Nitric Oxide 93 (2019) 102–114

Contents lists available at ScienceDirect

Nitric Oxide

journal homepage: www.elsevier.com/locate/yniox

Review

Nitric oxide and its derivatives in the cancer battlefield

Anna Kamm[a], Paulina Przychodzen[a], Alicja Kuban-Jankowska[a], Dagmara Jacewicz[b], Aleksandra M. Dabrowska[b], Stephan Nussberger[c], Michal Wozniak[a], Magdalena Gorska-Ponikowska[a,c,d,*]

[a] Department of Medical Chemistry, Faculty of Medicine, Medical University of Gdansk, Gdansk, Poland
[b] Department of Chemistry, University of Gdansk, Gdansk, Poland
[c] Department of Biophysics, Institute of Biomaterials and Biomolecular Systems, University of Stuttgart, Stuttgart, Germany
[d] Euro-Mediterranean Institute of Science and Technology, Palermo, Italy

ARTICLE INFO

Keywords:
Nitric oxide
Peroxynitrite
Nitrogen dioxide
Nitrate fatty acids
Cancer

ABSTRACT

Elevated levels of reactive nitrogen species, alteration in redox balance and deregulated redox signaling are common hallmarks of cancer progression and chemoresistance. However, depending on the cellular context, distinct reactive nitrogen species are also hypothesized to mediate cytotoxic activity and are thus used in anticancer therapies. We present here the dual face of nitric oxide and its derivatives in cancer biology. Main derivatives of nitric oxide, such as nitrogen dioxide and peroxynitrite cause cell death by inducing protein and lipid peroxidation and/or DNA damage. Moreover, they control the activity of important protein players within the pro- and anti-apoptotic signaling pathways. Thus, the control of intracellular reactive nitrogen species may become a sophisticated tool in anticancer strategies.

1. Introduction

Nitro-oxidative stress is characterized by high cellular levels of reactive nitrogen and oxygen species. Their formation is a natural consequence of the cellular metabolism and nitro-oxidative stress [1]. They play an important physiological role in the regulation of the cardiovascular and neuronal system, respectively, as well as in the control of human immune response (Fig. 1). The pathophysiological effect of these compounds is manifested by impaired antioxidant enzyme function, by accelerated cellular aging, immune deficiency and carcinogenesis [2–5].

Nitric oxide ($^{\bullet}NO$) is synthetized from L-arginine, nicotinamide adenine dinucleotide phosphate (NADPH) and oxygen by enzymes of the nitric oxide synthase family (NOS), using flavin adenin dinucleotid (FAD) and flavin adenin mononucleotid (FMN), tetrahydrobiopterin (BH4) and calmodulin [6] (Fig. 2). Three NOS isoforms have been isolated and characterized, i.e. neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS) [7]. They are localized in the cytosol but can also be found in nucleus [8,9] and mitochondria (mtNOS) [8,10–15].

An alternative way to produce bioactive $^{\bullet}NO$ involves the reduction of nitrate (NO_3^-) and nitrite (NO_2^-) [16,17]. Both molecules are taken up from exogenous sources or endogenously synthesized. Approximately 80% of nitrate is derived from vegetable consumption [18–20]. While sources of nitrite include vegetables, fruits and processed meat. Alternatively, nitrate and nitrite are generated from L-arginine and molecular oxygen in reactions catalyzed by NOS [18,21] (Fig. 2). In addition, nitrite is generated by reduction of nitrate in the upper gastrointestinal tract via entero-salivary circulation [22–24] or by intracellular oxidoreductases [25,26].

There are few possible mechanisms by which nitrite is converted to $^{\bullet}NO$. It occurs through nitrosyl intermediates, nitrogen oxides [27,28] and by reduction of nitrite catalyzed by reducing compounds or enzymes. These include Fe(II), formic acid, cytochrome *c* oxidase (complex IV) or NOS, respectively [29–31]. Also molybdenum-dependent enzymes such as xanthine oxidoreductase, aldehyde oxidase, sulfite oxidase, nitrite reductase and mitochondrial amidoxime reductase complex were shown to reduce nitrite to $^{\bullet}NO$ [30–39].

$^{\bullet}NO$ has dichotomous effect on cancer cells [40–42]. At concentrations below 100 nM $^{\bullet}NO$ was found to promote angiogenesis, cells proliferation, metastasis, and chemoresistance in a cGMP-dependent manner [43–45]. On the other hand, concentrations of $^{\bullet}NO$ higher than approximately 500 nM inhibit cancer cell proliferation and induce cancer cell death [45–49]. In this review, we will attempt to summarize the current knowledge of $^{\bullet}NO$ signaling in human cells and discuss its dual face in cancer biology.

* Corresponding author. Department of Medical Chemistry, Medical University of Gdansk, Debinki 1, 80-211, Gdansk, Poland.
E-mail address: magdalena.gorska-ponikowska@gumed.edu.pl (M. Gorska-Ponikowska).

https://doi.org/10.1016/j.niox.2019.09.005
Received 12 April 2019; Received in revised form 6 August 2019; Accepted 16 September 2019
Available online 18 September 2019
1089-8603/

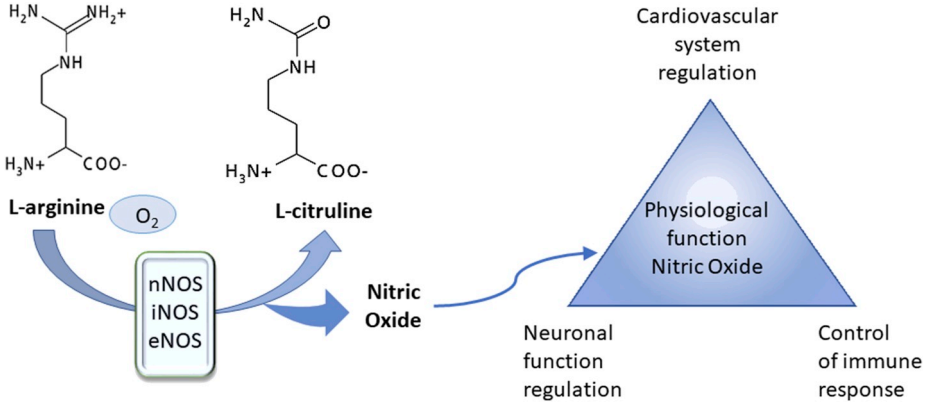

Fig. 1. The main physiological roles of nitric oxide in cardiovascular, neuronal and immune systems.

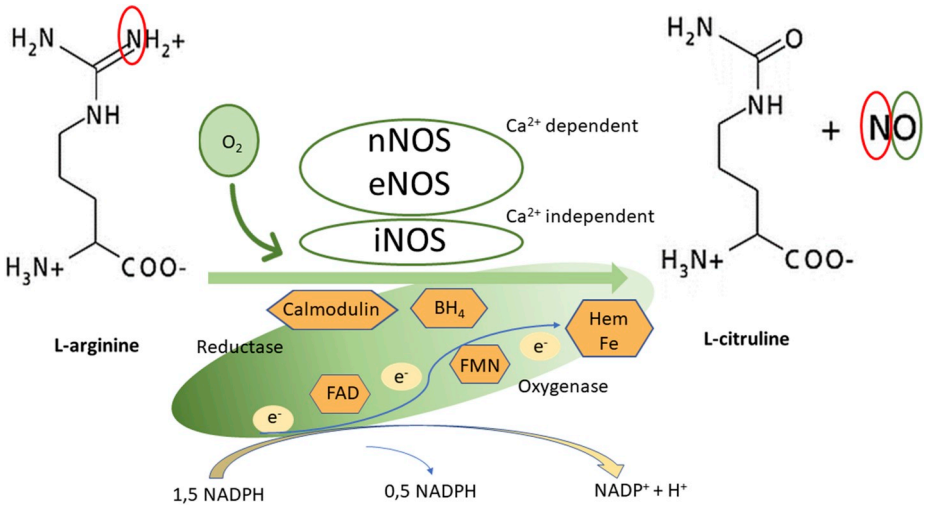

Fig. 2. NOS pathway. *Synthesis of nitric oxide catalyzed by nitric oxide synthases.*

Herein, we address the question whether and in what manner derivatives of ˙NO, such as peroxynitrite or nitrogen dioxide, mediate cytotoxic activity of their mother molecule.

2. Chemistry of nitric oxide

The chemistry of ˙NO determines its biological properties. Not all reactions that occur in the test tube are relevant *in* vivo because ˙NO is unstable in an oxygen environment. It is a small, diatomic, linear radical gaseous molecule with one unpaired electron (Fig. 3). ˙NO is soluble in aqueous solutions up to a concentration of ~2 mM at standard conditions [50,51] and unlike other reactive nitrogen species, does not produce the corresponding acid in solution (i.e. does not undergo hydration). The fact that ˙NO is not remarkably soluble in aqueous solutions is an advantage in terms of cellular access. In nonpolar solvents and lipid membranes it possesses a 6–8 fold higher solubility than in water [51-53]. Thus, ˙NO can easily diffuse through cell membranes [51]. In this context, it is interesting to note that ˙NO rapidly partitions into red blood cells where it quickly converts into nitrate using heme-bound oxygen of hemoglobin [54–56]. This limits the biological half-life of nitric oxide *in vivo* to less than a second, whereas the concentration of nitric oxide relevant for cellular signaling can persist in phosphate-buffered saline for ~1 h. Thus NO itself is not particularly toxic *in vivo* [57].

A closer look into the nature of the chemical bonds of the molecule is relevant for understanding its physiological functions. Both, symmetry and energy level of the single occupied molecular orbital (SOMO) of the ˙NO radical are critical to its reactivity with other molecules (Fig. 3). The low ionization potential of ˙NO (9.25 eV) [58] indicates that the electron residing in the π* anti-bonding orbital can be readily lost, resulting in the formation of an NO^+ nitrosonium ion.

The radical nature of ˙NO is evidenced by its ability to react with unpaired electrons of other molecules, e.g. biradical O_2 and superoxide anion ($O_2^{\bullet -}$). The product of radical oxygen and ˙NO still has one unpaired electron that has the ability to further react with other molecules. Taken together, the reaction of radical ˙NO with oxygen consumes two equivalents of ˙NO to give two equivalents of nitrogen dioxide (˙NO_2), via the following reactions (1)–(3):

$$^{\bullet}NO + O_2 \rightarrow {}^{\bullet}OONO \quad (1)$$

$$^{\bullet}OONO + {}^{\bullet}NO \rightarrow ONOONO \quad (2)$$

$$ONOONO \rightarrow 2\ {}^{\bullet}NO_2 \quad (3)$$

Nitrogen monoxide's dimer exists, but it is very unstable. ˙NO consists of dimers only at low temperatures (about −163 °C). Solid ˙NO seems to consist mostly of dimers. This is surprising since dimerization of ˙NO molecule could lead to a structure where all atoms have a full complement of eight valence electrons satisfying the octet rule (ON–NO). In order to reconcile this apparent anomaly, the molecular orbitals of ˙NO must be considered.

Simple combination of the nitrogen and oxygen atomic orbitals gives set of molecular orbitals (Fig. 3). In the order of increasing energy, the atomic orbitals (2s and 2p) of nitrogen and oxygen splits into a sigma-bonding (σ) and corresponding sigma-antibonding (σ*) orbitals, two degenerate pi-bonding (π) and two degenerate pi-antibonding (π*)

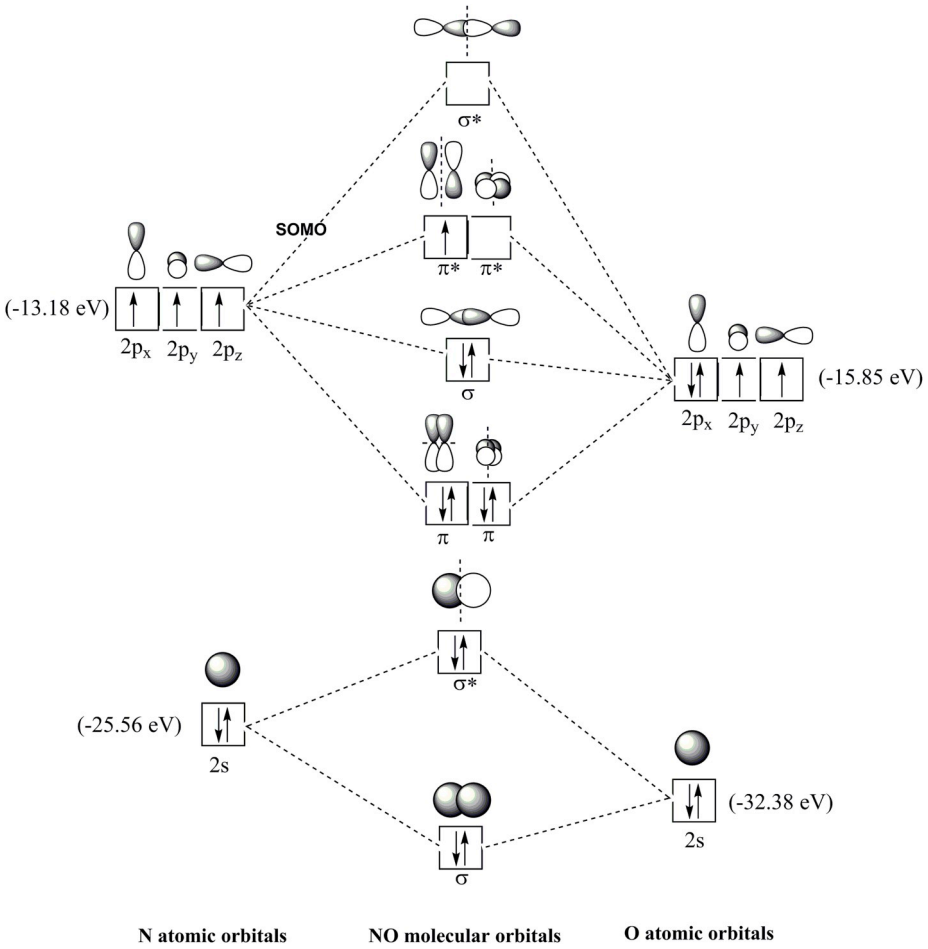

Fig. 3. Molecular orbital diagram of NO.

orbitals [59]. Since the total number of valence electrons in the ˙NO molecule is 11 (five from nitrogen and six from oxygen), the low-lying σ bonding and σ antibonding orbitals along with the bonding π and σ orbitals are all filled.

