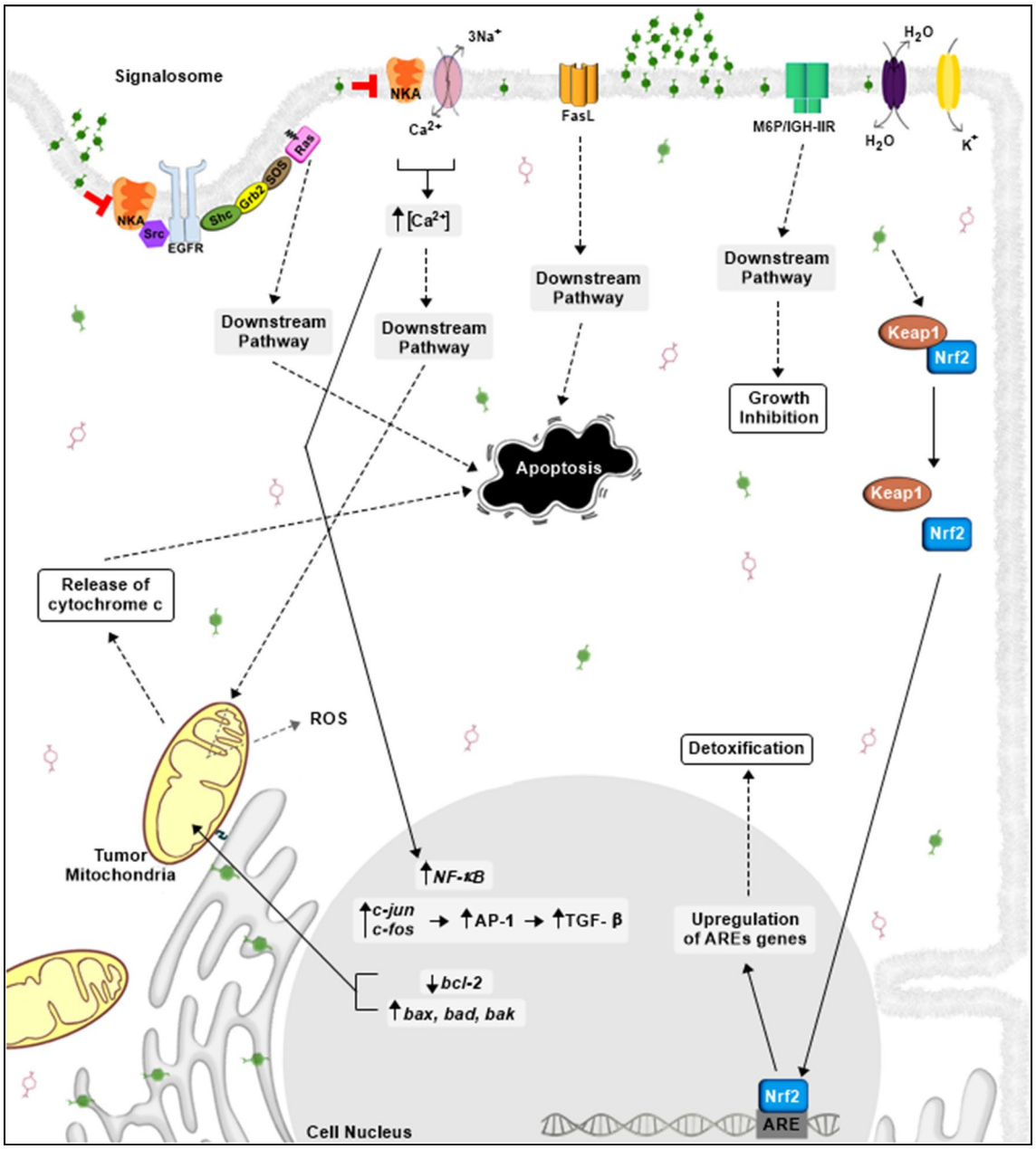

Fig. 2 Perillyl alcohol (POH) partition into plasma membrane alters the functionality of Na/K-ATPase (NKA). Ion homeostasis imbalance activates voltage-dependent Ca^{2+} channels, and Na^+/Ca^{2+} exchanger further activates cell death pathways due to mitochondrial bioenergetics failure. High intracellular Ca^{2+} content activates NF-κB, AP-1 and transcriptional regulation of early response genes (*c-fos, c-jun*). POH upregulates aquaporin expression to provide specific transcellular water and ion (K^+ and Cl^-) transport for maintenance of brain osmotic homeostasis and to decrease vasogenic edema. POH also induces Nrf2 dissociation from Keap1 repressor and subsequent translocation into the nucleus where it transactivates ARE (antioxidant-responsive elements) in the promoter region of genes encoding antioxidant/detoxifying enzymes. NKA acts as a signal transducer in the caveolae activating Src kinase and EGFR. POH increases expression of mannose-6-phosphate receptor/insulin-like growth factor II receptor (MP6/IGF-IIR), which acts as a growth inhibitor and triggers apoptosis via FasL death receptor. POH exerts pro-oxidant properties partly through the endoplasmic reticulum (ER) stress pathway inducing cytotoxicity. POH may interfere with gene regulation responsible for increased mitochondrial membrane permeability and cell death pathway. Chemical structure of POH depicted completely painted and perillic acid structure depicted with white center

