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Apoptosis-Inducing High •NO Concentrations Are Not Sustained Either in Nascent or in Developed Cancers

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Nitric oxide (•NO) induces apoptosis at high concentrations by S-nitrosating proteins such as glyceraldehyde-3-phosphate dehydrogenase. This literature analysis revealed that failure to sustain high •NO concentrations is common to all cancers. In cervical, gastric, colorectal, breast, and lung cancer, the cause of this failure is the inadequate expression of inducible nitric oxide synthase (iNOS), resulting from the inhibition of iNOS expression by TGF-β1 at the mRNA level. In bladder, renal, and prostate cancer, the reason for the insufficient •NO levels is the depletion of arginine, resulting from arginase overexpression. Arginase competes with iNOS for arginine, catalyzing its hydrolysis to ornithine and urea. In gliomas and ovarian sarcomas, low •NO levels are caused by inhibition of iNOS by N*-chlorotaurine, produced by infiltrating neutrophils. Stimulated neutrophils express myeloperoxidase, catalyzing H_2O_2 oxidation of Cl^- to HOCl, which N-chlorinates taurine at its concentration of 19 mM in neutrophils. In squamous cell carcinomas of the skin, ovarian cancers, lymphomas, Hodgkin's disease, and breast cancers, low •NO concentrations arise from the inhibition of iNOS by* N*-bromotaurine, produced by eosinophil-peroxidase-expressing infiltrating eosinophils. Eosinophil peroxidase catalyzes the H_2O_2 oxidation of Br^- to HOBr, which N-brominates taurine to* N*-bromotaurine at its concentration of 15 mM in eosinophils. In microvascularized tumors, the •NO concentration is further depleted; •NO is rapidly consumed by red blood cells (RBCs) through S-nitrosation of RBC glutathione and hemoglobin, and by oxidation to nitrate by RBC oxyhemoglobin. Angiogenesis-inhibiting antibodies are currently used to treat cancers; their mode of action is not, as previously thought, reduction of the tumor O_2 or nutrient supply. They actually decrease the loss of •NO to RBCs.*

A common cause of cancers: failure to induce apoptosis by maintaining high •NO concentrations

At high concentrations ($>10^{-6}$ M), nitric oxide (•NO) induces apoptosis by S-nitrosating glyceraldehyde-3-phosphate dehydrogenase (GAPDH)[1–3] and other proteins. This analysis of 195 publications indicates that a failure to attain high •NO concentrations is characteristic of all cancers. In cases of cervical,[4] gastric,[5] colorectal,[6] breast,[7,8] and lung[9] cancers, the reason for the inadequate level of •NO is the insufficient expression of inducible nitric oxide synthase (iNOS), resulting from TGF-β1-mediated inhibition of iNOS expression at the mRNA level.[10] Additionally, in some cases of bladder,[11] renal,[12,13] and prostate[11,14,15] cancer, the cause of failure is depletion of arginine, resulting from arginase overexpression. Arginase competes with iNOS for arginine, catalyzing its hydrolysis to ornithine and urea. In certain gliomas[16,17] and ovarian sarcomas,[18] inhibition of iNOS by *N*-chlorotaurine (taurine chloramine) leads to decreased •NO levels.[19] Stimulated neutrophils express myeloperoxidase,[20,21] which catalyzes H_2O_2-mediated oxidation of Cl^- to HOCl, which in turn N-chlorinates taurine[22,23] at the cellular taurine concentration of 19 mM[24] in neutrophils. In cases of squamous cell carcinoma of the skin,[25] ovarian cancer,[26] lymphoma,[26] Hodgkin's disease,[26] and breast cancer,[27] *N*-bromotaurine (taurine bromamine) inhibits iNOS through a similar mechanism. *N*-bromotaurine, produced by eosinophil-peroxidase-expressing infiltrating eosinophils,[28] is formed by the oxidation of Br^- to HOBr by H_2O_2, which in turn N-brominates taurine to *N*-bromotaurine[29,30] at a cellular concentration of 15 mM in eosinophils.[24]

