


Influence of nitric oxide signaling mechanisms in cancer

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Abstract

Nitric oxide (NO) is a molecule with multiple biological functions that is involved in various pathophysiological processes such as neurotransmission and blood vessel relaxation as well as the endocrine system, immune system, growth factors, and cancer. However, in the carcinogenesis process, it has a dual behavior; at low doses, NO regulates homeostatic functions, while at high concentrations, it promotes tissue damage or acts as an agent for immune defense against microorganisms. Thus, its participation in the carcinogenic process is controversial. Cancer is a multifactorial disease that presents complex behavior. A better understanding of the molecular mechanisms associated with the initiation, promotion, and progression of neoplastic processes is required. Some hypotheses have been proposed regarding the influence of NO in activating oncogenic pathways that trigger carcinogenic processes, because NO might regulate some signaling pathways thought to promote cancer development and more aggressive tumor growth. Additionally, NO inhibits apoptosis of tumor cells, together with the deregulation of proteins that are involved in tissue homeostasis, promoting spreading to other organs and initiating metastatic processes. This paper describes the signaling pathways that are associated with cancer, and how the concentration of NO can serve a beneficial or pathological function in the initiation and promotion of neoplastic events.

Keywords

Cancer, nitric oxide, metastasis, signaling mechanisms, angiogenesis, homeostasis

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Introduction

Nitric oxide (NO) is a liposoluble free radical that is synthesized from L-arginine by three different enzymes: endothelial NO synthase (eNOS), inducible NO synthase (iNOS), and neuronal NO synthase (nNOS). It has a reduced half-life of 1–5 s in vivo, and it is characterized as a pleiotropic molecule with diverse biological functions. NO acts as a signaling molecule and its biological actions can occur via direct or indirect chemical reactions. For example, NO reacts with soluble guanylate cyclase (sGC) at its haem moiety enabling its activation and the catalytic transformation of guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP), leading to the relaxation of smooth muscle and vasodilation.^{1,2} In addition, its involvement in the immune, cardiovascular, and nervous systems and in the neoplastic process has been documented.^{3–9}

The molecular mechanism of NO participation in carcinogenesis has not been well established, several studies have documented a significant reduction in the prometastatic behavior on melanoma cell lines, as well as a reduction in cell growth in colon cancer cell lines in a NO-dependent manner through the inhibition of the PI3K and MAPK pathways.^{10,11} However, NO plays a dual role on carcinogenesis and its biological effects might depend on its concentration.¹² A release of variable amounts of NO into the tumor microenvironment can activate oncogenic pathways and stimulate tumor microvascularization.^{13,14} Furthermore, several theories have been postulated that attempt to explain the complex interaction of certain molecules and signaling pathways that are activated by NO because of its pleiotropic behavior. These pathways may directly or indirectly induce the activation of oncogenic pathways and promote cancer initiation and progression. NO has been shown to have tumor-promoting effects depending on the type of cancer and several other factors.^{15–17} The initiation of cellular transformation occurs by the modification of nitrogenous bases in the human genome, which can be caused by peroxynitrite and dinitrogen trioxide that can damage DNA and proteins. Then, the cells may undergo new mutations, which increase resistance to apoptosis, and confer a greater proliferation rate by stimulation of external factors such as interleukin (IL)-8 and vascular endothelial growth factor (VEGF).¹⁸ NO is also involved in the activation of cyclooxygenase (COX-2) and macrophages promote the synthesis of prostaglandins and tumor necrosis factor (TNF)-alpha, which may stimulate the inflammatory process; these are the major events that promote the carcinogenesis process.^{19,20} Additionally, it has been reported that increased *Bcl-2* gene expression and *p53* tumor suppressor gene mutations block apoptosis during carcinogenesis because NO promotes the expression of transcription factors, inactivation of caspases, and

the synthesis of reactive nitrogen species (RNS).^{21,22} Finally, genetic variations of the c-myc gene and alterations in the Akt/PI3K signaling pathway can promote tumor progression²³ and increase the likelihood of spreading to other organs by the reducing the expression of adhesion molecules E-cadherin and transformation of epithelial to mesenchymal tissue.^{24,25} In conclusion, NO may promote lesions in DNA and other biomolecules and initiate the development of carcinogenesis, which is also involved in multiple complex phenomena and signaling pathway characteristics of cancer. The relevant articles were searched in PubMed using the key words cancer, NO, metastasis, signaling mechanisms, and angiogenesis.

