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Nitric Oxide Molecule and Human Cancers

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Review Article

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Abstract

Nitric Oxide (NO) is a short-lived, endogenously produced free radical that is synthesized by the enzyme nitric oxide synthase conversion during arginine to citrulline and serves as a key signalling molecule in various physiological and pathophysiological processes. On the other hand, excessive and unregulated NO synthesis has been implicated as a causal or contributing factor to pathophysiological conditions including cancer. NO has been suggested to modulate different cancer-related events and several lines of research have indicated that NO may have dual effects in cancer i.e. cyto-protective as well as tumour promoting. NO seems to promote tumour growth and proliferation. In contrast, NO is said to have tumoricidal properties and is being investigated for therapeutic purposes. Peroxynitrite, the product of NO and superoxide is potent oxidising agent which is the main product that mediates tissue and cell injury. Peroxynitrite is highly reactive with bio-molecules like amino acids, nucleic acids, proteins, bases and metal containing compounds. NO has been reported to exert dichotomous effects within the multistage model of cancer. It modulates different cancer-related events including angiogenesis, cell cycle, apoptosis, invasion, and metastasis. Understanding its role in tumour biology will help in developing novel NO used treatment which will provide the useful information in preventing and treating various cancers. The effects of NO in tumour biology are quite broad, spanning its involvement in formation of neoplastic lesions, cellular transformation, regulation and initiation of the metastatic lesion. NO plays an important role in tumour progression by regulation of angiogenesis. Endogenous NO promotes tumour blood flow via dilatation of arteriolar vessels. It decreases leukocyte endothelial adhesive interactions and increases vascular permeability. The understanding of different actions of NO in these cancers at the molecular level and cellular level can help in identification of NO used prognostic and diagnostic markers and also in devising potential strategies for treatment, prevention and control of cancers.

Keywords: Nitric oxide; Cancer; Peroxynitrite; Tumour

Abbreviations: NO: Nitric Oxide; EDRF: Endothelium derived relaxing factor; FAD: Flavin Adenine Dinucleotide; FMN: Flavin Mononucleotide; iNOS: Inducible Nitric Oxide; NOS: Nitric Oxide Synthase; GC: Guanine Cytosine; AT: Adenine Thymine; DNA: Deoxyribonucleic acid; Hsp: Heat-shock protein; VEG F: Vascular Endothelial Growth Factor; MMP: Matrix Metalloproteinases; CNS: Central Nervous System; CSG: Chronic Superficial Gastritis; IM: Intestinal Metaplasia; CAG: Chronic Atrophic Gastritis; DYS: Dysplasia

Introduction

Nitrogen oxide (NO) was first discovered by Dr. Robert Furchgott in 1980 as a vasodilating substance produced by the cells lining of the blood vessels or endothelial cells. He first described the relaxing substance as "endothelium derived relaxing factor" (EDRF). Dr. Louis Ignarro later discovered that EDRF is nitric oxide [1]. Ten years prior, Dr Ferid Murad discovered that nitro-glycerine actually works through the release of NO and activation of an important enzyme. These three scientists were awarded the Noble Prize in 1998 for the discovery of the critical cardiovascular role of nitric oxide [2]. We are now beginning to appreciate its vital role in health and disease as a signalling molecule. NO can easily and quickly penetrate nearby membrane and cells sending signals: arteries to relax and expand, immune cells to kill bacteria and cancer cells and brain cells to communicate with each other [3]. In fact, NO sends crucial signals within every cells, tissues, organs and system of the body. But perhaps its most important signalling function is within the circulatory system. In animal systems most of the NO produced is due to the enzyme nitric oxide synthase. This enzyme catalyzes the oxygen and NADPH dependent oxidation of arginine to NO and citrulline in a complex reaction requiring FAD (Flavin Adenine Dinucleotide), FMN (Flavin Mononucleotide), tetrahydrobioprotein, calcium and calmodulin [3,4].