Circulating red blood cells deplete tumoral •NO levels and arrest •NO-induced apoptosis

Nitric oxide S-nitrosates red blood cell (RBC) glutathione[31] and hemoglobin (Hb),[32,33] and is rapidly oxidized to nitrate by oxyhemoglobin.[34] The three reactions decrease the concentration of •NO, decrease apoptosis, and increase cancer virulence. Angiogenesis-inhibiting antibodies currently used in the treatment of cancers are thought to limit the supply of O_2 or nutrient levels in the tumor;[35–40] however, they actually decrease the •NO loss to the RBCs in the microvasculature.

High concentrations of •NO are reached when tumor stromal cells[41] and infiltrating macrophages are stimulated to express iNOS, which catalyzes the O_2-mediated oxidation of arginine to •NO and citrulline. Stimulated iNOS-expressing macrophage cultures sustain the highest reported concentrations of •NO, as high as 2×10^{-4} M.[42] In contrast, the highest reported neuronal nitric oxide synthase (nNOS)-sustained •NO concentrations are 10^{-6} M,[43] and endothelial nitric oxide synthase (eNOS)-sustained •NO concentrations are only 2×10^{-8} M.[44] iNOS is expressed in most, but not in all, cancers.

Daughter products of •NO are mutagenic,[45] and at low concentrations, •NO induces VEGF-mediated cancer-aggravating angiogenesis.[41,46–50] For these rea-

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sons, many researchers view •NO as a cause of cancer, rather than as a long-range cancer-fighting weapon of the immune system. •NO is the immune system's weapon of choice against large, multicellular bodies recognized as foreign, such as transplanted organs[51–53] and invasive parasites,[54,55] because the diffusion length of •NO is particularly long. •NO diffuses rapidly in water ($D = 3.3 \times 10^{-5}\ cm^2 s^{-1}$),[56] is lipid- and water-soluble, and permeates biological membranes.[57] Its half-life in biological fluids, other than blood, is 1–20 s.[58–60] At a $t_{1/2}$ value of >3 s, the diffusion length of •NO is $>10^{-2}$ cm, permitting permeation through multiple cell layers.

Induction of apoptosis at high [•NO] and maintenance of high [•NO]

Nitric oxide induces apoptosis at high concentrations by S-nitrosating proteins such as GAPDH.[1–3,61] iNOS expression induces immune system cytokines, including interferon-γ (IF-γ), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β).[62] These cytokines stimulate iNOS expression in stromal cells[63] and in tumor-infiltrating macrophages.[64–68] Most nascent neoplasms are eliminated by apoptosis before growing and vascularizing to become large and virulent cancers.[69–73] Elimination of the nascent neoplasms fails, however, when the expression of iNOS is inhibited or when arginine, the iNOS substrate, is depleted. If a neoplasm does survive and becomes densely microvascularized, •NO is further depleted by circulating RBCs, and apoptosis is fully arrested.

To induce apoptosis, the concentration of •NO must be high enough to right-shift the electrochemical half-cell reaction of cysteine residues, such as those of GAPDH.[1–3] The thermodynamic threshold concentration at which a protein is S-nitrosated is defined by the concentration of •NO, the pH, the redox potential, and the protein concentration. Apoptosis is consequently induced only above a •NO concentration defined by Reaction (**1**).

$$RSH + {}^{\bullet}NO \rightarrow RS{-}NO + H^+ + e^- \qquad (1)$$

At a sufficiently high •NO concentration, apoptosis is extensive, and remission of tumors is observed.[66,74,75] Maintenance of a sufficiently high •NO concentration by the local application of a •NO-releasing drug has resulted in the remission of tumors.[76] Furthermore, tumorigenicity and metastasis are suppressed in iNOS-overexpressing mice.[74,75,77–93] Also, iNOS expression and malignancy are inversely correlated in animal and human cancers, and in cancer cell lines,[63,94–96] and high •NO concentrations produced by iNOS suppress breast tumors.[97] Tumor development and iNOS expression are inversely correlated in human cancers;[41,98–105] iNOS-expressing macrophage infiltration increases the likelihood of remission in gastric,[67,68] colorectal,[106] and prostate cancers,[65] and survival improves with increased tumor iNOS expression in colorectal,[107] ovarian,[108,109] and in non-small-cell lung cancers.[104]