Thus, ˙NO has a net bond order of 2.5 because there is one electron in the π* antibonding orbital. When ˙NO forms a dimer (O═N–N═O), seems that unpaired electrons on antibonding orbitals can only π-overlap. In ˙NO the electronic density is shifted towards oxygen atom, and the "petals" of π-orbitals don't have enough electronic density to support a stable bond (some call it a half-bond). So the dimer bond is weak - its enthalpy of formation is about 17 kJ [60]. Therefore, since there is no net gain in overall bonding when ˙NO dimerizes and entropy would favor the monomer, ˙NO exists as a monomer at room temperature and pressure.

The antibonding orbitals that are occupied in ˙NO are in fact π symmetry, but when the dimer forms that is no longer relevant. It is a sigma-bond. The enthalpy of the newly formed sigma bond in the dimer is weak because the net gain in bond is off set by the loss of a very odd set of single-electron resonance forms available for ˙NO monomer. Given $\Delta G = -17$ J/mol, and that dimerization is entropically disfavored, when the total free energy is considered there is no gain since entropic effects are on the order of 10–30 kJ/mol. Thus any small gain in enthalphy is offset by the loss of entropy.

The above rationale for the observation that ˙NO exists primarily as a monomeric species at room temperature and pressure is purely qualitative. This issue has also been examined quantitatively. The experimental dimerization energy for two ˙NO molecules has been measured to be in the range of only 2–4 kcal/mol [61–63]. In order to understand the low magnitude of this bond energy, one needs to examine the ˙NO dimer itself.

The ˙NO dimer has been the subject of considerable experimental and theoretical study [61–68]. The experimental structure is *cis*-ONNO, with ONN angle of 99.6°. The NN bond in the dimer is extremely long (2.263 Å) [69], while the N–O bond lengths are 1.161 Å [68]. No single Lewis structure can accurately describe the electronic state of this molecule; however, considering the bond lengths, a single N–N bond and triple N–O bonds would be better.

Thus, the NN interaction in the ˙NO dimer is considerably weaker than a covalent bond and yet cannot be explained entirely by van der Waals interactions, which provide stabilization on the order of only tenths of a kilocalorie per mole. Interestingly, ˙NO dimer formation does very little to disturb the nitrogen–oxygen orbital overlap. A partial rationale for the unusually long and weak NN bond in the ˙NO dimer may also be found in an examination of the nature of the unpaired electron in the ˙NO monomer.

3. Chemistry of nitric oxide derivatives

˙NO can easily be oxidized [56,70,71]. In biological systems, it often is closely associated with nitrogen dioxide (˙NO_2), dinitrogen trioxide (N_2O_3), dinitrogen tetroxide (N_2O_4), nitrate (NO_3^-), nitrite (NO_2^-) and peroxynitrite ($ONOO^-$) (Fig. 4). Most of these compounds form *in vitro*. Only a few can be detected *in vivo* [72].

˙NO reacts with dioxygen or molecular oxygen which like ˙NO, is also a radical species. ˙NO undergoes decomposition when it is auto-oxidized gas, nitrogen dioxide reaction in the gas phase to form the characteristic brown gas, nitrogen dioxide (reaction (4)). However, since the reaction between ˙NO and O_2 follows third order kinetics, the

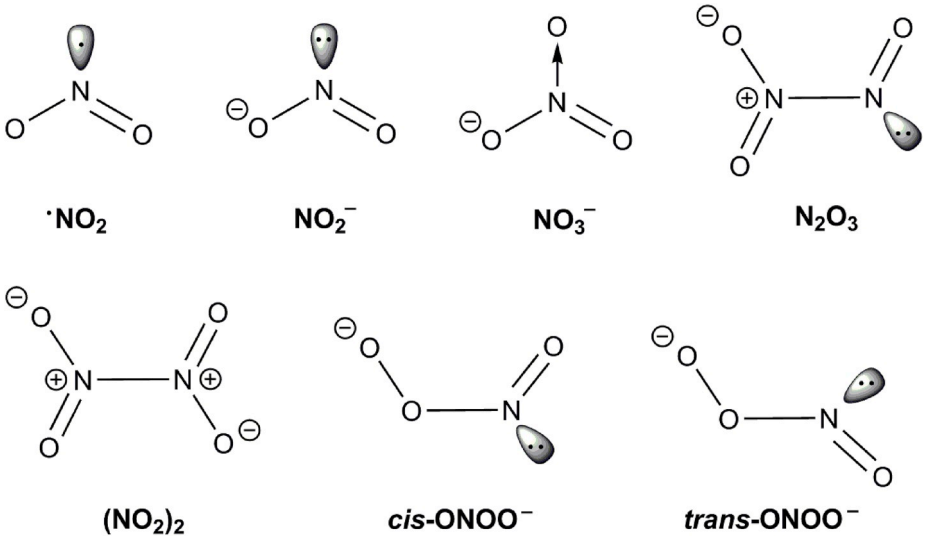

Fig. 4. Structure of simple nitrogen-oxygen containing species associated.

rate it proceeds will depend on the concentration of ·NO, where at high concentrations of both O_2 and ·NO, the reaction proceeds rapidly while at low NO concentrations the oxidation of ·NO will be very slow [73,74]:

$$2\ {}^{\cdot}NO + O_2 \rightarrow 2\ {}^{\cdot}NO_2 \quad (4)$$

$$2\ {}^{\cdot}NO_2 \rightarrow 2\ (NO_2)_2 \quad (5)$$

$${}^{\cdot}NO_2 + {}^{\cdot}NO \rightarrow N_2O_3 \quad (6)$$

·NO_2 either dimerises to form dimeric $(NO_2)_2$ (reaction (5)) or reacts again with ·NO to form N_2O_3 (reaction (6)), which may donate a ·NO moiety to various nucleophilic targets, such as thiols [50]. In the aqueous phase, this reaction proceeds slowly to eventually produce the water-soluble terminal products nitrite (NO_2^-) or nitrate (NO_3^-) (Fig. 5) [75].

·NO reacts with the one-electron reduction product of oxygen, superoxide $O_2^{\cdot -}$, at near-diffusion controlled rate to produce peroxynitrite ($ONOO^-$) (reaction 7) [70,76]. It has also been put forth recently that peroxynitrite could form during the reaction between molecular oxygen and NO^- (reaction 8) [70,77], although this may depend on the excitation state of NO^- and has been deemed by some authors to be thermodynamically unviable [54],[77]:

$${}^{\cdot}NO + O_2^{\cdot -} \rightarrow ONOO^- \quad (7)$$

$$NO^- + O_2 \rightarrow ONOO^- \quad (8)$$

Peroxynitrite plays an important role *in vivo* as the reaction of superoxide with ·NO kinetically competes with the enzymatic activity of superoxide dismutase [70], which catalyzes the reaction of superoxide with protons to hydrogen peroxide. The peroxynitrite anion is a strong oxidant, which is relatively stable in alkaline solutions [78]. At physiological conditions peroxynitrite rearranges to nitrite and nitrate in 30% and 70%, respectively [79]. However, its protonated form in acidic solutions (HOONO, $pK_a = 6.8$) decomposes rapidly within < 1s [78-81] mostly towards nitrate (reaction 9) [82]. Thus, the fate of peroxynitrite is highly dependent on its environmental conditions.

$$HOONO \rightarrow [HO^{\cdot} + {}^{\cdot}NO_2] \rightarrow NO_3^- + H^+ \quad (9)$$

$$HOONO + O_2^{\cdot -} + H^+ \rightarrow O_2 + {}^{\cdot}NO_2 + H_2O \quad (10)$$

$$HOONO + {}^{\cdot}NO \rightarrow {}^{\cdot}NO_2 + NO_2^- + H^+ \quad (11)$$

The potential physiological generation of $^-$OONO/HOONO results from the rapid reaction of $O_2^{\cdot -}$ with ·NO, both known to be generated in significant amounts under certain pathophysiological conditions. However, HOONO can react further with either ·NO or $O_2^{\cdot -}$ to generate, among other things, ·NO_2 [reactions (10) and (11)] [83,84].

In contrast to peroxynitrite, peroxynitrous acid can easily partition into the hydrophobic phase of lipid membranes [51,52,83,84]. Intracellular accumulation of peroxynitrous acid thus results in significant flux of this molecule across cellular membranes via passive or facilitated diffusion [51,84]. The overall distance that peroxynitrous acid can diffuse is given by its concentration and biological half-life [84]. Several studies have reported a displacement of peroxynitrous acid up to several cell diameters away [51][84].

Peroxynitrous acid may undergo homolytic cleavage to hydroxyl and the nitrogen dioxide radicals or alternatively heterolytic cleavage to a nitronium cation and a hydroxide anion [55,56,70,78].

Recent studies indicated that the yield of hydroxyl and the nitrogen dioxide radicals formation approximates 25–35% in the absence of competitive reactions [56,85,86]. However, it has to be taken into consideration that under physiological conditions, where bicarbonate abounds, the formation of hydroxyl and the nitrogen dioxide radicals is limited by the reaction of peroxynitrite with CO_2 forming nitrosoperoxocarbonate ($ONOOCO_2^-$) [56,87]. 33% of which subsequently decomposes to carbonate radicals and nitrogen dioxide 51,87,88].

Another important aspect related to the generation of peroxynitrite *in vivo* is the timing and the stoichiometry of ·NO and superoxide radical formation. The production of peroxynitrite is maximal, when the molar ratio between ·NO and superoxide is around 1 (1.1–1) [53,78,89,90]. This stoichiometry sharply limits the capability of peroxynitrite to attack biomolecules. The molar ratio between ·NO and superoxide thus rules the cytotoxic potential of *in situ* generated peroxynitrite.

Although nitrogen dioxide can also be formed by oxidation of nitrite for example via myeloperoxidase using hydrogen peroxide [89,91], peroxynitrite also is considered as an important endogenous source of nitrogen dioxide [88].

4. Post-translational modifications of proteins mediated by nitric oxide and its derivatives

·NO -mediated signaling involves the modifications of tyrosine and cysteine residues of the proteins. Apoptotic and necrotic cell death induced by its derivatives are consequence of lipid peroxidation, cysteine oxidation, protein nitration and S-nitrosylation (S-nitrosation) [54-56,71,86,91,92].

Nitration of protein tyrosine residues occurs by the reaction with peroxynitirite and nitrogen dioxide [88,93,94]. Both oxidants may

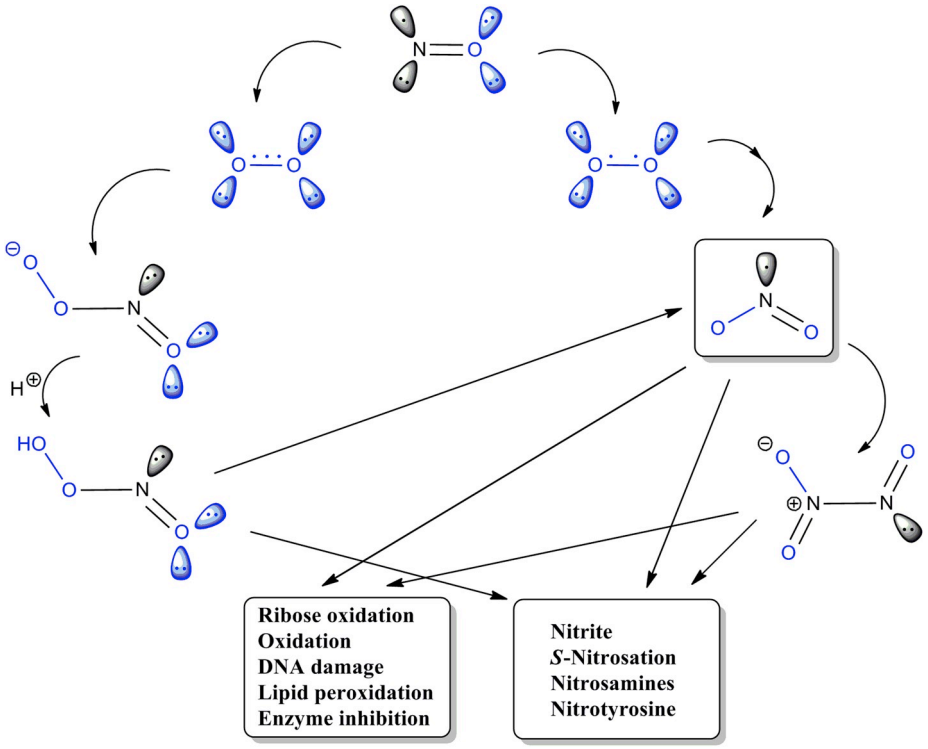

Fig. 5. Plausible cytotoxic mechanism of nitric oxide and its derivatives.

nitrate tyrosine at position 3 of the phenolic ring, generating 3-nitrotyrosine, the predominant final product in neutral solution. 3-nitrotyrosine is an indicator of nitro-oxidative stress under pathophysiological conditions [93]. However, it was evidenced that peroxynitrite does not contribute to protein tyrosine nitration *in vitro* and *in vivo* models [91,95,96]. As suggested by Pfeiffer and Mayer peroxynitrite at physiological pH does not react with carbon dioxide and thus does not nitrate tyrosine [91]. It was furthermore proved that it is the nitrogen dioxide that directly nitrates tyrosine residues within hydrophobic regions under *in vivo* conditions [88,94-96]. Induction of secondary oxidative processes is dependent on nonlinear relationships among nitrogen dioxide flux rates, antioxidant concentrations, and diffusivity of secondary reactive species [51,94].

Tyrosine nitration also interferes directly and indirectly with tyrosine phosphorylation/dephosphorylation signaling pathways [97] i.e. several tyrosine residues in the manganese superoxide dismutase (MnSOD) can be nitrated, what results in decreased enzyme activity. MnSOD is considered as a tumor suppressor in various cancer models [98,99]. On the other side, in light of its antioxidant enzymatic function, many types of malignant tumors often are characterized by decreased activity of MnSOD [100–102]. These observation seems to be quite puzzling. Indeed, the inverse correlation between cellular proliferative potential and MnSOD activity has been previously established [98].

S-glutathionylation refers to the incorporation of glutathione thiol group into a protein and the formation of a mixed disulfide bond between the cysteine residue and glutathion thiol. It can be induced by peroxynitirite, nitrogen dioxide or formed by the reaction with nitrosothiol [[103],104]. Moreover, it was evidenced that nitrogen dioxide causes the widespread increases in protein S-glutathionylation in lung tissue animal model [104].