Antitumor effects of NO

The tumor microenvironment is characterized by a complex interaction of cells and molecules that surround the tumor. Macrophages, fibroblast and mesenchymal stem cells, and some cytokines and growth factors are some of the key components involved in the growth and spread of tumors.^{26,27} It has been described that some molecules such as NO play a dual role in carcinogenesis depending on its concentration, cell status, redox state, and exposure time.^{12,28} It has also been observed that NO can regulate the antitumor response of CD8⁺ lymphocytes, which led to a potential role of NO as an anticancer agent. As such, experimental strategies using gene transfer have been developed in murine models with the purpose of over-expressing iNOS and NO production.²⁹ The results showed a significant reduction in tumor size and radioresistance, as well as a decrease in metastatic spread to the lung. In addition, some studies have shown its antitumor capacity in cell lines when these tumor cells have been exposed to adequate concentrations of NO donors. The decrease in the expression of COX-2 and the inhibition of the PI3K and MAPK pathways have been proposed as mechanisms involved in the antitumor capacity of NO.^{10,11} Additionally, others mechanisms of action that lead to the anticancer properties of NO have been investigated. For example, high concentrations of NO (>200 nM) can cause cell death through p53 upregulation, degradation of anti-apoptotic mediators, cytochrome release induction, cytostasis and cytotoxicity, and cell cycle arrest.³⁰

NO and oxidative stress

Oxidative stress is defined as an imbalance between antioxidant capacity and concentration of reactive metabolites in the cellular microenvironment. It is known that reactive oxygen species (ROS) can react with NO, which is a reactive and unstable molecule, and consequently produce RNS such as peroxynitrite, which subsequently forms a conjugate with its acid form to decompose to dinitrogen

trioxide.¹⁵ In addition, RNS are biochemically synthesized by various enzymatic reactions in aerobic organisms when NO reacts with molecular oxygen.³¹

NO plays an important role in maintaining homeostasis. However, currently NO is proposed to be a characteristic phenomenon in some diseases such as cancer. During cellular stress, ROS and RNS are capable of damaging lipids and proteins, and modifying DNA, which may result in damage to structure and function and cause genotoxic effects and promote fragmentation of the double helix by interaction with the sugar-phosphate backbone. Consequently, cellular stress leads to the formation of eight hydroxydeoxyguanosine, a biomarker for measurement of oxidative stress in different types of cancer. Moreover, some studies have reported that proteins undergo mechanical fragmentation, carbonylation, oxidation of thiols, and misfolding during the transition to produce more complex forms that have a three-dimensional structure.^{32,33} ROS and RNS can also damage histones and other proteins from the DNA packaging system and promote the cancer development.³⁴ In addition, these ROS were shown to hinder the formation of disulfide bridges and some post-translational modifications, which causes accumulation of misfolded proteins within the endoplasmic reticulum. However, for a normal cell to undergo malignant transformation for exposure to genotoxic compounds, the interaction of multiple events and other pathophysiological mechanisms that trigger uncontrolled cell growth is required.^{35–38}

p53 and NO

Cellular homeostasis in the tissue is maintained by the balance between cell proliferation and apoptosis.^{20,33,39} However, this balance can be upset by multiple *de novo* mutations that confer cells with a tumor survival ability, which begins the neoplastic process.⁴⁰ p53 was shown to be prone to undergo mutations that can promote the initiation, promotion, and progression of cancer. Therefore, the activity of p53 is essential in suppressing tumors by different routes, such as inducing apoptosis and DNA repair and participating in cell cycle arrest.^{41–45}