Cancers associated with inadequate iNOS expression

Certain types of human tumors express little or no iNOS.[110] This deficiency is caused by the suppression of iNOS expression at the mRNA level by TGF-β1,[111] *N*-chlorotaurine, or *N*-bromotaurine. Elevated TGF-β1 has been reported in advanced colorectal cancers.[6] Furthermore, the level of TGF-β1 mRNA observed in cervical smears (pap tests) correlates with the progression of cervical intra-epithelial neoplasia to cancer,[4] and relapse of patients with breast carcinomas is known to be associated with TGF-β1.[7] *N*-chlorotaurine inhibits iNOS expression;[16,19,112–124] in particular, it suppresses iNOS expression in inflamed tissues[16,19,117–121,123–126] and protects healthy cells from injury resulting from the overproduction of •NO.[19] *N*-chlorotaurine is formed by Reactions (**2**) and (**3**). Reaction (**2**) is catalyzed by myeloperoxidase,[127–132] expressed in neutrophils.[133,134] Reaction (**3**) proceeds without enzymatic catalysis[21,135,136] at a taurine concentration of 19 mM in neutrophils.[24] Neutrophil myeloperoxidase is expressed in both human and animal brain tumors.[17,137] Furthermore, the (−463)G→A point mutation in the promoter region of the myeloperoxidase gene decreases its transcription, significantly lowering the risk of lung cancer in men.[138–145]

$$H_2O_2 + H^+ + Cl^- \rightarrow HOCl + H_2O \qquad (2)$$

$$HOCl + NH_2CH_2CH_2SO_3^- \rightarrow ClNHCH_2CH_2SO_3^- + H_2O \qquad (3)$$

The analogous *N*-bromotaurine is produced by the eosinophil-peroxidase-catalyzed Reaction (**4**)[30,146] followed by Reaction (**5**), which proceeds without enzymatic catalysis in eosinophils when the taurine concentration is 15 mM.[24,30] Eosinophilia is characteristic of hematologic tumors, such as Hodgkin's disease,[26] lymphomas,[26] and certain breast carcinomas.[26,27]

$$H_2O_2 + H^+ + Br^- \rightarrow HOBr + H_2O \qquad (4)$$

$$HOBr + NH_2CH_2CH_2SO_3^- \rightarrow BrNHCH_2CH_2SO_3^- + H_2O \qquad (5)$$

Cancers associated with arginine depletion through overexpression of arginase

Arginase catalyzes the hydrolysis of arginine, the precursor of •NO, to urea and ornithine. When arginase is overexpressed, tumoral arginine levels are depleted, and insufficient •NO is produced by iNOS. Pathogens avoid being killed by iNOS-expressing macrophages through switching the macrophages from iNOS-expressing to arginase-expressing.[147–151] Furthermore, while iNOS is active in fresh wounds, arginase is active in healing wounds,[147,152,153] where the macrophages are again switched from iNOS-expressing to arginase-expressing.[154–157] Macrophage arginase promotes tumor cell growth and suppresses •NO tumor cytotoxicity.[158] Several cancer cell lines express arginase,[12,158–162] and arginase activity is elevated in prostate,[14,163,164] bladder,[11] and renal[12,13] carcinomas.

Overall, inhibition of iNOS expression and arginine depletion underlie the survival of nascent neoplasms. Subsequent microvascularization makes the cancer more virulent by fully arresting apoptosis through a further decrease in the excess

Table 1. Causes of inadequate •NO concentrations to induce apoptosis in nascent human malignancies.