Importantly, altered *S*-glutathionylation patterns occur in diseases characterized by redox deregulation, such as cancer. S-glutathionylation of the tumor suppressor p53 has been found in human cancers, and functional inactivation of p53 by *S*-glutathionylation inhibits its DNA binding in cancer cells [103]. Moreover, changes in redox homeostasis induced by nitro-oxidative stress cause S-glutathionylation of protein disulfide isomerase and mediate cancer cell death through activation of the unfolded protein response and abrogation of ERα stability and signaling [105].

Protein S-nitrosation is defined as the addition of nitroso group moiety to a thiol group of cysteine residue in peptide or proteins. S-nitrosation is modulated by nitric oxide oxides (N_2O_3/NOx), or metal–nitric oxide complexes (M − NO) [106]. Protein S-nitrosation has been considered as a mechanism for signal transduction by nitric oxide and S-nitrosothiols. Specificity of S-nitrosation can be associated with accumulation of high concentrations of nitrosylating species in the vicinity of specific cysteine residues in subcellular compartments [106].06 Signaling events regulated by S-nitrosylation may lead to either progression or inhibition of cancer. Notably, at least 1.000 proteins modified by S-nitrosation have been identified in mammalian cells [97].

$^{\bullet}$NO –mediated signaling involves also S-nitrosation of the regulatory ferrous heme of the soluble isoform of the guanyl cyclase leading to its activation and increased production of second messenger, cGMP [107,108]. Recently, the statement that $^{\bullet}$NO produced by activated macrophages inactivates the iron/sulfur centers in mitochondria of tumor cells has been re-evaluated by a series of experiments, what revealed that $^{\bullet}$NO -dependent inactivation of iron/sulfur centers may be mediated by peroxynitrite [109,110] However, it was further evidenced that peroxynitrite is not itself a nitrosating agent, in contrast to its decomposition products like nitrogen dioxide [111]. Notably, S-nitrosation induced by peroxynitrite occurs at low efficacy and seems not to be an important signaling pathway *in vivo* [107,108]. While, it was proved that nitrogen dioxide triggers the biosynthesis of nitraosamines in mice model [111].

Protein S-nitrosation may affect the transcriptional activity i.e. the activity of nuclear transcription factor NF-κB [112]. Hypoxia-inducible factor-1 (HIF-1) and estrogen receptors are redox sensitive transcription actors are either regulated by S-nitrosation [106,113-115]. Interestingly, S-nitrosation of NF-κB and matrix metalloproteinase 9 (MMP9) promotes cell death whereas S-nitrosation of caspase-3, caspase-9, and

c-Jun N-terminal kinase prevents activity and inhibits apoptosis [106,116]. Death receptors were also found to be regulated by S-nitrosation such as death receptor DR4 [106,117]. Notably, ˙NO can indirectly influence the apoptotic caspase cascade via S-nitrosation of FLICE inhibitory protein (FLIP) and Bcl-2. S-nitrosation of FLIP and Bcl-2 inhibits their proteasomal degradation, stabilizing both of these anti-apoptotic proteins to enhance their pro-survival function in cancer [118]. Moreover, it was established that co-generation of ˙NO and superoxide decreased accumulation of pro-apoptotic BAX [119]. It was further demonstrated that both p53 and BAX are early components in ˙NO and superoxide-induced apoptosis in mesangial cells [119]. Decrease in phospho-Akt was also an essential event upstream from BAX integration in breast cancer cells [120].

Due to the above, we hypothesize that the main deteriorating derivative of ˙NO *in vivo* is nitrogen dioxide (Fig. 5). Notably, as much as 20 nM of nitrogen dioxide/mg protein was correlated with severe deterioration of pancreatic acinar cell ultrastructure [121].

5. Nitric oxide and its derivatives impacts on mitochondria

Mitochondria are highly specialized organelles that are crucial players in fundamental aspects of cell pathophysiology. However, beyond energy production, they play an important role in regulation of cell signaling, cell death, and biosynthetic metabolism [122,123]. Dysregulation of mitochondrial biogenesis and elimination is a reason of great number of diseases including neurodegeneration and cancers [124,125]. ˙NO and its derivatives have multiple effects on mitochondria that impact on cell physiology and cell death [71]. It is well established that nitro-oxidative stress-associated cell death is linked to mitochondrial membrane depolarization and mitochondrial dynamics via mitochondrial biogenesis, fission, fusion or mitophagy [10,122,126]. Notably, ˙NO does stimulate mitochondrial biogenesis, but it is also produced and consumed by mitochondria [127,128]. The crucial factor regulating the mitochondrial biogenesis is peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PARGC1A, PGC-1α) [127-129]. Interestingly, Nisoli et al. evidenced that PGC-1α –mediated induction of mitochondrial biogenesis is driven by ˙NO in cultured mouse brown adipocytes [130]. They have further confirmed that ˙NO generated by eNOS plays a role in mitochondrial biogenesis in a cGMP-dependent manner [130]. Notably, invasive tumor cells, via upregulation of PGC-1α, increase oxidative phosphorylation, oxygen consumption rate and ultimately, mitochondrial biogenesis. Indeed, the relationship between level of ˙NO, expression of PGC-1α in cancer cells and the formation of metastases was found [128,129].

Our research team also proved that anticancer activity of 2-methoxyestradiol, a physiological metabolite of 17β-estradiol, is associated with generation of ˙NO and regulation of mitochondrial biogenesis [127]. 2-methoxyestradiol, branded as PANZEM, is currently being evaluated in advanced phases of clinical trials [131–139]. In our studies we have revealed that anticancer mode of the chemotherapeutic is strictly based on nuclear hijacking of nNOS and local generation of ˙NO [140]. Indeed, nuclear recruitment of nNOS and the production of ˙NO in the nucleus are necessary for the induction of the mitochondrial biogenesis pathway [128].

6. DNA-damaging effects mediated by nitric oxide and its derivatives

˙NO and its derivatives are also able to induce direct- and mediated-genotoxic effects [141,142]. However, ˙NO *per se* is not very reactive with DNA and does not directly attack DNA, as was initially believed, but this effect instead depends on its conversion into its derivatives [53,143]. Indeed, several studies demonstrated that ˙NO itself is not able to induce single strand breaks [144]. The biochemical nature of DNA damage mediated by reactive nitrogen species is associated with induction of genomic instability and cell death [140][143]. It is well known that DNA is a polyanion making direct interactions between molecules in probable electrostatic manner. However, it is also clear that base pairing in DNA is the result of hydrogen bonding interactions and base stacking, what explains hydrophobicity and partially non-polar feature of DNA [145]. The well-established DNA damaging factor is peroxynitrite [144,146]. DNA strand breaks induced by peroxynitrite activate the repair enzyme, poly (ADP)-ribose (PARS). Excessive activation of PARS can lead to rapid consumption of NAD^+ + and ATP, and consequently to cell dysfunction and death by apoptosis or necrosis [147].

However, beyond peroxynitrite, nitrogen dioxide formed from protonated peroxynitrite or by nitric oxide autooxidation seems to be responsible for ˙NO -mediated DNA damage. The life time of nitrogen dioxide in cytosol is < 10 μs. The diffusion distance of nitrogen dioxide is 0.2 μm in the cytoplasm and < 0.8 μm in plasma [73]. Notably, peroxynitrite due to its negative charge at physiological pH seems to be electrostatically repelled from DNA. While, nitrogen dioxide, due to its electron neutral and lipophilic radical nature, may be a direct cause of DNA strand breaks [148,149]. Nitrogen dioxide has a preference to dissolve in organic solvents as compared with water [51-53]. Due to its electro-chemical nature, DNA is an ideal target for nitrogen dioxide during nitro-oxidative stress [51]. Interestingly, nitric oxide tends to accumulate in the hydrophobic layers of biological membranes, where it often undergoes oxidation to its derivatives such as peroxynitrite or nitrogen dioxide (in case of the former, only under conditions of superoxide anion bioavailability). Indeed, in our data obtained by means of stopped flow spectrophotometry using specific nitrogen dioxide tracker - complex ion *cis*-$[Cr(C_2O_4)(AaraNH_2)(OH_2)_2]^+$ [72,121,150,151], we observed that anti 2-methoxyestradiol, may induce DNA damage most plausibly via nitrogen dioxide generation, what results in cancer cell death (data not yet published). Notably, DNA damage mediated by nitrogen dioxide was previously reported *in vivo* studies [149].

7. Current nitric oxide-based anticancer strategies

7.1. Nitrated fatty acids against cancer

Nitrate fatty acids (NO_2–FAs) are considered reactive lipid species (RLS) derived from the non-enzymatic oxidation of polyunsaturated fatty acids by nitric oxide and nitric oxide-derived species, such as peroxynitrite or nitrogen dioxide [152,153]. Nitrate fatty acids are also called nitro-fatty acids, nitrolipids or nitroalkenes. Nitroalkylation, the addiction of NO_2–FAs to protein, is a reversible post-translational modification [153,154]. Nitrate fatty acids were found both in animal and plant kingdom [155]. They were detected in healthy human plasma and urine at nanomolar concentrations and in cardiac mitochondria after ischemia at micromolar concentrations [156]. In plants nitrate fatty acids can be found in fresh olive oil, extra virgin olive oil and rockcress [157].

Due to electrophilic properties of lipid-derived species, nitrolipids modulate cell signaling in both physiological and pathophysiological processes [156]. The generation of nitrate fatty acids is promoted under pathological conditions [156]. In oxidative inflammatory environment, the immune system activates lipases, causing the cleavage of fatty acids from cellular membranes. The electrophilic RLS allows nucleophiles to attack proteins, leading to modification of their structures, catalytic activities, charge, hydrophobicity and in their localization [158].

On the other hand, an electrophilic character of nitrate fatty acids promotes adaptive and anti-inflammatory cell signaling responses [158–160]. Cui T et al. reported that inflammatory effects nitroalkene derivatives of linoleic acid and oleic acid (LNO2 and OA-NO2, respectively) are associated with inhibited secretion of proinflammatory cytokines in macrophages and endothelial cells [158]. In the light of above, Woodcock CC et al. investigated the effect of nitro-oleic acid on multiple preclinical models of triple-negative breast cancer - the most aggressive mammary breast cancer subtype [159]. Nitrated oleic acid

inhibited cancer cell viability and tumor cell proliferation–related signaling reactions *in vivo*. What is more, after oral admiration, the compound reduced tumor growth in MDA-MB-231 xenograft mice model [159,160]. The study revealed that, in comparison with non-tumorigenic human breast epithelial MCF-10A cells, nitrated oleic acid NO_2-OA more selectively inhibited triple-negative breast cancer function [159]. It was attributed to easier mechanisms for maintaining redox homeostasis in non-tumorigenic breast epithelium than in cancer tissue. Woodcock CC et al. reported that the lipid electrophile NO_2-OA impacts NF-κB signaling in triple-negative breast cancer at multiple levels, including the suppression of IKKβ phosphorylation, inhibition of IκBα degradation, and enhanced ubiquitination and proteasomal degradation of RelA [159]. These observations reveal that electrophilic fatty acid nitroalkenes react with more alkylation-sensitive targets in triple-negative breast cancer cells to inhibit growth and viability [159].

A unique pharmacokinetic profile is expected from nitrated fatty acids because of their ability to undergo reversible reactions, such as Michael addition and esterification [161,162]. Fazzari et al. confirmed different distribution profile of 10-nitro-oleic acid (10-NO_2-OA) *in vivo* in the adipose tissue of NO_2-OA-treated mice [163]. This study lends new insight into the unique pharmacokinetics and pharmacologic properties of NO2–FAs, what makes them perfect drug candidates [163]. Due to its unique pharmacological properties and effective tumor proliferation inhibition, further investigation on utilization of nitrolipids in anticancer therapy is needed.

7.2. Nitric oxide donors

˙NO donors belong to a group of novel anticancer agents. Their inhibitory effect on survival and induction of tumor cell death has been demonstrated on various tumor models [164]. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been considered as promising chemopreventive agents due to their potent antioxidant and anti-inflammatory properties [165][166]. ˙NO-NSAIDs consist of a traditional non-steroidal anti-inflammatory drugs that bears a nitric oxide-releasing moiety which reduces gastric toxicity [167]. ˙NO-NSAID has been shown to be very effective in prevention of colon and pancreatic cancers in vitro and in animal tumor models [168].

Acetylsalicylic acid (ASA), commonly known as aspirin, is the archetype of the nonsteroidal anti-inflammatory drug family. Decreased effectiveness of aspirin during long term use associated with side effects such as gastrointestinal bleeding and hemorrhagic stroke led to the development of more potent and safe aspirin derivatives. One of these compounds is nitric oxide-donating aspirin (˙NO-Aspirin, ˙NO ASA) in which ˙NO-donating group is attached to aspirin through a linker molecule. The development of ˙NO-Aspirin plays important role of ˙NO in mucosal defense [169]. The gastroduodenal toxicity of ˙NO -ASA in healthy volunteers was reported to be equivalent to that of placebo [170,171]. ˙NO-Aspirin inhibited lung tumorigenesis *in vitro* and *in vivo* and these effects were associated with reduced activation of EGFR and its downstream effectors. The cancer preventive activities and gastrointestinal safety profile of ˙NO-Aspirin were improved as compared with the aspirin [170].

Among the ˙NO donors, NONOates are reported to be the most commonly used low-molecular-weight nitric oxide donors in biomedical applications [172]. Indeed, administration of the NONOate diethylenetriamine ˙NO adduct (DETA/˙NO) at range of concentrations from 250 to 1000 μmol/L inhibited cell growth of the human leukemia line HL-60 [173]. Examination of human metastatic prostate cells confirmed, that high levels of ˙NO, derived from the DETA-NONOate, inhibits epithelial-mesenchymal transition (EMT) and reverses both the mesenchymal phenotype and the tumor invasive properties [174].

Notably, also ˙NO-derived HIV protease inhibitors are potential novel class of anticancer drugs. A nitric oxide-modified derivative of saquinavir (saquanivir-˙NO) has reported strong antitumoral effects with low toxic adverse effects [175–182]. Its anticancer effects was examined in numerous cancer cells, including primary acute lymphoblastic, acute myeloid leukemia, prostate, glioma and melanoma cells [175–182]. In contrast to saquinavir, saquinavir-˙NO had no effect on the viability of primary cells [177–179]. p70S6 kinase and activation of p53 were indicated as a plausible targets of saquanivir-NO [177–179]. The HIV protease inhibitors such as saquinavir-NO, are used with great success in treating HIV-related Kaposi's sarcoma [180]. Another ˙NO-releasing derivative of the *anti*-HIV protease inhibitor is lopinavir-˙NO. It exhibits a two-fold stronger anticancer activity as compared to lopinavir *in vitro* [181]. Importantly, lopinavir-˙NO reduces the viability of glioblastoma cells at significantly lower concentrations than the parental drug. The anticancer effect of lopinavir-˙NO seem to be present even upon drug elimination [182].