Recent studies have suggested the involvement of NO in the suppression of p53 by reactive nitrogen species, which are produced from the reaction of NO with superoxide anion and other free radicals and nitration of tyrosine residues by the action of peroxynitrite generated from NO. Thus, the tyrosine residues are “nitro” group acceptors and they become 3-nitrotyrosine; this event can alter the structure and function of p53, reducing its activity and contributing to cancer development.⁴⁶ Several studies have also shown that p53 negatively regulates endothelial-dependent vasodilation, and consequently, angiogenesis is promoted. In addition, experimental studies have

evaluated the effect of NO on p53 expression and although the molecular mechanisms are not clear, there is evidence that NO induces the expression of miRNAs, specifically miR-1301 in colorectal cancer cells. miRNAs play an important role in the function and activity of p53, for example, miR-34a regulates the activity of SIRT-1, which is a negative regulator of p53 through direct negative regulation of SIRT-1.⁴⁷ Furthermore, NO plays an important role in the regulation of specific genes through molecular mechanisms that can activate or inhibit transcription. For example, nitrosylation in transcription factors such as EGF-1 and NF- κ B can generate conformational changes and modify their DNA binding.⁴⁸ NO was shown to increase the p53 concentration in *in vitro* studies of MCF-7 breast cancer cell lines, but these results are controversial.^{49,50} Moreover, although the exact mechanisms between NO and apoptosis are unknown, some hypotheses have proposed that nitrosylation of caspases is a phenomenon that can inhibit the activation of cell death⁵¹ and lead to the beginning of neoplastic processes.

NO and activation of COX-2

NO that is produced by iNOS and prostaglandins (PGs) that are produced by the COX-1/COX-2 enzymes are actively involved in the pathogenesis of cancer^{52–54} through lymphocyte migration and increased nitrate and nitrite levels. NO has dual activities, and, on the one hand, it stimulates tumor growth and metastasis, but, on the other hand, it can inhibit tumor progression by its antioxidant activity, induce angiogenesis, cancer cell death, and increase vasodilation, differentiation and apoptosis.⁵⁵ Different studies have demonstrated the involvement of NO and NOS and COX expression levels in cancer cells. COX enzymes catalyze the conversion of arachidonic acid (AA) to PGs. Particularly, the COX-2 isoform is actively involved in carcinogenesis.^{56,57} Thus, it is possible to selectively inhibit COX-2 and production of prostaglandin E2 (PGE2), which is influenced by NO synthesis in the tumor microenvironment (Figure 1). Three isoforms of COX have been identified: COX-1 overlap; COX-2 regulated by growth factors, cytokines, and oncogenes; and COX-3 that is constitutively expressed in tissues. To date, several mechanisms by which COX-2 contributes to carcinogenesis have been identified. They include inhibition of apoptosis, stimulation of angiogenesis, metastasis, and inflammation, and modulating immunosuppression or converting procarcinogens to cancer-causing factors.^{58,59} During tumor development and metastasis, it is postulated that NO is involved in tumor regulation depending on its local concentration, exposure time, the stage of the tumor microenvironment, and even their direct interactions between tumor cells and stromal.^{60,61} Moreover, some *in vitro*