Organ	Cancer Type	Factor limiting [•NO] before vascularization	References
Bladder	Carcinoma	Depletion of arginine by its hydrolysis, catalyzed by overexpressed arginase	[11]
Breast	Carcinoma	TGF-β1 inhibition of iNOS expression	[7,8]
Breast	Carcinoma	Eosinophil-peroxidase-associated iNOS expression inhibition by *N*-bromotaurine	[27]
Brain	Glioma	Myeloperoxidase-associated-*N*-chlorotaurine inhibition of iNOS expression	[16,17]
Cervix	Carcinoma	TGF-β1 inhibition of iNOS expression	[4]
Colon	Carcinoma	TGF-β1 inhibition of iNOS expression	[6]
Kidney	Carcinoma	Depletion of arginine by its hydrolysis, catalyzed by overexpressed arginase	[12–13]
Lung	Non-small-cell carcinoma	TGF-β1 inhibition of iNOS expression	[9]
Lung	Squamous cell carcinoma	Myeloperoxidase-associated-*N*-chlorotaurine inhibition of iNOS expression	[138–144]
Lymph nodes	Lymphoma, Hodgkin's disease	Eosinophil-peroxidase-associated iNOS expression inhibition by *N*-bromotaurine	[26]
Ovaries	Sarcoma	Myeloperoxidase-associated-*N*-chlorotaurine inhibition of iNOS expression	[18]
Ovaries	Carcinoma	Eosinophil-peroxidase-associated iNOS expression inhibition by *N*-bromotaurine	[26]
Prostate	Carcinoma	Depletion of arginine by its hydrolysis, catalyzed by overexpressed arginase	[11,14,15]
Skin	Squamous cell carcinoma	Eosinophil-peroxidase-associated iNOS expression inhibition by *N*-bromotaurine	[25]
Stomach	Carcinoma	TGF-β1 inhibition of iNOS expression	[5]

•NO concentration. RBCs scavenge •NO so rapidly that the concentration of •NO in a volume element of tissue is defined by its distance from the nearest capillary.[60] Circulating blood exports the residual excess •NO from tumors through S-nitrosation of GAPDH and Hb [Reaction (**6**)], which constitute 37–52% of the blood volume.[59,60,165–176] •NO is also stripped by oxyhemoglobin oxidation to nitrate [Reaction (**7**)].[177,178] The concentration of oxyhemoglobin in the blood is ~2 mM, and the bimolecular rate constant for the oxidation of •NO to nitrate is $9\times10^{7}\,\text{M}^{-1}\,\text{s}^{-1}$.[34] Hence, the half-life of •NO in blood is as short as 2×10^{-3} s,[59] three orders of magnitude less than in other tissues.[58–60]

$$^{\bullet}NO + R{-}SH \leftrightarrow R{-}SNO + H^{+} + e^{-} \quad (6)$$

$$^{\bullet}NO + Hb(Fe^{II})O_2 \rightarrow Hb(Fe^{III}) + NO_3^{-} \quad (7)$$

VEGF-antibody-based anticancer drugs that slow angiogenesis were designed to starve tumors of oxygen and nutrients.[47,48,179–184] Bevacizumab,[185,186] cetuximab,[187] erlotinib,[188] and trastuzumab,[189,190] which are already in use, retard the growth of cancers by preventing angiogenesis.[35–40,191–195] However, critical analysis of the literature suggests that they act by reducing the draining of tumoral •NO by the microvasculature.

Association of organ-specific cancers with causes of their insufficient •NO concentrations for induction of apoptosis

Table 1 summarizes the factors that limit the •NO concentration before vascularization. The model predicts that agents designed to sustain high local •NO concentrations should be useful in treating cancers, particularly before microvascularization occurs. For example, locally delivered antibodies against TGF-β1 should be of value in treating certain cervical,[4] gastric,[5] colorectal,[6] breast,[7,8] and lung[9] cancers. Inhibitors of myeloperoxidase and prevention of neutrophil recruitment should be effective against some gliomas[16,17] and ovarian sarcomas.[18] Inhibitors of eosinophil peroxidase and prevention of eosinophil recruitment should be useful in treating some squamous cell carcinomas of the skin,[25] lymphomas,[26] Hodgkin's disease,[26] ovarian,[26] and breast cancers.[27] Inhibitors of arginase should be active against some bladder,[11] renal,[12,13] and prostate cancers.[11,14,15]