7.3. Nanoparticles

Unfortunately, the majority of ˙NO donors do not release free radical in a controlled manner directly to specific target. Moreover, low-molecular-weight ˙NO donors that disperse rapidly in biological medium are easily cleared in kidneys and liver. Due to above, utilization of ˙NO donors in target therapy is very difficult. To overcome these issues, ˙NO donors can be incorporated into nanomaterials or chemically linked to their surface. Nanomaterials have ability to load high levels of nitric oxide, are considerably stable, and mimic endogenous ˙NO production by iNOS [183].

The administration of exogenous ˙NO represents a challenge, because the non-systemic route of administration is relatively difficult to achieve. There is a growing interest in a development of nitric oxide eluting materials as potent anticancer agents. Targeted- ˙NO directly and continuously released into the tumor site may be a key in the treatment of cancer [184]. Polymeric nanoparticles are the most commonly used class of nanomaterials used to carry and deliver nitric oxide in tumor cells. NONOate-multiarm-polymer-nanocarriers, composed of poly-(6-O-methacryloyl-D-galactose), release therapeutic micromolar concentrations of nitric oxide. The cytotoxicity of polymeric nanoparticles loaded with ˙NO was confirmed in human cancer cell lines. Nitric oxide-releasing nanomaterials may be successfully co-administered with traditional chemotherapy agents, such as cisplatin. They sensitize cancer cells, decrease the used concentration of cisplatin, and reduce traditional chemotherapy side effects [185].

Under physiological conditions, ˙NO release is induced by increased temperature and pH [186]. Due to above, zwitterionic NONOate was encapsulated into thermosensitive liposomes. The half-life of ˙NO released from free NONOate was about 1 h in contrast to 3 h - 7 h for NONOate incorporated into the thermo-sensitive liposomes [186]. The increased temperature found in the tumor site may be sufficient to trigger nitric oxide release from the thermo-sensitive liposomes. Induction of nitric oxide release might also be achieved in the case of cancer with external stimuli, such as with hyperthermia [186].

Silica nanoparticles are another molecular carriers that support anticancer activity of nitric oxide. However, release of ˙NO from silica nanoparticles completed in less than 1 h was the most valuable therapeutic effect. Prolonged release of nitric oxide took several hours. This is comparable to the physiological effect of endogenous nitric oxide production by iNOS [187].

The use of metal nanoparticles and liposomes in therapies gives the possibility of controlling nanoparticles in the human body. Example of particles with ability to control in an organism are iron oxide (Fe_3O_4) magnetic nanoparticles coated with mercaptosuccinic acid (MSA) and dimercaptosuccinic acid (DMSA). The transformation of the Fe_3O_4 nanoparticles allows to obtain S-nitrosated nanoparticles, which act as spontaneous nitric oxide donors. Their cytotoxicity depends on the concentration in the body and duration of action. However, the most promising in cancer therapy are the supermagnetic nanoparticles active at room temperature [188]. Moreover, they can be guided directly to the tumor cells upon application of an external magnetic field what

result in site-specific nitric oxide release to tumor cells [188]. Furthermore, cytotoxicity of gold nanoparticles (AuNPs), capped with 2-mercapto-5-nitrobenzimidazole (MNBI) releasing •NO to cervical cancer cells (HeLa cells) was confirmed in the dark and under visible light irradiation. The cell mortality was higher after treatment under light irradiation in comparison with the dark condition. Moreover, the cytotoxicity of •NO-photo-releasing capped AuNPs with cisplatin was found to possess similar antitumor effects. In fact, an 80% lower dose of AuNPs was found to have a similar cytotoxicity as cisplatin. The structure of the nanomaterial strengthens the apoptotic properties by releasing nitric oxide after irradiation with visible light [189]. Nitro-oxidative stress is also one of the mechanisms inducing cell death by nanoparticles. A study conducted on human pancreatic ductal adenocarcinoma cells (PANC-1), demonstrated anti-cancer potential of silver nanoparticles (AgNP), by an induction of ROS and RNS [150].

The control under the light nanoparticles is also possible with quantum dots (QD) [190]. •NO donors linked to QDs may have important applications as anti-tumoral agents. The RSNO S-nitrosocysteine (Cys-•NO) was combined with multiwall T_iO_2 nanotube-doped PbS quantum dots (PbS QDs) to release free nitric oxide. The obtained nitric oxide-eluting hybrid nanomaterial (3.6 nm diameter and several hundred nanometer lengths) was able to release millimolar amounts of •NO in a few minutes. This can lead to significant cytotoxicity of cancer cells and is extremely promising in future therapies [190].

7.4. Regulation of intracellular level of nitro-oxidative stress as the sophisticated anticancer tool

Notably, beyond release the molecule of nitric oxide from a carrier, some anticancer agents may also regulate NOS-dependent intracellular level of nitro-oxidative stress. One of the compounds is 2-methoxyestradiol, described also above. Our research group evidenced that 2-ME selectively induces nNOS expression and drives nuclear translocation of the enzyme resulting in cancer cell death [93,127,140,191]. The anticancer mechanism of 2-methoxyestradiol was strictly associated with local •NO generation and DNA damage [140]. We have also evidenced that 2-ME regulates mitochondrial biogenesis pathway in cancer cells under control of •NO [127]. Moreover, our preliminary data, obtained by means of stopped flow spectrophotometry using specific nitrogen dioxide tracker - complex ion *cis*-$[Cr(C_2O_4)(AaraNH_2)(OH_2)_2]^+$ [72,121,150,151], suggest that nitrogen dioxide is a mediator of cytotoxic activity of 2-methoxyestradiol (data not yet published).

8. The second side of the coin – nitric oxide abrogates efficiency of anticancer therapy

As above-mentioned, low concentrations of •NO may support tumor proliferation, migration and resistance to anticancer therapies. Furthermore, the role of iNOS and •NO signaling on modulation of anticancer efficacy is well documented. iNOS overexpression is found in great number of malignancies including breast cancer, ovarian cancer, melanoma or glioblastoma [192–194]. Moreover, overexpression of iNOS is correlated with aggressive phenotype, disease progression and poor survival outcome of patients with ovarian cancer and estrogen receptor-negative breast cancer [45][195][196]. Especially, iNOS was reported to be a strong predictor of survival in patients with very aggressive phenotype of estrogen receptor negative breast cancer, namely: triple negative breast cancer [193,194]. Interestingly, iNOS participate in poor survival outcomes among estrogen receptor-negative breast cancer in contrast to estrogen receptor-positive tumors [195]. This may be due to •NO-mediated induction of interleukin 8 selectively in estrogen receptor-negative breast cancer cells [195]. Alternatively, the differences between estrogen receptor-positive and negative-breast cancer cells may be associated with tumor microenvironment i.e. additional effects of estrogens on •NO level [195].

•NO promotes overall cancer progression via activating several oncogenic signaling pathways i.e. extracellular signal-regulated kinase (ERK)/Akt, c-myc or PP2A phosphatase [193]. Pro-cancerogenic activity of •NO is strictly dependent on its concentrations. As reported low/physiological concentrations of nitric oxide, below or equal to 100 nM, promotes glycolysis for ATP production, oxidative defense and cell proliferation of cancer cells [197]. While, activation of extracellular signal-regulated kinase (ERK) and Akt, and stabilization of hypoxia-inducible factor (Hif 1α) occurs at concentrations range of 200 nM up to 500 nM concentrations of •NO [198]. In addition, phosphorylation of p53 occurs at 700–800 nM concentrations of •NO [45,195,198].

Interestingly, PP2A phosphatase, a tumor suppressor, negatively regulates the same cancer-related signaling pathways activated by •NO [193]. It was thus found the potential therapeutically target for therapy of estrogen receptor-negative breast cancer [193]. Indeed, in our previous study we have evidenced that 2-ME activate PP2A. 2-ME in a concentration-dependent manner had impacts on the gene and protein expressions, as well as phosphorylation status of PP2A-α phosphatase in osteosarcoma cancer cells [199]. We further demonstrated that 2-methoxyestradiol decreases the level of nNOS phosphorylated at position of serine 847 referred to as inactive pool of enzyme via activation of PP2A phosphatase [199].

Notably, it was reported by numerous *in vitro* and *in vivo* studies that endogenous •NO lead to development of resistance to photodynamic therapy. What is even more interesting, it was only the nitric oxide derived from iNOS responsible for cytoprotective effects. Photodynamic therapy activates iNOS/nitric oxide signaling pathway leading to increased proliferation and aggressiveness of cancer cells, involving breast and prostate cancers or glioblastoma [200–202]. Effector proteins responsible for photokilling resistance and cellular survival are among others MAP kinases, cyclooxygenase 2, integrins, Bcl-xl or matrix metaloproteinase-9 [197,203,204]. Importantly, both constitutive and stress-induced iNOS seem to be engaged in the enhanced aggressiveness and resistance to photodynamic therapy [205].

Thus, specific iNOS inhibitors may complete the anticancer adjuvant therapy [203]. NOS inhibitors like 1400 W, L-NIO, JQ1, has potent anticancer potential stated in preclinical studies [203,204,206]. The future of iNOS inhibitors as anticancer agents will be clearer over the next years as results of the current clinical trials become available. Up to date ASP9853, inhibitor of iNOS dimerization, in combination with docetaxel was evaluated in Phase I study in advanced solid tumors. Inhibition of NOS significantly enhances the efficacy of docetaxel response in triple negative breast cancer [194]. Unfortunately, due to toxicity and lack of clear efficacy, the study was terminated [206]. Nonetheless, control under the endogenous nitric oxide levels may constitute an important tool in fight with cancer.

9. Conclusions

•NO may both inhibit or increase tumor progression depending on the biological context, its concentration and duration of its production. Elevated levels of reactive nitrogen species produced in cancer cells are essential for the carcinogenesis and activation of signaling pathways responsible for proliferation, metabolism and angiogenesis. However, the increased status of oxidative stress in cancer cells makes them more sensitive to reactive nitrogen species, which can lead to oxidation of proteins, lipids and DNA. Despite the established contribution of •NO to the pathogenesis of cancer, the implementation of •NO-based- anticancer drugs requires the necessary further research.

Funding

The manuscript was funded by the Iuventus Plus project of Polish Ministry of Science and Higher Education No IP 2015 022074. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.niox.2019.09.005.

References

[1] J. Egea, I. Fabregat, Y.M. Frapart, et al., European contribution to the study of ROS: a summary of the findings and prospects for the future from the COST action BM1203 (EU-ROS), Redox Biol 13 (2017) 94–162, https://doi.org/10.1016/j.redox.2017.05.007.

[2] L.B. Sullivan, N.S. Chandel, Mitochondrial reactive oxygen species and cancer, Cancer Metabol. 2 (2014) 17, https://doi.org/10.1186/2049-3002-2-17.

[3] S. Rajendran, X. Shen, J. Glawe, G.K. Kolluru, G. Kevil C, Nitric oxide and hydrogen sulfide regulation of ischemic vascular growth and remodeling, Comp. Physiol. 9 (3) (2019 Jun 12) 1213–1247, https://doi.org/10.1002/cphy.c180026.

[4] S. Rybárová, D. Kluchová, K. Lovásová, M. Kocisová, K. Schmidtová, Expression of peptidergic and nitrergic structures in dorsal root ganglia of the rabbit, Eur. J. Histochem. 44 (4) (2000) 377–384 PubMed PMID: 11214863.

[5] R.M. Rapoport, M.B. Draznin, F. Murad, Endothelium-dependent relaxation in rat aorta may be mediated through cyclic GMP-dependent protein phosphorylation, Nature 306 (1983) 174–176.

[6] W.K. Alderton, C.E. Cooper, Nitric oxide synthases: structure, function and inhibition, Knowles RG Biochem J 357 (Pt 3) (2001) 593–615.

[7] R.G. Knowles, S. Moncada, Nitric oxide synthases in mammals, Biochem. J. 298 (1994) 249–258.

[8] C. Villanueva, C. Giulivi, Subcellular and cellular locations of nitric oxide synthase isoforms as determinants of health and disease, Free Radic. Biol. Med. 49 (3) (2010 Aug 1) 307–316, https://doi.org/10.1016/j.freeradbiomed.2010.04.004 Epub 2010 Apr 11. Review. PubMed PMID: 20388537; PubMed Central PMCID: PMC2900489.

[9] L. Zhou, D.Y. Zhu, Neuronal nitric oxide synthase: structure, subcellular localization, regulation, and clinical implications, Nitric Oxide 20 (4) (2009 Jun) 223–230, https://doi.org/10.1016/j.niox.2009.03.001 Epub 2009 Mar 17. Review. PubMed PMID: 19298861.

[10] G.C. Brown, Nitric oxide and mitochondria, Front. Biosci. 12 (2007 Jan 1) 1024–1033 PMID: 17127357.

[11] L. Litvinova, D.N. Atochin, N. Fattakhov, M. Vasilenko, P. Zatolokin, E. Kirienkova, Nitric oxide and mitochondria in metabolic syndrome, Front. Physiol. 6 (2015) 20, https://doi.org/10.3389/fphys.2015.00020.

[12] P. Ghafourifar, E. Cadenas, Mitochondrial nitric oxide synthase, Trends Pharmacol. Sci. 26 (4) (2005 Apr) 190-5. Review. PubMed PMID: 15808343.

[13] Z. Lacza, E. Pankotai, D.W. Busija, Mitochondrial nitric oxide synthase: current concepts and controversies, Front. Biosci. 14 (2009 Jan 1) 4436–4443 Review. PubMed PMID: 19273361; PubMed Central PMCID: PMC4570492.

[14] S.L. Elfering, T.M. Sarkela, C. Giulivi, Biochemistry of mitochondrial nitric-oxide synthase, J. Biol. Chem. 277 (41) (2002 Oct 11) 38079–38086 Epub 2002 Aug 1. PubMed PMID: 12154090.

[15] P. Ghafourifar, C.K. Sen, Mitochondrial nitric oxide synthase, Front. Biosci. 12 (2007 Jan 1) 1072–1078 Review. PubMed PMID: 17127362.