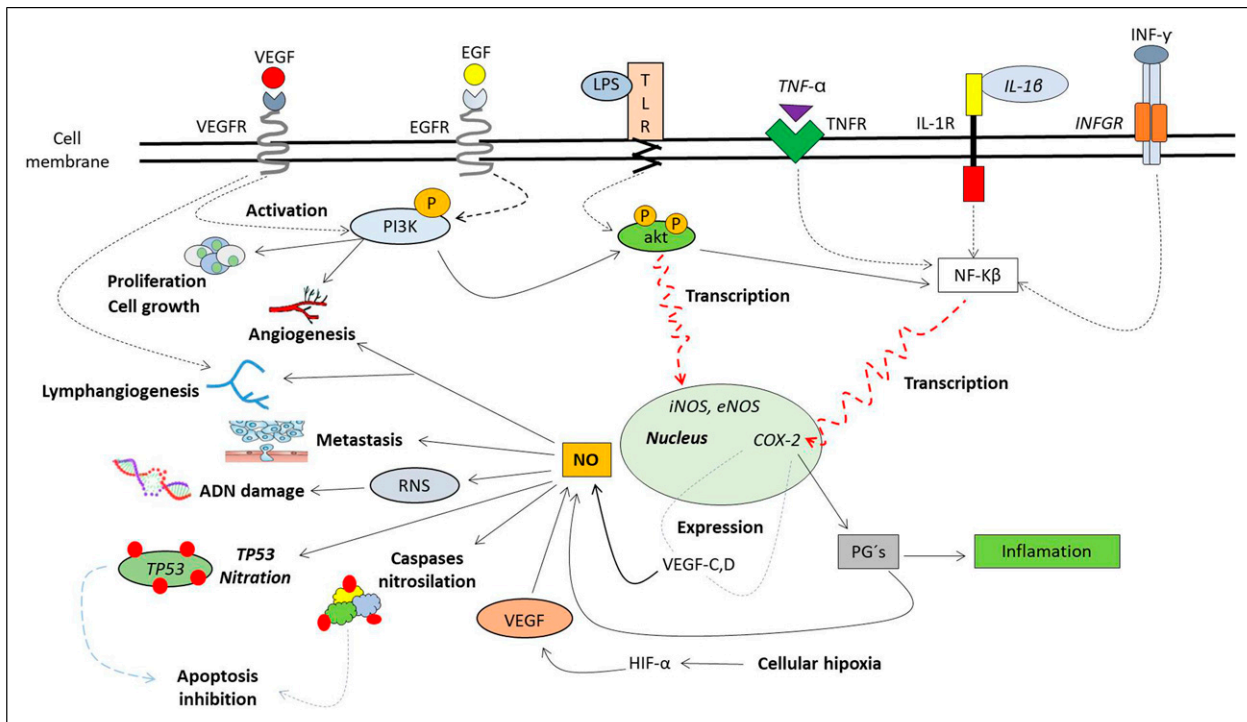


Figure 1. Nitric oxide and signaling pathways. Synthesis of nitric oxide and inflammatory microenvironment (red dashed arrows) by the activation of signaling pathways (black dashed arrows) could trigger key events are characteristic during the development and invasion of tumors (continuous black arrows).

studies have reported that COX-2 expression for prostaglandin synthesis may induce new vessel and microvasculature generation. However, the exact mechanisms are unknown.⁶² COX-2 encodes an inducible enzyme that is present in the cell membranes. Thus, some hypotheses have been proposed to explain the mechanisms that induce COX-2 activation. It is thought that the stimulus for lipopolysaccharide, proinflammatory molecules, and specific key events are mitogens that induce gene expression through complex signaling pathways.⁶³ Phosphorylation of target molecules like serine/threonine protein kinase (Akt) is a characteristic phenomenon during pathway activation. Once phosphorylated, Akt, the p65 subunit of NF- κ B, translocates to the cell nucleus where it stimulates COX-2 gene transcription.⁶⁴ However, under normal conditions it is regulated by members of the mitogen-activated protein kinase (MAPK) family. Experimental studies have shown that activation of COX-2 induces the synthesis alpha factor, IL-6, and TNF-alpha, which are molecules that promote NO synthesis in macrophages and fibroblasts.²⁰

Activation of Akt/PI3K route and NO

In some cancers, including breast cancer, tumor cells overexpress membrane receptors that are activated by binding to its extracellular ligand. One of the most common

receptors is the epidermal growth factor receptor (EGFR).⁶⁵ Ligand/receptor promotes the dimerization and autophosphorylation of tyrosine residues in the EGFR and causes activation of the Akt/PI3K pathway. The complex signaling cascade is characterized by phosphorylation of some essential molecules that are present downstream and the conformational change in the p85 subunit of PI3K complex. Generally, phosphorylation of serine residues activates Akt and promotes eNOS expression in endothelial cells.⁷ Previous studies have shown that NO increases Akt activation depending on the concentration and exposure time because it promotes the phosphorylation of serine-473 and threonine-308 residues and their translocation to the cell nucleus. In fact, the activation of Akt by NO can block apoptosis through the mediation of Cgmp.^{66,67} Recent findings have shown that Akt/PI3K is induced by the VEGF-C/VEGFR-3 interaction, suggesting a possible dependence of the transmembrane receptor VEGFR-3 for the synthesis of NO by Akt/PI3K pathway.⁶⁸