(Na^+, K^+-ATPase; Ca^{2+}-ATPase; calmodulin-associated Ca^{2+}-ATPase; Na^+-Ca^{2+} exchanger), which are known targets for ROS-induced damage.

Glioma cells are characterized by increased Fas receptor expression and FasL down-regulation, which partly explain the resistance to trigger the extrinsic Fas-mediated apoptosis pathway, and further requiring exposure to a sensitizing agent such as cytotoxic drugs (e.g. vincristine, taxol; cisplatinum) and/or ionizing radiation. The monoterpene POH triggers apoptosis by activating the FasL death receptor via a p53-independent pathway and increases the susceptibility of radioresistant glioma cells to Fas-mediated apoptosis (Rajesh et al. 2003) (Fig. 2). Moreover, POH increases the expression of mannose-6-phosphate receptor/insulin-like growth factor II receptor (MP6/IGF-IIR) transmembrane glycoprotein (Azzoli et al. 2003) with functions in the transport of M6P-bearing glycoproteins, proteolytic activation of TGF-β, and degradation of IGF-receptors after internalization. MP6/IGF-IIR acts as a growth inhibitor (Fig. 2), and the loss of its function generates tumorigenesis (Hébert 2006).

Dietary phytochemicals exert their chemopreventive effects through multiple mechanisms, including the induction of enzymes involved in both cellular antioxidant defenses and elimination/inactivation of electrophilic carcinogens (Lee et al. 2013; Surh et al. 2008). Monoterpene POH not only possesses anti-inflammatory activity, but also plays an important role in preventing the generation of ROS and their harmful consequences. In conclusion, POH exerts multiple antioxidant functions by inducing several classes of genes implicated in detoxifying ROS. POH may interfere with regulation of genes involved in activation/inhibition of apoptosis, such as *bax, bad* and *bak*, which are pro-apoptotic genes up-regulated by POH action, and down-regulation of *bcl-2*, an anti-apoptotic gene. This regulation is responsible for increased mitochondrial membrane permeability, cytochrome c release rise and activation of cell death pathways. POH has a potential repressor activity against different tumors and clinical trials with recurrent malignant glioma patients further demonstrated that intranasal inhalation of POH was well tolerated and exerted significant antitumor therapeutic activity. It substantially reduced brain vasogenic edema and increased survival rates with virtually no adverse side effects (da Fonseca et al. 2013), including in recurrent patients that presented with resistance to the DNA alkylating agent temozolomide. Altogether, experimental evidence strongly suggests that the chemotherapeutic and chemopreventive activity of POH is a result of multifaceted functions inherent in this dietary component (Bhalla et al. 2013; Teiten et al. 2012).

Conclusions and future directions

Our review presented some of the dynamics between ROS and important aspects of tumor biology, such as the microenvironment, the inflammatory status and angiogenesis, which are essential for the maintenance and evolution of tumors. Being a product of cellular metabolism, specifically the respiratory chain, production and elimination of ROS must be carefully controlled, because ROS levels significantly impinge on many cellular mechanisms that impact cell survival or cell death. In general, low levels of ROS are important for cell cycle progression and cell growth, and also for controlled apoptosis under physiological conditions. Conversely, under pathological conditions within tumor tissues, high levels of ROS are important for ECM degradation, genetic and epigenetic alterations important for neovascularization, tumor progression, and invasion. Understanding the influence of the tumor microenvironment on the behavior of stromal and tumor cells, and the pathways that can be activated during the neoplastic process is of great value for the choice of therapeutic intervention. An example is the use of POH inhalation for the treatment of GBM and the potential to combine POH with different standard of care treatments. The tumor microenvironment is a major producer of ROS, which supports the emergence of radioresistant and chemotherapy refractory tumors via recruitment of BMDC. The combination of cytotoxic therapies with intranasal administration of POH shows great potential, since POH is an inhibitor of the angiogenic process and potent modulator of ROS activity.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no competing financial or non-financial interests in relation to the present manuscript.

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