[16] G.M. McKnight, C.W. Duncan, C. Leifert, M.H. Golden, Dietary nitrate in man: friend or foe? Br. J. Nutr. 81 (1999) 349–358 Lundberg JO, Feelisch M, Bjorne H, Jansson EA, Weitzberg E. Cardioprotective effects of vegetables: is nitrate the answer? Nitric Oxide 2006;15:359–62.

[17] J.O. Lundberg, M.T. Gladwin, A. Ahluwalia, N. Benjamin, N.S. Bryan, A. Butler, P. Cabrale, A. Fago, M. Feelisch, P.C. Ford, B.A. Freeman, M. Frenneaux, J. Friedman, M. Kelm, C.G. Kevil, D.B. Kim-Shapiro, A.V. Kozlov, J.R. Lancaster Jr., D.J. Lefer, K. McColl, K. McCurry, R.P. Patel, J. Petersson, T. Rassaf, V.P. Reutov, G.B. Richter-Addo, A. Schechter, S. Shiva, K. Tsuchiya, E.E. van Faassen, A.J. Webb, B.S. Zuckerbraun, J.L. Zweier, E. Weitzberg, Nitrate and nitrite in biology, nutrition and therapeutics, Nat. Chem. Biol. 5 (12) (2009 Dec) 865–869, https://doi.org/10.1038/nchembio.260.

[18] J.O. Lundberg, E. Weitzberg, M.T. Gladwin, The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics, Nat. Rev. Drug Discov. 7 (2) (2008 Feb) 156–167, https://doi.org/10.1038/nrd2466. Review PubMed PMID: 18167491.

[19] A. Machha, A.N. Schechter, Dietary nitrite and nitrate: a review of potential mechanisms of cardiovascular benefits, Eur. J. Nutr. 50 (5) (2011 Aug) 293–303, https://doi.org/10.1007/s00394-011-0192-5 Epub 2011 May 31. Review. PubMed PMID: 21626413;PubMed Central PMCID: PMC3489477.

[20] N.G. Hord, Y. Tang, N.S. Bryan, Food sources of nitrates and nitrites: the physiologic context for potential health benefits, Am. J. Clin. Nutr. 90 (2009) 1–10.

[21] C.P. Bondonno, K.D. Croft, J.M. Hodgson, Dietary nitrate, nitric oxide, and cardiovascular health, Crit. Rev. Food Sci. Nutr. 56 (12) (2016 Sep 9) 2036–2052, https://doi.org/10.1080/10408398.2013.811212. Review PubMed PMID: 25976309.

[22] A. Petersen, S. Stoltze, Nitrate and nitrite in vegetables on the Danish market: content and intake, Food Addit. Contam. 16 (1999) 291–299.

[23] M. Govoni, E.A. Jansson, E. Weitzberg, J.O. Lundberg, The increase in plasma nitrite after a dietary nitrate load is markedly attenuated by an antibacterial mouthwash, Nitric Oxide 19 (2008) 333–337.

[24] A.J. Webb, N. Patel, S. Loukogeorgakis, M. Okorie, Z. Aboud, S. Misra, R. Rashid, P. Miall, J. Deanfield, N. Benjamin, R. MacAllister, A.J. Hobbs, A. Ahluwalia, Acute blood pressure lowering, vasoprotective, and antiplatelet properties of dietary nitrate via bioconversion to nitrite, Hypertension 51 (2008) 784–790.

[25] E.A. Jansson, L. Huang, R. Malkey, M. Govoni, C. Nihlen, A. Olsson, M. Stensdotter, J. Petersson, L. Holm, E. Weitzberg, J.O. Lundberg, A mammalian functional nitrate reductase that regulates nitrite and nitric oxide homeostasis, Nat. Chem. Biol. 4 (2008) 411–417.

[26] C.P. Bondonno, K.D. Croft, J.M. Hodgson, Dietary nitrate, nitric oxide and cardiovascular health, Crit. Rev. Food Sci. Nutr. 56 (12) (2016 Sep 9) 2036–2052, https://doi.org/10.1080/10408398.2013.811212. Review PubMed PMID: 25976309.

[27] M.T. Gladwin, J.H. Shelhamer, A.N. Schechter, M.E. Pease-Fye, M.A. Waclawiw, J.A. Panza, F.P. Ognibene, R.O. Cannon, Role of circulating nitrite and S-nitrosohemoglobin in the regulation of regional blood flow in humans, Proc. Natl. Acad. Sci. U.S.A. 97 (2000) 11482.

[28] N.S. Bryan, T. Rassaf, R.E. Maloney, C.M. Rodriguez, F. Saijo, J.R. Rodriguez, M. Feelisch, Cellular targets and mechanisms of nitros (yl) ation: an insight into their nature and kinetics in vivo, Proc. Natl. Acad. Sci. U.S.A. 101 (2004) 4308.

[29] S. Shiva, Mitochondria as metabolizers and targets of nitrite, Nitric Oxide 22 (2) (2010 Feb 15) 64–74, https://doi.org/10.1016/j.niox.2009.09.002 Epub 2009 Sep 27. Review. PubMed PMID: 19788924; PubMed Central PMCID: PMC2819587.

[30] A.V. Kozlov, K. Staniek, H. Nohl, Nitrite reductase activity is a novel function of mammalian mitochondria, FEBS Lett. 454 (1999) 127–130.

[31] A.F. Vanin, L.M. Bevers, A. Slama-Schwok, E.E. Van Faassen, Nitric oxide synthase reduces nitrite to NO under anoxia, Cell. Mol. Life Sci. 64 (2007) 96–103.

[32] C.E. Sparacino-Watkins, J. Tejero, B. Sun, M.C. Gauthier, V. Ragireddy, B.A. Merchant, J. Wang, I. Azarov, P. Basu, M.T. Gladwin, Nitrite reductase and NO synthase activity of the mitochondrial molybdopterin enzymes mARC1 and mARC2, J. Biol. Chem. 289 (2014) 10345–10358.

[33] J. Wang, S. Krizowski, K. Fischer-Schrader, D. Niks, J. Tejero, C. Sparacino-Watkins, L. Wang, V. Ragireddy, S. Frizzell, E.E. Kelley, et al., Sulfite oxidase catalyzes single-electron transfer at molybdenum domain to reduce nitrite to nitric oxide, Antioxidants Redox Signal. 23 (2015) 283–294.

[34] J.J. Doel, B.L.J. Godber, T.A. Goult, R. Eisenthal, R. Harrison, Reduction of organic nitrites to nitric oxide catalyzed by xanthine oxidase: possible role in metabolism of nitrovasodilators, Biochem. Biophys. Res. Commun. 270 (2000) 880–885.

[35] H. Li, T.K. Kundu, J.L. Zweier, Characterization of the magnitude and mechanism of aldehyde oxidase-mediated nitric oxide production from nitrite, J. Biol. Chem. 284 (2009) 33850–33858.

[36] Z. Zhang, D.P. Naughton, D.R. Blake, N. Benjamin, C.R. Stevens, P.G. Winyard, M.C. Symons, R. Harrison, Human xanthine oxidase converts nitrite ions into nitric oxide (NO), Biochem. Soc. Trans. 25 (1997) 524S.

[37] D. Bender, A. Tobias Kaczmarek, D. Niks, R. Hille, G. Schwarz, Mechanism of nitrite-dependent NO synthesis by human sulfite oxidase, Biochem. J. 476 (12) (2019 Jun 28) 1805–1815, https://doi.org/10.1042/BCJ20190143 PubMed PMID: 31167903.

[38] G. Schwarz, R.R. Mendel, Molybdenum cofactor biosynthesis and molybdenum enzymes, Annu. Rev. Plant Biol. 57 (2006) 623–647 Review. PubMed PMID: 16669776.

[39] G. Schwarz, R.R. Mendel, M.W. Ribbe, Molybdenum cofactors, enzymes and pathways, Nature 460 (7257) (2009 Aug 13) 839–847, https://doi.org/10.1038/nature08302. Review PubMed PMID: 19675644.

[40] J.D. Malhotra, R.J. Kaufman, Endoplasmic reticulum stress and oxidative stress: a vicious cycle or a double-edged sword? Antioxidants Redox Signal. 9 (2007) 2277–2293, https://doi.org/10.1089/ars.2007.1782.

[41] C. Gorrini, I.S. Harris, T.W. Mak, Modulation of oxidative stress as an anticancer strategy, Nat. Rev. Drug Discov. 12 (2013) 931–947, https://doi.org/10.1038/nrd4002.

[42] L. Ying, L.J. Hofseth, An emerging role for endothelial nitric oxide synthase in chronic inflammation and cancer, Cancer Res. 67 (4) (2007) 1407–1410, https://doi.org/10.1158/0008-5472.CAN-06-2149.

[43] B. Oronsky, G.R. Fanger, N. Oronsky, S. Knox, J. Scicinski, The implications of hyponitroxia in cancer, Transl Oncol 7 (2) (2014) 167–173, https://doi.org/10.1016/j.tranon.2014.02.001.

[44] D. Fukumura, S. Kashiwagi, R.K. Jain, The role of nitric oxide in tumour progression, Nat. Rev. Cancer 6 (2006) 521–534.

[45] D. Basudhar, V. Somasundaram, G.A. de Oliveira, A. Kesarwala, J.L. Heinecke, R.Y. Cheng, S.A. Glynn, S. Ambs, D.A. Wink, L.A. Ridnour, Nitric oxide synthase-2-derived nitric oxide drives multiple pathways of breast cancer progression, Antioxidants Redox Signal. 26 (18) (2017 Jun 20) 1044–1058, https://doi.org/10.1089/ars.2016.6813.

[46] S.K. Choudhari, M. Chaudhary, S. Bagde, A.R. Gadbail, V. Joshi, Nitric oxide and cancer: a review, World J. Surg. Oncol. 11 (1) (2013) 118, https://doi.org/10.1186/1477-7819-11-118.

[47] A. Friebe, D. Koesling, Regulation of nitric oxide-sensitive guanylyl cyclase, Circ. Res. 93 (2) (2003) 96–105, https://doi.org/10.1161/01.RES.0000082524.34487.31.

[48] C. Gorrini, I.S. Harris, T.W. Mak, Modulation of oxidative stress as an anticancer strategy, Nat. Rev. Drug Discov. 12 (12) (2013) 931–947, https://doi.org/10.1038/nrd4002.

[49] S. Maraj, S. Khan, X.-Y. Cui, R. Cammack, C.L. Joannou, M.N. Hughes, The interaction of NO and redox-related species with biological targets, Analyst 120 (1995) 699–703, https://doi.org/10.1039/AN9952000699.