VEGF, angiogenesis, and NO

The microvasculature increment is a key characteristic of malignant tumor events.^{7,69} The vascular network in the tumor mass functions as scaffolding to provide nutrients and oxygen to cancer cells by promoting their proliferation

and to contribute to cancer progression.⁷⁰ Some molecules function as positive regulators of angiogenesis, and the most studied are acid fibroblast growth factor (aFGF), transforming growth factor alpha (TGF- α), hepatocyte growth factor (HGF), TNF-alpha, angiogenin, IL-8, platelet-derived growth factor (PDGF), and the angiopoietins (Ang-1 and -2).¹⁸ However, VEGF plays an essential role in regulating the expression of specific genes encoding enzymes that catalyze the synthesis of NO from L-arginine in the tumor environment. Under conditions of cellular hypoxia, hypoxia inducing factor 1 (HIF-1)⁷¹ increases the expression of VEGF in biological systems. VEGF binding to its receptor (VEGFR) with tyrosine kinase activity results in the dimerization and subsequent phosphorylation of the cytoplasmic region. This event induces protein kinase-C, phospholipase C-gamma, and other proteins in the river below signaling cascade phosphorylation. Finally, iNOS and eNOS expression in endothelial cells and NO synthesis is activated.⁷ Also some studies have shown that VEGF is essential and necessary for eNOS expression in murine models.⁷²

NO and apoptosis (activation of the BCL-2 pathway)

Apoptosis is a complex phenomenon that is highly regulated by different pathways. Dysregulation of this process results in the disruption of homeostasis in the tissue, generating pathological conditions such as cancer.⁷³ Experimental studies have demonstrated that low NO concentrations block cell death by apoptosis. For example, in prostate tumor cells eNOS inhibits apoptosis through ROS and some ligands such as tumor necrosis factor. Also, NO can decrease apoptosis and increase survival through some pathways such as cGMP and Bcl-2.⁶⁹ The *Bcl-2* gene was originally discovered near the site of translocation between chromosomes 18 and 14 and it is known that this phenomenon produces an alteration in its expression that may lead to cancer. However, in some subgroups of Bcl-2 and BAX (with pro-apoptotic capacity), a channel forms through the mitochondrial membrane once the cell undergoes unfavorable conditions, which allows the release of cytochrome C and caspase activation that initiates intrinsic apoptosis.²¹ Furthermore, experimental studies have noted increased apoptosis in liver cells by inhibiting the NOS enzymes. These findings suggest that NO may be responsible for inhibiting programmed cell death in some cell types⁷⁴ and although the exact mechanisms between NO and inhibition of apoptosis are unknown, some hypotheses have been proposed. Previous studies have reported that NO can inhibit caspase activation through cyclic guanosine monophosphate (cGMP) production, S-nitrosylation, and activation of protein kinase G at PC12⁷⁵ cells, and low concentrations of NO were also

observed to block the apoptotic trigger TNF-alpha on endothelial cells.⁵¹ However, Bcl-2 is a proto-oncogene, and its protein product is able to hijack PUMA pro-apoptotic proteins, which is essential for the progress of apoptosis.⁷⁶ eNOS was also reported to be capable of blocking the apoptotic process in prostate cancer and exerting anti-apoptotic effects on epithelial tumor cells through the sGC/cGMP pathway. However, there are conflicting results because the NO synthesized by eNOS behaves as both a pro-apoptotic and anti-apoptotic molecule.⁶⁹

The relationship between Bcl-2 and NO is not clear and the effect of NO in cancer depends on the concentration and duration of NO exposure. Some hypotheses describe that NO can interact with cellular fractions of the outer cell membrane of the mitochondria such as cyclooxygenases, guanylyl cyclases, ribonucleotide reductases, and Bcl-2. In fact, in vitro studies with human osteoarthritic chondrocytes observed that inhibiting the release of NO causes an increase in the concentration of Bcl-2. In contrast, when the release of NO is induced Bcl-2 expression decreases following exposure to shear stress.⁷⁷ In addition, NO has been shown to inhibit autophagy in liver cancer cells because it can reduce Bcl-2 phosphorylation and inactivation of kinases such as JNK1.⁷⁸

On the other hand, studies with rat osteoblast showed that pretreatment with NO increases Bcl-2 levels because it promotes the expression of GATA-5, a transcription factor that regulates the expression of the *Bcl-2* gene.⁷⁹