Table 2 lists the deductions and the facts on which they are based. Monitoring the variation of •NO concentration in tumors should be of value in diagnosing and in determining the effectiveness of cancer treatments. Analytical methods for classifying the tumor according to iNOS or TGF-β1 expression, the activity of arginase, myeloperoxidase, and eosinophil peroxidase, as well as the level of microvascularization are needed, as each indicates a different course of treatment.

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Table 2. Knowledge base of the model and the results of its analysis.

Previously reported:	Deduced through this analysis:
	Mode of action of angiogenesis-reducing biological drugs
Half-life of ˙NO in blood is 2 ms. Half-life of ˙NO in other tissues is 2-30 s. ˙NO is soluble and diffuses rapidly in water and lipids. Membranes are permeable to ˙NO. ˙NO is rapidly oxidized to NO_3^- by oxyhemoglobin. ˙NO rapidly S-nitrosates glutathione. ˙NO rapidly S-nitrosates Hb.	Blood is the major ˙NO sink in microvascularized tumors. Microvascularized tumors do not sustain sufficient ˙NO concentrations to induce apoptosis. The presently used and developed angiogenesis-preventing drugs act by preventing the vascularization-associated depletion of tumor ˙NO.
	Role of neutrophils and microglia
Gliomas are neutrophil infiltrated. Ovarian sarcomas are neutrophil infiltrated. Neutrophils express myeloperoxidase. Microglia express myeloperoxidase. Myeloperoxidase catalyzes the oxidation of Cl^- by H_2O_2 to HOCl. HOCl N-chlorinates taurine. The concentration of taurine in neutrophils is 19 mM. *N*-chlorotaurine inhibits expression of iNOS.	Expression of iNOS is inhibited in gliomas and ovarian sarcomas by *N*-chlorotaurine generated by tumor-infiltrating neutrophils and by microglia. In the absence of iNOS, the ˙NO concentration in gliomas and ovarian sarcomas is insufficient to induce apoptosis and cause tumor remission.
	The role of eosinophils
Eosinophils express eosinophil peroxidase: Br^- by H_2O_2 to HOBr. HOBr N-brominates taurine. The concentration of taurine in eosinophils is 15 mM. *N*-bromotaurine inhibits the expression of iNOS	Expression of iNOS is inhibited in squamous cell carcinomas of the skin, ovarian cancers, lymphomas, Hodgkin's disease, and breast cancers by *N*-bromotaurine generated by tumor-infiltrating eosinophils. In the absence of iNOS, the ˙NO concentration in squamous cell carcinomas of the skin, ovarian cancers, lymphomas, Hodgkin's disease, and breast cancers is insufficient to induce apoptosis and cause tumor remission.
	The role of TGF-β1 in cancer
TGF-β1 inhibits iNOS expression. TGF-β1 is expressed in cervical, gastric, and colorectal cancers, and in some breast and lung cancers.	TGF-β1 inhibits iNOS expression in cervical, gastric, and colorectal cancers and in some breast and lung cancers. In the absence of iNOS, the ˙NO concentration in cervical, gastric, and colorectal cancers and some breast and lung cancers is insufficient to induce apoptosis and cause tumor remission.
	The role of arginase in cancers
Arginase competes with iNOS for arginine by catalyzing its hydrolysis to ornithine and urea. Arginase is expressed in healing macrophages. Pathogens escape being killed by inducing arginase expression. Arginase is expressed in cancers of the prostate, bladder, and kidneys.	In prostate, bladder, and renal cancers, arginine is depleted because of arginase overexpression. In the absence of enough tumoral arginine, cancers of the prostate, bladder, and kidneys do not sustain apoptosis-inducing ˙NO concentrations.

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