[50] J.M. Fukuto, Chemistry of nitric oxide: biologically rele¬vant aspects, Adv. Pharmacol. 34 (1995) 1–16.
[51] M.N. Möller, E. Cuevasanta, F. Orrico, A.C. Lopez, L. Thomson, A. Denicola, Diffusion and Transport of Reactive Species Across Cell Membranes. Adv Exp Med Biol. 1127 (2019) 3–19, https://doi.org/10.1007/978-3-030-11488-6_1.
[52] S. Signorelli, M.N. Möller, E.L. Coitiño, A. Denicola, Nitrogen dioxide solubility and permeation in lipid membranes, Arch. Biochem. Biophys. 512 (2) (2011) 190–196.
[53] G.L. Squadrito, E.M. Postlethwait, On the hydrophobicity of nitrogen dioxide: could there be a "lens" effect for NO(2) reaction kinetics? Nitric Oxide 21 (2) (2009) 104–109, https://doi.org/10.1016/j.niox.2009.05.008.
[54] M.N. Hughes, Relationships between nitric oxide, nitroxyl ion, nitrosonium cation and peroxynitrite, Biochim. Biophys. Acta 1411 (2–3) (1999) 263–272 PMID: 10320662.
[55] J.M. Fukuto, L.J. Ignarro, In vivo aspects of nitric oxide (NO) chemistry: does peroxynitrite (-OONO) play a major role in cytotoxicity? Acc. Chem. Res. 30 (4) (1997) 149–152, https://doi.org/10.1021/ar960010y.
[56] R. Radi, Oxygen radicals, nitric oxide, and peroxynitrite: redox pathways in molecular medicine, Proc. Natl. Acad. Sci. U. S. A. 115 (23) (2018) 5839–5848, https://doi.org/10.1073/pnas.1804932115.
[57] P. Pacher, J.S. Beckman, L. Liaudet, Nitric oxide and peroxynitrite in health and disease, Physiol. Rev. 87 (1) (2007) 315–424, https://doi.org/10.1152/physrev.00029.2006.
[58] G. Reiser, W. Habenicht, K. Müller-Dethlefs, E.W. Schlag, The ionization energy of nitric oxide, Chem. Phys. Lett. 152 (2–3) (1988) 119–123, https://doi.org/10.1016/0009-2614(88)87340-8.
[59] W.L. Jorgensen, L. Salem, The Organic Chemist's Book of Orbitals, Academic Press, New York, 1973, p. 80.
[60] K.A. Nguyen, M.S. Gordon, J.A. Montgomery Jr., H.H. Michels, Structures, bonding, and energetics of N_2O_2 isomers, J. Phys. Chem. 98 (1994) 10072–10078.
[61] J.R. Hetzler, M.P. Casassa, D.S. King, Product energy correlations in the dissociation of overtone excited NO dimer, J. Phys. Chem. 95 (1991) 8086–8095.
[62] A. Dkhissi, P. Soulard, A. Perrin, N. Lacome, The NO dimer, J. Mol. Spectrosc. 183 (1997) 12–17.
[63] E. Forte, H. van den Bergh, The heat of formation of the nitric oxide dimer and its UV spectrum, Chem. Phys. 30 (1978) 325–331.
[64] A.L.L. East, The 16 valence electronic states of nitric oxide dimer (NO)(2), J. Chem. Phys. 109 (1998) 2185–2193.
[65] A.L.L. East, A.R.W. McKellar, J.K.G. Watson, The intermolecular vibrations of the NO dimer, J. Chem. Phys. 109 (1998) 4378–4383.
[66] M.P. Casassa, J.C. Stephenson, D.S. King, Vibrational predissociation of the nitric oxide dimer: total energy distribution in the fragments, J. Chem. Phys. 85 (1986) 2333–2334.
[67] J.E. Williams, J.N. Murrell, Structure and stability of the nitric oxide dimer, J. Am. Chem. Soc. 93 (1971) 7149–7152.
[68] S.G. Kukolich, Structure of the NO dimer, J. Am. Chem. Soc. 104 (1982) 4715–4716.
[69] A.R.W. McKellar, J.K.G. Watson, B.J. Howard, The NO dimer: 15N isotopic infrared spectra, line widths and force field, Mol. Phys. 86 (1995) 273–286.
[70] J.S. Beckman, W.H. Koppenol, Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly, Am. J. Physiol. 271 (5 Pt 1) (1996 Nov) C1424–C1437 Review.PubMed PMID: 8944624.
[71] D.A. Wink, J.B. Mitchell, Chemical biology of nitric oxide: insights into regulatory, cytotoxic, and cytoprotective mechanisms of nitric oxide, Free Radic. Biol. Med. 25 (4–5) (1998) 434–456 PMID: 9741580.
[72] A. Dabrowska, D. Jacewicz, A. Łapińska, B. Banecki, A. Figarski, M. Szkatuła, J. Lehman, J. Krajewski, J. Kubasik-Juraniec, M. Woźniak, L. Chmurzyński, Pivotal participation of nitrogen dioxide in L-arginine induced acute necrotizing pancreatitis: protective role of superoxide scavenger 4-OH-TEMPO, Biochem. Biophys. Res. Commun. 326 (2) (2005) 313–320, https://doi.org/10.1016/j.bbrc.2004.11.032.
[73] E. Ford, M.N. Hughes, P. Wardman, Kinetics of the reactions of nitrogen dioxide with glutathione, cysteine, and uric acid at physiological pH, Free Radic. Biol. Med. 32 (12) (2002) 1314–1323 PMID: 12057769.
[74] A.R. Butler, F.W. Flitney, D.L. Williams, NO, nitrosonium ions, nitroxide ions, nitrosothiols and iron-nitrosyls in biology: a chemist's perspective, Trends Pharmacol. Sci. 16 (1995) 18–22 Bonner F.T., Stedman G. The Chemistry of Nitric Oxide and Redox-Related Species, New York: John Wiley & Sons Ltd, 1996:3–27.
[75] M. Kelm, J. Schrader, Control of coronary vascular tone by nitric oxide, Circ. Res. 66 (1990) 1561–1575.
[76] R.E. Huie, S. Padmaja, The reaction of no with superoxide, Free Radic. Res. Commun. 18 (1993) 195–199.
[77] M. Kirsch, H. de Groot, Formation of peroxynitrite from reaction of nitroxyl anion with molecular oxygen. J Biol Chem. 277 (16) (2002) 13379–13388.
[78] C.E. Richeson, P. Mulder, V.W. Bowry, K.U. Ingold, The complex chemistry of peroxynitrite Decomposition: new Insights1, J. Am. Chem. Soc. 120 (1998) 7211–7219.
[79] S. Pfeiffer, A.C. Gorren, K. Schmidt, E.R. Werner, B. Hansert, D.S. Bohle, B. Mayer, Metabolic fate of peroxynitrite in aqueous solution. Reaction with nitric oxide and pH-dependent decomposition to nitrite and oxygen in a 2:1 stoichiometry, J. Biol. Chem. 272 (6) (1997 Feb 7) 3465–3470 PubMed PMID: 9013592.
[80] D. Trotti, S. Nussberger, A. Volterra, M.A. Hediger, Differential modulation of the uptake currents by redox interconversion of cysteine residues in the human neuronal glutamate transporter EAAC1, Eur. J. Neurosci. 9 (10) (1997 Oct) 2207–2212 PubMed PMID: 9421181.
[81] S.V. Lymar, J.K. Hurst, CO2-catalyzed one-electron oxidations by peroxynitrite: properties of the reactive intermediate, Inorg. Chem. 37 (2) (1998) 294–301.
[82] J.W. Coddington, J.K. Hurst, S.V. Lymar, Hydroxyl radical formation during peroxynitrous acid decomposition, J. Am. Chem. Soc. 121 (1999) 2438–2443.
[83] A.M. Miles, D.S. Bohle, P.A. Glassbrenner, B. Hansert, D.A. Wink, M.B. Grisham, Modulation of superoxide-dependent oxidation and hydroxylation reactions by nitric oxide, J. Biol. Chem. 271 (1996) 40–47.
[84] W.A. Pryor, G.L. Squadrito, The chemistry of peroxynitrite: a product from the reaction of nitric oxide with superoxide, Am. J. Physiol. 268 (5 Pt 1) (1995) L699–L722.
[85] M.B. Grisham, D. Jourd'heuil, D.A. Wink, Nitric oxide I Physiological chemistry of nitric oxide and its metabolites: implications in inflammantion, Am. J. Physiol. 39 (1999) G315–G321.
[86] S. Goldstein, G. Czapski, J. Lind, G. Merenyi, Tyrosine nitration by simultaneous generation of ·NO and O÷2 under physiological conditions, J. Biol. Chem. 275 (2000) 3031–3036.
[87] S. Goldstein, G. Czapski, Formation of Peroxynitrate from the Reaction of Peroxynitrite with CO_2: Evidence for Carbonate Radical Production, J. Am. Chem. Soc. 120 (14) (1998) 3458–3463 https://doi.org/10.1021/ja9733043.
[88] M. Kirsch, H.G. Korth, R. Sustmann, H. de Groot, The pathobiochemistry of nitrogen dioxide, Biol. Chem. 383 (3–4) (2002 Mar-Apr) 389–399 Review. PubMed PMID: 12033430.
[89] A. van der Vliet, J.P. Eiserich, B. Halliwell, C.E. Cross, Formation of reactive nitrogen species during peroxidase-catalyzed oxidation of nitrite. A potential additional mechanism of nitric oxide-dependent toxicity, J. Biol. Chem. 272 (12) (1997 Mar 21) 7617–7625 PubMed PMID: 9065416.
[90] H. Gunaydin, K.N. Houk, Mechanisms of peroxynitrite-mediated nitration of tyrosine. Chem Res Toxicol. 22 (5) (2009) 894–898, https://doi.org/10.1021/tx800463y.
[91] S. Pfeiffer, B. Mayer, Lack of tyrosine nitration by peroxynitrite generated at physiological pH, J. Biol. Chem. 273 (42) (1998 Oct 16) 27280–27285 PubMed PMID: 9765252.
[92] I. Kovacs, C. Lindermayr, Nitric oxide-based protein modification: formation and site-specificity of protein S-nitrosylation, Front. Plant Sci. 4 (2013) 137, https://doi.org/10.3389/fpls.2013.00137. eCollection 2013.
[93] M. Gorska, A. Kuban-Jankowska, M.A. Zmijewski, M. Gorzynik, M. Szkatula, M. Wozniak, Neuronal nitric oxide synthase induction in the antitumorigenic and neurotoxic effects of 2-methoxyestradiol, Molecules 19 (9) (2014) 13267–13281, https://doi.org/10.3390/molecules190913267.
[94] L.W. Velsor, C.A. Ballinger, J. Patel, E.M. Postlethwait, Influence of epithelial lining fluid lipids on NO(2)-induced membrane oxidation and nitration, Free Radic. Biol. Med. 34 (6) (2003 Mar 15) 720–733 PubMed PMID: 12633749.
[95] S. Pfeiffer, A. Lass, K. Schmidt, B. Mayer, Protein tyrosine nitration in mouse peritoneal macrophages activated in vitro and in vivo: evidence against an essential role of peroxynitrite, FASEB J. 15 (13) (2001 Nov) 2355–2364 PMID: 11689461. 2:.
[96] S. Pfeiffer, A. Lass, K. Schmidt, B. Mayer, Protein tyrosine nitration in cytokine-activated murine macrophages. Involvement of a peroxidase/nitrite pathway rather than peroxynitrite, J. Biol. Chem. 276 (36) (2001 Sep 7) 34051–34058 PMID: 11425852.
[97] H.P. Monteiro, P.E. Costa, A.K. Reis, A. Stern, Nitric oxide: protein tyrosine phosphorylation and protein S-nitrosylation in cancer, Biomed. J. 38 (2015) 380–388, https://doi.org/10.4103/2319-4170.158624.
[98] A. Kim, Modulation of MnSOD in cancer: epidemiological and experimental evidence, Toxicol Res 26 (2) (2010) 83–93, https://doi.org/10.5487/TR.2010.26.2.083.
[99] L.W. Oberley, Mechanism of the tumor suppressive effect of MnSOD overexpression, Biomed. Pharmacother. 59 (2005) 143–148, https://doi.org/10.1016/j.biopha.2005.03.006.
[100] N. Yamanaka, D. Deamer, Superoxide dismutase activity in WI-38 cell cultures:effects of age, trypsinization and SV-40 transformation, Physiol. Chem. Phys. 6 (2) (1974) 95–106 PubMed PMID: 4369250.
[101] O. Dionisi, T. Galeotti, T. Terranova, A. Azzi, Superoxide radicals and hydrogen peroxide formation in mitochondria from normal and neoplastic tissues, Biochim. Biophys. Acta 403 (1975) 292–300.
[102] S.K. Sahu, L.W. Oberley, R.H. Stevens, E.F. Riley, Superoxide dismutase activity of Ehrlich ascites tumor cells, J. Natl. Cancer Inst. 58 (1977) 1125–1128.
[103] C.L. Grek, J. Zhang, Y. Manevich, D.M. Townsend, K.D. Tew, Causes and consequences of cysteine S-glutathionylation, J. Biol. Chem. 288 (37) (2013) 26497–26504, https://doi.org/10.1074/jbc.R113.461368.
[104] S.W. Aesif, V. Anathy, M. Havermans, A.S. Guala, K. Ckless, D.J. Taatjes, Y.M. Janssen-Heininger, In situ analysis of protein S-glutathionylation in lung tissue using glutaredoxin-1-catalyzed cysteine derivatization, Am. J. Pathol. 175 (1) (2009 Jul) 36–45, https://doi.org/10.2353/ajpath.2009.080736 PubMed PMID: 19556513; PubMed Central PMCID: PMC2708792.
[105] Y. Xiong, Y. Manevich, K.D. Tew, D.M. Townsend, S-glutathionylation of protein disulfide isomerase regulates estrogen receptor α stability and function, Int J Cell Biol 2012 (2012) 273549.
[106] D.T. Hess, A. Matsumoto, S.O. Kim, H.E. Marshall, J.S. Stamler, Protein S-nitrosylation: purview and parameters, Nat. Rev. Mol. Cell Biol. 6 (2) (2005) 150–166, https://doi.org/10.1038/nrm1569.
[107] T.A. Heinrich, R.S. da Silva, K.M. Miranda, C.H. Switzer, D.A. Wink, J.M. Fukuto, Biological nitric oxide signalling: chemistry and terminology, Br. J. Pharmacol. 169 (7) (2013 Aug) 1417–1429, https://doi.org/10.1111/bph.12217. Review PubMed PMID: 23617570; PubMed Central PMCID: PMC3724101.
[108] B. Mayer, S. Pfeiffer, A. Schrammel, D. Koesling, K. Schmidt, F. Brunner, A new pathway of nitric oxide/cyclic GMP signaling involving S-nitrosoglutathione, J.