Inflammation and NO

Chronic inflammation is a risk factor for the development of cancer.^{80,81} NO has been observed to participate in various stages of tumor development, and it has recently been shown to play an essential role during malignant transformation, besides being a phenomenon in malignancies.^{43,82,83} Although the exact mechanisms of inflammatory phenomenon are unknown, several studies have concluded that M1 macrophage activation is consistently observed.^{84,85} Macrophage activation promotes the synthesis of proinflammatory molecules, such as TNF-alpha and some interleukins, activating endothelial cells and eNOS gene expression, which increases NO levels in the tumor microenvironment. However, these results are controversial because eNOS can exert inflammatory as well as anti-inflammatory effects.^{69,86,87} The expression of cyclooxygenases and other molecules in the inflammatory process, such as NF- κ B, can be regulated even by residual amounts of NO that are released into the tissue microenvironment.⁶⁹ However, some studies have found an association between elevated serum NO levels in patients with autoimmune diseases and cancer.⁸⁸ This evidence suggests that NO may be an important mediator in the development and course of chronic inflammation and neovascularization

of the tumor and thereby contribute directly or indirectly in the complex etiology of carcinogenesis.⁸²

NO and metastasis

During cancer progression, the transition of epithelial to mesenchymal tissue is a characteristic phenomenon of metastasis. The increase in markers such as N-cadherin, vimentin, alpha actin, and fibronectin smooth muscle, are frequent findings in mesenchymal cells that are characteristic of cancer.⁸⁹ Thus, it is necessary to understand the molecular mechanisms that trigger the spread to other organs and thereby increase the possibility of reducing mortality that is associated with cancer. Some theories have proposed microRNA involvement in the modulation of the metastases through adhesion molecules such as E-cadherin.⁹⁰ Studies in lung cancer cell lines have also demonstrated the ability of NO to induce cell aggregation, in addition to participating in the epithelial-to-mesenchymal transition in tissue. This results in neoplastic cells acquiring a selective advantage, and these cells are capable of withstanding apoptosis processes.²⁴ Other studies have described the influence of NO in the spread of cancer through the activation of oncogenic pathways such as PI3K-AKT-mTOR. In this connection, some authors have suggested that NO can activate the intracellular serine-threonine kinase and that mTOR contributes to the progression of carcinogenesis.

This has also been observed when there is altered expression of genes that are involved in this pathway, and tumor cells induce resistance to chemotherapeutic drugs, ultimately contributing to the development of metastases.⁹¹ Others studies have observed that NO concentrations above 100 nM can induce protein S-nitrosylation, an event that is associated with intracellular traffic, protein phosphorylation, and protein-protein interactions. Finally, it has been observed that S-nitrosylation that is induced by NO is a key event for the invasion of the tumors into other organs and it increases the risk of developing cancer.⁹² For this reason, the aim of our review has been to describe the main signaling pathways that promote neoplastic processes and their influence with NO. However, NO plays a dual role in cancer and it is not possible to exclusively establish a deleterious effect because NO can exert antitumor and cytotoxic effects. Furthermore, it is possible that other signaling pathways in cancer are associated with NO and have not been described in our review. Finally, it is not possible to establish exact concentrations of NO that promote or inhibit carcinogenic events because its biological effects depend on other factors such as cellular state, redox state, and exposure time.

Conclusion

NO is a highly unstable gaseous compound with multiple biological functions in humans. Because of its ability to

react with different molecules that are involved in angiogenesis and stimulate activation of oncogenic pathways in mammalian cells, NO plays an essential role in the initiation, promotion, and progression of cancer. However, its activity may depend on several factors, including location, exposure time, and concentration at a given time. The expression of specific genes encoding enzymes that are responsible for NO synthesis, can be regulated by internal and external factors, both through various mechanisms and complex signaling pathways within the tumor microenvironment. In cancer, both the interaction between multiple events and key molecules are required to trigger the progression of neoplastic processes. However, it is important to consider that there is evidence that NO has antitumor properties, therefore further studies are required to understand the exact mechanisms by which NO influences cancer promotion.

Author contributions

The authors Ramírez-Patiño R. and Avalos-Navarro G, contributed in the same proportion. All authors contributed to the study conception and design. Ramírez-Patiño R and Avalos-Navarro G, drafted the manuscript, and all authors commented on previous versions of the manuscript and assisted to read and approved the final manuscript. Gallegos-Arreola MP has overseen the entire work.

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