Biol. Chem. 273 (6) (1998 Feb 6) 3264–3270 PubMed PMID: 9452441.
[109] C.-F. Chang, A.R. Dier, N. Hogg, Cancer Cell Metabolism and the Modulating Effects of Nitric Oxide, Free Radic Biol Med. 79 (2015) 324–336, https://doi.org/10.1016/j.freeradbiomed.2014.11.012.
[110] J.C. Drapier, J.B. Hibbs Jr., Murine cytotoxic activated macrophages inhibit aconitase in tumor cells. Inhibition involves the iron-sulfur prosthetic group and is reversible. J Clin Invest. 78 (1986) 790–797.
[111] Z.M. Iqbal, K. Dahl, S.S. Epstein, Role of nitrogen dioxide in the biosynthesis of nitraosamines in mice, Science 207 (4438) (1980 Mar 28) 1475–1477 PubMed PMID:7361099.
[112] C.H. Switzer, L.A. Ridnour, R. Cheng, J. Heinecke, A. Burke, S. Glynn, S. Ambs, D.A. Wink, S-nitrosation mediates multiple pathways that lead to tumor progression in estrogen receptor-negative breast cancer, Forum Immunopathol. Dis. Ther. 3 (2) (2012) 117–124 PubMed PMID: 23543871; PubMed Central PMCID: PMC3609660.
[113] G.L. Semenza, Hypoxia-inducible factor 1 (HIF-1) pathway, Sci. STKE 407 (2007) cm8, https://doi.org/10.1126/stke.4072007cm8.
[114] L. Fang, P. Sonveaux, Z.N. Rabban, S. Liu, B. Yan, Q. Huang, Z. Vujaskovic, M.W. Dewhirst, C.-Y. Li, Regulation of HIF-1α Stability through S-nitrosylation, Mol Cell. 26 (1) (2007) 63–74, https://doi.org/10.1016/j.molcel.2007.02.024.
[115] H.J. Garbán, D.C. Márquez-Garbán, R.J. Pietras, L.J. Ignarro, Rapid nitric oxide-mediated S-nitrosylation of estrogen receptor: regulation of estrogen-dependent gene transcription. Proc Natl Acad Sci U S A. 102 (7) (2005) 2632–2636.
[116] F. Vannini, K. Kashfi, N. Nath, The dual role of iNOS in cancer, Redox Biol. 6 (2015) 334–343, https://doi.org/10.1016/j.redox.2015.08.009.
[117] L. Leon-Bollotte, S. Subramaniam, O. Cauvard, S. Plenchette-Colas, C. Paul, C. Godard, A. Martinez-Ruiz, P. Legembre, J.F. Jeannin, A. Bettaieb, S-nitrosylation of the death receptor fas promotes fas ligand - mediated apoptosis in cancer cells, Gastroenterology 140 (7) (2011), https://doi.org/10.1053/j.gastro.2011.02.053 2018.e1-4.
[118] N. Azad, V. Vallyathan, L. Wang, V. Tantishaiyakul, C. Stehlik, S.S. Leonard, Y. Rojanasakul, S-nitrosylation of Bcl-2 inhibits its ubiquitin-proteasomal degradation. A novel antiapoptotic mechanism that suppresses apoptosis, J. Biol. Chem. 281 (45) (2006) 34124–34134, https://doi.org/10.1074/jbc.M602551200.
[119] K. Sandau, J. Pfeilschifter, B. Brüne, Nitric oxide and superoxide induced p53 and Bax accumulation during mesangial cell apoptosis, Kidney Int. 52 (2) (1997) 378–386 PMID: 9263993.
[120] S. Pervin, R. Singh, G. Chaudhuri, Nitric-oxide-induced Bax integration into the mitochondrial membrane commits MDA-MB-468 cells to apoptosis: essential role of Akt, Cancer Res. 63 (17) (2003) 5470–5479 PMID: 14500383.
[121] D. Jacewicz, A. Dabrowska, D. Wyrzykowski, J. Pranczk, M. Wozniak, J. Kubasik-Juraniec, N. Knap, K. Siedlecka, A.J. Neuwelt, L. Chmurzynski, A novel biosensor for evaluation of apoptotic or necrotic effects of nitrogen dioxide during acute pancreatitis in rat, Sensors 10 (1) (2010) 280–291, https://doi.org/10.3390/s100100280.
[122] A.V. Kulikov, et al., Mitophagy: link to cancer development and therapy, Biochem. Biophys. Res. Commun. 482 (3) (2017) 432–439.
[123] I. Kim, S. Rodriguez-Enriquez, J.J. Lemasters, Selective degradation of mitochondria by mitophagy, Arch. Biochem. Biophys. 462 (2) (2007) 245–253, https://doi.org/10.1016/j.abb.2007.03.034.
[124] S. Vyas, et al., Mitochondria and cancer, Cell 166 (3) (2016) 555–566.
[125] C.A. Piantadosi, H.B. Suliman, Redox regulation of mitochondrial biogenesis, Free Radic. Biol. Med. 53 (11) (2012) 2043–2053, https://doi.org/10.1016/j.freeradbiomed.2012.09.014.
[126] J. Lee, S. Giordano, J. Zhang, Autophagy, mitochondria and oxidative stress: cross-talk and redox signalling, Biochem. J. 441 (2) (2012) 523–540, https://doi.org/10.1042/BJ20111451.
[127] M. Gorska-Ponikowska, A. Kuban-Jankowska, S. Eisler, U. Perricone, G. Lo Bosco, G. Barone, S. Nussberger, 2-Methoxyestradiol affects mitochondrial biogenesis pathway and succinate dehydrogenase complex flavoprotein subunit a in osteosarcoma cancer cells, Cancer Genomics Proteomics 15 (1) (2018) 73–89, https://doi.org/10.21873/cgp.20067.
[128] K. Aquilano, S. Baldelli, M.R. Ciriolo, Nuclear recruitment of neuronal nitric-oxide synthase by α-syntrophin is crucial for the induction of mitochondrial biogenesis, J. Biol. Chem. 289 (1) (2014) 365–378, https://doi.org/10.1074/jbc.M113.506733.
[129] C. Luo, H.R. Widlund, P. Puigserver, PGC-1 coactivators: shepherding the mitochondrial biogenesis of tumors, Trends Cancer 2 (10) (2016) 619–631, https://doi.org/10.1016/j.trecan.2016.09.006.
[130] E. Nisoli, E. Clementi, C. Paolucci, V. Cozzi, C. Tonello, C. Sciorati, R. Bracale, A. Valerio, M. Francolini, S. Moncada, M.O. Carruba, Mitochondrial biogenesis in mammals: the role of endogenous nitric oxide, Science 299 (5608) (2003) 896–899 PMID: 12574632.
[131] D. Matei, J. Schilder, G. Sutton, S. Perkins, T. Breen, C. Quon, C. Sidor, Activity of 2 methoxyestradiol (Panzem NCD) in advanced, platinum-resistant ovarian cancer and primary peritoneal carcinomatosis: a Hoosier Oncology Group trial, Gynecol. Oncol. 115 (1) (2009) 90–96, https://doi.org/10.1016/j.ygyno.2009.05.042.
[132] J.Y. Bruce, J. Eickhoff, R. Pili, T. Logan, M. Carducci, J. Arnott, A. Treston, G. Wilding, G. Liu, A phase II study of 2-methoxyestradiol nanocrystal colloidaldispersion alone and in combination with sunitinib malate in patients with metastatic renal cell carcinoma progressing on sunitinib, Investig. New Drugs 30 (2) (2012) 794–802.
[133] W.L. Dahut, N.J. Lakhani, J.L. Gulley, P.M. Arlen, E.C. Kohn, H. Kotz, D. McNally, Nguyen D. ParrA, S.X. Yang, S.M. Steinberg, J. Venitz, A. Sparreboom, W.D. Figg, Phase I clinical trial of oral 2-methoxyestradiol, an antiangiogenic and apoptotic agent,in patients with solid tumors, Cancer Biol. Ther. 5 (1) (2006) 22–27.
[134] M.H. Kulke, J.A. Chan, J.A. Meyerhardt, A.X. Zhu, T.A. Abrams, L.S. Blaszkowsky, E. Regan, C. Sidor, C.S. Fuchs, A prospective phase II study of 2-methoxyestradiol administered in combination with bevacizumab in patients with metastatic carcinoid tumors, Cancer Chemother. Pharmacol. 68 (2) (2011) 293–300.
[135] M.R. Harrison, N.M. Hahn, R. Pili, W.K. Oh, H. Hammers, C. Sweeney, K. Kim, S. Perlman, J. Arnott, C. Sidor, G. Wilding, G. Liu, A phase II study of 2-methoxyestradiol (2ME2) Nano Crystal dispersion (NCD) in patients with taxane-refractory, metastatic castrate-resistant prostate cancer (CRPC), Investig. New Drugs 29 (6) (2011) 1465–1474.
[136] A.J. Tevaarwerk, K.D. Holen, D.B. Alberti, C. Sidor, J. Arnott, C. Quon, G. Wilding, G. Liu, Phase I trial of 2-methoxyestradiol NanoCrystal dispersion in advanced solid malignancies, Clin. Cancer Res. 15 (4) (2009) 1460–1465.
[137] S.V. Rajkumar, P.G. Richardson, M.Q. Lacy, A. Dispenzieri, P.R. Greipp, T.E. Witzig, R. Schlossman, C.F. Sidor, K.C. Anderson, M.A. Gertz, Novel therapy with 2-methoxyestradiol for the treatment of relapsed and plateau phase multiple myeloma, Clin. Cancer Res. 13 (20) (2007) 6162–6167.
[138] J. James, D.J. Murry, A.M. Treston, A.M. Storniolo, G.W. Sledge, C. Sidor, K.D. Miller, Phase I safety, pharmacokinetic and pharmacodynamic studies of 2-methoxyestradiol alone or in combination with docetaxel in patients with locally recurrent or metastatic breast cancer, Investig. New Drugs 25 (1) (2007) 41–48.
[139] C. Sweeney, G. Liu, C. Yiannoutsos, J. Kolesar, D. Horvath, M.J. Staab, K. Fife, V. Armstrong, A. Treston, C. Sidor, G. Wilding, A phase II multicenter, randomized, double-blind, safety trial assessing the pharmacokinetics, pharmacodynamics, and efficacy of oral 2-methoxyestradiol capsules in hormone-refractory prostate cancer, Clin. Cancer Res. 11 (18) (2005) 6625–6633.
[140] M. Gorska, A. Kuban-Jankowska, M.A. Zmijewski, A. Marino Gammazza, F. Cappello, M. Wnuk, M. Gorzynik, I. Rzeszutek, A. Daca, A. Lewinska, M. Wozniak, DNA strand breaks induced by nuclear hijacking of neuronal NOS as an anti-cancer effect of 2-methoxyestradiol, Oncotarget 6 (17) (2015) 15449–15463, https://doi.org/10.18632/oncotarget.3913.
[141] L.K. Folkes, P. O'Neill, DNA damage induced by nitric oxide during ionizing radiation is enhanced at replication, Nitric Oxide 34 (2013) 47–55, https://doi.org/10.1016/j.niox.2013.04.005.
[142] H. Wiseman, B. Halliwell, Damage to DNA by reactive oxygen and nitrogen species: role in inflammatory disease and progression to cancer, Biochem. J. 313 (1) (1996) 17–29 PMCID: PMC1216878.
[143] T. Sawa, H. Ohshima, Nitrative DNA damage in inflammation and its possible role in carcinogenesis, Nitric Oxide 14 (2) (2006) 91–100, https://doi.org/10.1016/j.niox.2005.06.005.
[144] E.J. Spek, L.N. Vuong, T. Matsuguchi, M.G. Marinus, B.P. Engelward, Nitric Oxide-Induced Homologous Recombination in Escherichia coli Is Promoted by DNA Glycosylases, J Bacteriol. 184 (13) (2002) 3501–3507, https://doi.org/10.1128/JB.184.13.3501-3507.2002.
[145] B.A. Schweitzer, E.T. Kool, Hydrophobic, non-hydrogen-bonding bases and base pairs in DNA, J. Am. Chem. Soc. 117 (7) (1995) 1863–1872, https://doi.org/10.1021/ja00112a001.
[146] W. Chen, J. Zhuang, Y. Li, Y. Shen, X. Zheng, Myricitrin protects against peroxynitrite-mediated DNA damage and cytotoxicity in astrocytes, Food Chem. 141 (2) (2013) 927–933, https://doi.org/10.1016/j.foodchem.2013.04.033.
[147] L. Gębicka, J. Didik, Oxidative stress induced by peroxynitrite, Adv. Biochem. 56 (2) (2010) 103–106 http://docplayer.pl/16335863-Postepy-biochemii-polskie-towarzystwo-biochemiczne-warszawa-2010-tom-56-numer-2-http-rcin-org-pl.html.
[148] S. Görsdorf, K.E. Appel, C. Engeholm, G. Obe, Nitrogen dioxide induces DNA single-strand breaks in cultured Chinese hamster cells. Carcinogenesis. 11 (1) (1990) 37–41.
[149] E. Bermúdez, S.F. Ferng, C.E. Castro, M.G. Mustafa, DNA strand breaks caused by exposure to ozone and nitrogen dioxide, Environ. Res. 81 (1) (1999) 72–80 PMID: 10361028.
[150] E. Barcińska, J. Wierzbicka, A. Zauszkiewicz-Pawlak, D. Jacewicz, A. Dabrowska, I. Inkielewicz-S, Role of oxidative and nitro-oxidative damage in silver nanoparticles cytotoxic effect against human pancreatic ductal adenocarcinoma cells, Oxid Med Cell Longev 2018 (2018) 8251961, https://doi.org/10.1155/2018/8251961 Published 2018 Aug 16.
[151] D. Jacewicz, A. Dabrowska, D. Wyrzykowski, J. Pranczk, M. Wozniak, J. Kubasik-Juraniec, N. Knap, K. Siedlecka, A.J. Neuwelt, L. Chmurzynski, A novel biosensor for evaluation of apoptotic or necrotic effects of nitrogen dioxide during acute pancreatitis in rat, Sensors 10 (1) (2010) 280–291, https://doi.org/10.3390/s100100280.
[152] D.H. Giamalva, G.K. Kenion, D.F. Church, W.A. Pryor, Rates and mechanisms of reactions of nitrogen dioxide with alkenes in solution, J. Am. Chem. Soc. 109 (23) (1987) 7059–7063, https://doi.org/10.1021/ja00257a025.
[153] M. Fazzari, A. Trostchansky, F.J. Schopfer, S.R. Salvatore, B. Sanchez-Calvo, D. Vitturi, R. Valderrama, J.B. Barroso, R. Radi, B.A. Freeman, et al., Olives and olive oil are sources of electrophilic fatty acid nitroalkenes, PLoS One 9 (2014) e84884.
[154] V. Rudolph, T.K. Rudolph, F.J. Schopfer, G. Bonacci, S.R. Woodcock, M.P. Cole, P.R. Baker, R. Ramani, B.A. Freeman, Endogenous generation and protective effects of nitro-fatty acids in a murine model of focal cardiac ischaemia and reperfusion, Cardiovasc. Res. 85 (2010) 155–166.
[155] F.J. Schopfer, C. Cipollina, B.A. Freeman, Formation and signaling actions of electrophilic lipids, Chem. Rev. 111 (10) (2011) 5997–6021, https://doi.org/10.1021/cr200131e.
[156] R.L. Charles, O. Rudyk, O. Prysyazhna, A. Kamynina, J. Yang, C. Morisseau, B.D. Hammock, B.A. Freeman, P. Eaton, Protection from hypertension in mice by the Mediterranean diet is mediated by nitro fatty acid inhibition of soluble epoxide

hydrolase, Proc. Natl. Acad. Sci. 111 (2014) 8167–8172.
[157] L. Villacorta, L. Chang, S.R. Salvatore, T. Ichikawa, J. Zhang, D. Petrovic-Djergovic, L. Jia, H. Carlsen, F.J. Schopfer, B.A. Freeman, et al., Electrophilic nitro-fatty acids inhibit vascular inflammation by disrupting LPS-dependent TLR4 signalling in lipid rafts, Cardiovasc. Res. 98 (2013) 116–124.
[158] T. Cui, F.J. Schopfer, J. Zhang, K. Chen, T. Ichikawa, P.R. Baker, C. Batthyany, B.K. Chacko, X. Feng, R.P. Patel, A. Agarwal, B.A. Freeman, Y.E. Chen, Nitrated fatty acids: endogenous anti-inflammatory signaling mediators, J. Biol. Chem. 281 (47) (2006) 35686–35698 PMID: 16887803.
[159] C.C. Woodcock, Y. Huang, S.R. Woodcock, S.R. Salvatore, B. Singh, F. Golin-Bisello, N.E. Davidson, C.A. Neumann, B.A. Freeman, S.G. Wendell, Nitro-fatty acid inhibition of triple-negative breast cancer cell viability, migration, invasion, and tumor growth, J. Biol. Chem. 293 (4) (2018) 1120–1137, https://doi.org/10.1074/jbc.M117.814368.
[160] K.R. Bauer, M. Brown, R.D. Cress, C.A. Parise, V. Caggiano, Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype, Cancer 109 (2007) 1721–1728.
[161] M. Fazzari, N. Khoo, S.R. Woodcock, L. Li, B.A. Freeman, F.J. Schopfer, Generation and esterification of electrophilic fatty acid nitroalkenes in triacylglycerides, Free Radic. Biol. Med. 87 (2015) 113–124.
[162] W. Wang, C. Li, T. Yang, Protection of nitro-fatty acid against kidney diseases, Am. J. Physiol. Renal. Physiol. 310 (8) (2016) F697–F704, https://doi.org/10.1152/ajprenal.00321.2015.
[163] M. Fazzari, N.K. Khoo, S.R. Woodcock, D.K. Jorkasky, L. Li, F.J. Schopfer, B.A. Freeman, Nitro-fatty acid pharmacokinetics in the adipose tissue compartment, J. Lipid Res. 58 (2) (2017) 375–385, https://doi.org/10.1194/jlr.M072058.
[164] S. Korde Choudhari, G. Sridharan, A. Gadbail, V. Poornima, Nitric oxide and oral cancer: a review, Oral Oncol. 48 (6) (2012) 475–483, https://doi.org/10.1016/j.oraloncology.2012.01.003.
[165] J.L. Williams, S. Borgo, I. Hasan, E. Castillo, F. Traganos, B. Rigas, Nitric oxide-releasing nonsteroidal anti-inflammatory drugs (NSAIDs) alter the kinetics of human colon cancer cell lines more effectively than traditional NSAIDs: implications for colon cancer chemoprevention, Cancer Res. 61 (8) (2001) 3285–3289 PMID:11309281.
[166] C.M. Ulrich, J. Bigler, J.D. Potter, Non-steroidal anti-inflammatory drugs for cancer prevention: promise, perils and pharmacogenetics, Nat. Rev. Cancer 6 (2) (2006) 130–140, https://doi.org/10.1038/nrc1801.
[167] B. Rigas, K. Kashfi, Nitric-oxide-donating NSAIDs as agents for cancer prevention, Trends Mol. Med. 10 (2004) 324–330, https://doi.org/10.1016/j.molmed.2004.05.004.
[168] K. Kashfi, S. Borgo, J.L. Williams, J. Chen, J. Gao, A. Glekas, F. Benedini, P. Del Soldato, B. Rigas, Positional isomerism markedly affects the growth inhibition of colon cancer cells by nitric oxide-donating aspirin in vitro and in vivo, J. Pharmacol. Exp. Ther. 312 (3) (2005) 978–988, https://doi.org/10.1124/jpet.104.075994.
[169] J.M. Song, et al., Nitric oxide-donating aspirin (NO-Aspirin) suppresses lung tumorigenesis in vitro and in vivo and these effects are associated with modulation of the EGFR signaling pathway, Carcinogenesis 39 (7) (2018) 911–920, https://doi.org/10.1093/carcin/bgy049.
[170] S. Fiorucci, L. Santucci, P. Gresele, R.M. Faccino, P. Del Soldato, A. Morelli, Gastrointestinal safety of NO-aspirin (NCX-4016) in healthy human volunteers: a proof of concept endoscopic study, Gastroenterology 124 (2003) 600–607, https://doi.org/10.1053/gast.2003.50096.
[171] L. Gao, J.L. Williams, Nitric oxide-donating aspirin induces G2/M phase cell cycle arrest in human cancer cells by regulating phase transition proteins, Int. J. Oncol. 41 (1) (2012) 325–330, https://doi.org/10.3892/ijo.2012.1455.
[172] A.J. Burke, F.J. Sullivan, F.J. Giles, S.A. Glynn, The yin and yang of nitric oxide in cancer progression, Carcinogenesis 34 (3) (2013) 503–512, https://doi.org/10.1093/carcin/bgt034.
[173] S. Kumar, M.K. Barthwal, M. Dikshit, Cdk2 nitrosylation and loss of mitochondrial potential mediate NO-dependent biphasic effect on HL-60 cell cycle, Free Radic. Biol. Med. 48 (6) (2010) 851–861, https://doi.org/10.1016/j.freeradbiomed.2010.01.004.
[174] S. Baritaki, S. Huerta-Yepez, A. Sahakyan, I. Karagiannides, K. Bakirtzi, A. Jazirehi, B. Bonavida, Mechanisms of nitric oxide-mediated inhibition of EMT in cancer: inhibition of the metastasis-inducer Snail and induction of the metastasis-suppressor RKIP, Cell Cycle 9 (24) (2010) 4931–4940, https://doi.org/10.4161/cc.9.24.14229.
[175] D. Maksimovic-Ivanic, S. Mijatovic, D. Miljkovic, et al., The antitumor properties of a nontoxic, nitric oxide-modified version of saquinavir are independent of Akt, Mol. Cancer Ther. 8 (5) (2009) 1169–1178, https://doi.org/10.1158/1535-7163.MCT-08-0998.
[176] D. Maksimovic-Ivanic, et al., The NO-modified HIV protease inhibitor as a valuable drug for hematological malignancies: role of p70S6K, Leuk. Res. 39 (10) (2015) 1088–1095, https://doi.org/10.1016/j.leukres.2015.06.013.
[177] M. Donia, D. Maksimovic-Ivanic, S. Mijatovic, M. Mojic, et al., In vitro and in vivo anticancer action of Saquinavir-NO, a novel nitric oxide-derivative of the protease inhibitor saquinavir, on hormone resistant prostate cancer cells, Cell Cycle 10 (3) (2011) 492–499, https://doi.org/10.4161/cc.10.3.14727.
[178] D. Maksimovic-Ivanic, S. Mijatovic, D. Miljkovic, et al., The antitumor properties of a nontoxic, nitric oxide-modified version of saquinavir are independent of Akt, Mol. Cancer Ther. 8 (5) (2009) 1169–1178, https://doi.org/10.1158/1535-7163.MCT-08-0998.
[179] F. Rothweiler, M. Michaelis, P. Brauer, et al., Anticancer effects of the nitric oxide-modified saquinavir derivative saquinavir-NO against multidrug-resistant cancer cells, Neoplasia 12 (12) (2010) 1023–1030 PMID: 21170266.
[180] W.A. Chow, C. Jiang, M. Guan, Anti-HIV drugs for cancer therapeutics: back to the future? Lancet Oncol. 10 (1) (2009) 61–71, https://doi.org/10.1016/S1470-2045(08)70334-6.
[181] S. Paskas, E. Mazzon, M.S. Basile, E. Cavalli, Y. Al-Abed, M. He, S. Rakocevic, F. Nicoletti, S. Mijatovic, D. Maksimovic-Ivanic, Lopinavir-NO, a nitric oxide-releasing HIV protease inhibitor, suppresses the growth of melanoma cells in vitro and in vivo, Investig. New Drugs (2019), https://doi.org/10.1007/s10637-019-00733-3 [Epub ahead of print].
[182] M.S. Basile, E. Mazzon, T. Krajnovic, D. Draca, E. Cavalli, Y. Al-Abed, P. Bramanti, F. Nicoletti, S. Mijatovic, D. Maksimovic-Ivanic, Anticancer and differentiation properties of the nitric oxide derivative of lopinavir in human glioblastoma cells, Molecules 23 (10) (2018) E2463, https://doi.org/10.3390/molecules23102463 pii.
[183] J. Saraiva, S.S. Marotta-Oliveira, S.A. Cicillini, J.O. Eloy, J.M. Marchetti, Nanocarriers for nitric oxide delivery, J. Drug Deliv. (2011), https://doi.org/10.1155/2011/936438 ID 936438.
[184] A.B. Seabra, R. de Lima, M. Calderón, Nitric oxide releasing nanomaterials for cancer treatment: current status and perspectives, Curr. Top. Med. Chem. 15 (4) (2015) 298–308 https://doi.org/10.2174/1568026615666150108122918.
[185] S. Duan, S. Cai, Q. Yang, M.L. Forrest, Multi-arm polymeric nanocarrier as a nitric oxide delivery platform for chemotherapy of head and neck squamous cell carcinoma, Biomaterials 33 (11) (2012) 3243–3253, https://doi.org/10.1016/j.biomaterials.2012.01.026.
[186] L.A. Tai, Y.C. Wang, C.S. Yang, Heat-activated sustaining nitric oxide release from zwitterionic diazeniumdiolate loaded in thermo-sensitive liposomes, Nitric Oxide 23 (1) (2010) 60–64, https://doi.org/10.1016/j.niox.2010.04.003.
[187] E.V. Stevens, A.W. Carpenter, J.H. Shin, J. Liu, C.J. Der, M.H. Schoenfisch, Nitric oxide-releasing silica nanoparticle inhibition of ovarian cancer cell growth, Mol. Pharm. 7 (3) (2010) 775–785, https://doi.org/10.1021/mp9002865.
[188] M.M. Molina, A.B. Seabra, M.G. de Oliveira, R. Itri, P.S. Haddad, Nitric oxide donor superparamagnetic iron oxide nanoparticles, Mater Sci Eng C Mater Biol Appl 33 (2) (2013) 746–751, https://doi.org/10.1016/j.msec.2012.10.027.
[189] P. Sudhesh, K. Tamilarasan, P. Arumugam, S. Berchmans, Nitric oxide releasing photoresponsive nanohybrids as excellent therapeutic agent for cervical cancer cell lines, ACS Appl. Mater. Interfaces 5 (17) (2013) 8263–8266, https://doi.org/10.1021/am402086m.
[190] C. Ratanatawanate, A. Chyao, K.J. Balkus, S-nitrosocysteine decorated PbS QDs/TiO 2 nanotubes for enhanced production of singlet oxygen, J. Am. Chem. Soc. 133 (10) (2011) 3492–3497, https://doi.org/10.1021/ja109328a.
[191] M. Gorska, A. Kuban-Jankowska, R. Milczarek, M. Wozniak, Nitro-oxidative stress is involved in anticancer activity of 17β-estradiol derivative in neuroblastoma cells, Anticancer Res. 36 (4) (2016) 1693–1698 http://ar.iiarjournals.org/content/36/4/1693.long#fn-group-1.
[192] R. Akhavan-Sigari, M.R. Gaab, V. Rohde, A. Brandis, H. Tezval, M. Abili, K. von Eckardstein, H. Ostertag, Expression of vascular endothelial growth factor receptor 2 (VEGFR-2), inducible nitric oxide synthase (iNOS), and Ki-M1P in skull base chordoma: a series of 145 tumors, Neurosurg. Rev. 37 (1) (2014) 79–88, https://doi.org/10.1007/s10143-013-0495-5.
[193] C.H. Switzer, S.A. Glynn, L.A. Ridnour, R.Y. Cheng, M.P. Vitek, S. Ambs, D.A. Wink, Nitric oxide and protein phosphatase 2A provide novel therapeutic opportunities in ER-negative breast cancer, Trends Pharmacol. Sci. 32 (11) (2011 Nov) 644–651, https://doi.org/10.1016/j.tips.2011.07.001.
[194] D. Dávila-González, D.S. Choi, R.R. Rosato, S.M. Granados-Principal, J.G. Kuhn, W.F. Li, W. Qian, W. Chen, A.J. Kozielski, H. Wong, B. Dave, J.C. Chang, Pharmacological inhibition of NOS activates ASK1/JNK pathway augmenting docetaxel-mediated apoptosis in triple-negative breast cancer, Clin. Cancer Res. 24 (5) (2018 Mar 1) 1152–1162, https://doi.org/10.1158/1078-0432.CCR-17-1437.
[195] S.A. Glynn, B.J. Boersma, T.H. Dorsey, M. Yi, H.G. Yfantis, L.A. Ridnour, D.N. Martin, C.H. Switzer, R.S. Hudson, D.A. Wink, D.H. Lee, R.M. Stephens, S. Ambs, Increased NOS2 predicts poor survival in estrogen receptor-negative breast cancer patients, J. Clin. Investig. 120 (11) (2010 Nov) 3843–3854, https://doi.org/10.1172/JCI42059.
[196] J.L. Heinecke, L.A. Ridnour, R.Y. Cheng, C.H. Switzer, M.M. Lizardo, C. Khanna, S.A. Glynn, S.P. Hussain, H.A. Young, S. Ambs, D.A. Wink, Tumor microenvironment-based feed-forward regulation of NOS2 in breast cancer progression, Proc. Natl. Acad. Sci. U. S. A. 111 (17) (2014 Apr 29) 6323–6328, https://doi.org/10.1073/pnas.1401799111.
[197] L. Li, L. Zhu, B. Hao, et al., iNOS-derived nitric oxide promotes glycolysis by inducing pyruvate kinase M2 nuclear translocation in ovarian cancer, Oncotarget 8 (20) (2017) 33047–33063, https://doi.org/10.18632/oncotarget.16523.
[198] D.D. Thomas, M.G. Espey, L.A. Ridnour, L.J. Hofseth, D. Mancardi, C.C. Harris, D.A. Wink, Hypoxic inducible factor 1alpha, extracellular signal-regulated kinase, and p53 are regulated by distinct threshold concentrations of nitric oxide, Proc. Natl. Acad. Sci. U. S. A. 101 (24) (2004 Jun 15) 8894–8899 Epub 2004 Jun 3. PubMed PMID: 15178764; PubMed Central PMCID: PMC428443.
[199] M. Gorska, A. Kuban-Jankowska, J. Antoniewicz, M. Wozniak, Effect of 2-methoxyestradiol on dephosphorylation of neuronal nitric oxide synthase in osteosarcoma 143B cells. An in vitro study, J. Clin. Toxicol. 5 (2015) 240, https://doi.org/10.4172/2161-0495.1000240.
[200] A.W. Girotti, Upregulation of nitric oxide in tumor cells as a negative adaptation to photodynamic therapy, Lasers Surg. Med. 50 (5) (2018) 590–598, https://doi.org/10.1002/lsm.22807.
[201] J.M. Fahey, A.W. Girotti, Nitric oxide antagonism to anti-glioblastoma photodynamic therapy: Mitigation by inhibitors of nitric oxide generation, Cancers 11 (2) (2019) E231, https://doi.org/10.3390/cancers11020231 pii.

[202] A.W. Girotti, Modulation of the anti-tumor efficacy of photodynamic therapy by nitric oxide, Cancers 20 (10) (2016) E96, https://doi.org/10.3390/cancers8100096 pii.
[203] A.W. Girotti, J.M. Fahey, W. Korytowski, Multiple means by which nitric oxide can antagonize photodynamic therapy, Curr. Med. Chem. 23 (24) (2016) 2754–2769 PMID:27776475.
[204] Y. Gao, S. Zhou, Y. Xu, S. Sheng, S.Y. Qian, X. Huo, Nitric oxide synthase inhibitors 1400W and L-NIO inhibit angiogenesis pathway of colorectal cancer, Nitric Oxide 83 (2019) 33–39, https://doi.org/10.1016/j.niox.2018.12.008.
[205] A.W. Girotti, Upregulation of nitric oxide in tumor cells as a negative adaptation to photodynamic therapy, Lasers Surg. Med. 50 (5) (2018) 590–598, https://doi.org/10.1002/lsm.22807.
[206] J.J. Luke, P. LoRusso, G.I. Shapiro, et al., ASP9853, an inhibitor of inducible nitric oxide synthase dimerization, in combination with docetaxel: preclinical investigation and a Phase I study in advanced solid tumors, Cancer Chemother. Pharmacol. 77 (3) (2016) 549–558, https://doi.org/10.1007/s00280-016-2967-0.