Role of Nitric Oxide in Humans

Nitric Oxide (NO) plays multiple effective modulating roles on inflammation and the regulation of immune responses. NO affects directly every step of the development of inflammation and neoplasia [5]. The concentrations of nitric oxide produced by constitutive nitric oxide synthases inhibit adhesion molecule expression, cytokine and chemokine synthesis and leukocyte adhesion and transmigration. Large amounts of NO, generated primarily by iNOS (inducible Nitric Oxide) can be toxic and pro-inflammatory. Actions of nitric oxide are however not dependent primarily on the enzymatic source, but rather on the cellular content NO concentration (dependent on the distance from NO source) and initial priming of immune cells. In normal and allergic condition, it is very difficult to determine the role of NO in Th1 and Th2 lymphocytes in immune response observed in the scientific experiments. Similarly superoxide anion produced by NAD(P)H oxidases present in all cell types participating in inflammation in a far more discrete way, when continuously produced at low levels by NOXs (non-phagocytic oxidases) [5]. The effects of nitric oxide in immune response regulation are carried through multiple steps, which include interaction with cell signalling system like cAMP, cGMP, G-protein dependent signal transduction pathways. They may also lead to transcription modification of cellular activity and in this way it modulates the expression of multiple other mediators of inflammation. Moreover genetic polymorphism exists within genes encoding enzymes producing NO. The potential role of these polymorphisms in inflammation and in susceptibility is to infection. The increase role of NO and free radicals in mediating inflammatory responses drugs which is also used in the treatment of inflammation of body systems. These include statins, angiotensin receptor blockers, NADPH oxidase inhibitors, NO-aspirin and others. NO is definitely a miracle-maker. Because it can prevents high blood pressure (hypertension); keeps your arteries young and flexible; prevents, slow, or reverses the build-up of artery-clogging arterial plaques; helps to stop the formation of artery clogging blood clots-the result of plaques bursting and spilling their contents into the blood stream; reduces inflammation; by doing all of the above, it can reduce your risk of heart attack and stroke [5,6]. But this molecule has more miracles to perform. It can also reduces the risk of diabetes and disastrous diabetic complications, such as chronic kidney disease, blindness, hard-to-heal foot and leg ulcers, and amputations; limits the swelling and pain of arthritis, and boost the power of pain-relieving drugs; calms the choking inflammation of asthma; protects your bones from osteoporosis; helps provide the mood-lifting power behind antidepressant medications; assists the immune system in killing bacteria; limits the skin damage from the sun [7-16].

Nitric Oxide and Cancer

Nitric Oxide (NO) is a short-lived, endogenously produced free radical that acts as a signalling molecule in the body. It is synthesized by nitric oxide synthase (NOS) enzymes; produced by mammalian cells at an appropriate magnitude and tempo, it serves as a key signalling molecule in various physiological and pathophysiological

processes. On the other hand, excessive and unregulated NO synthesis has been directly involved or contributing to various pathophysiological conditions like cancer, cardiac, respiratory and mental disorder. Expression of NOS has been detected in various cancers such as cervical, breast, central nervous system, laryngeal, and oral and head and neck cancers [17-28]. NO has been suggested to modulate different cancer-related events. However, several lines of research have indicated that NO may have dual effects in cancer. At concentrations measurable in many different types of clinical samples, NO seems to promote tumour growth and proliferation. In contrast to this, NO is said to have tumoricidal effects; various direct and indirect mechanisms have been proposed for its antitumor properties, although there is lack of data directly on cancer patients. Nevertheless, the tumoricidal properties of NO are being investigated for therapeutic purposes. NO is used alone or in combination with other cytotoxic agents [27,28].

NO has been reported to exert dichotomous effects within the multistage model of cancer. It modulates different cancer-related events including angiogenesis, apoptosis, cell cycle, invasion, and metastasis [4]. Understanding its role in tumour biology will help in reducing the controversy and confusion and will help in developing novel NO based therapies which will prove helpful in preventing and treating various human cancers. The effects of NO in tumour biology are broad, spanning its involvement in cellular transformation, formation of neoplastic lesions, and in initiation and regulation of the metastatic cascade. NO is involved in genotoxic events, it may mediate deoxyribonucleic acid (DNA) lesions by formation of toxic and mutagenic species, by direct modification of DNA, or by inhibition of DNA repair mechanisms [29,30]. RNS can mediate DNA strand breaks and can also yield different types of mutations in DNA. The modification of guanine cytosine (GC) to adenine thymine (AT) mutations in p53 which may contribute to loss of its repressor activity due the NO generation by iNOS method. NO directly inhibits activity of caspases providing an efficient means to block apoptosis. Other antiapoptotic effects of NO rely on NO/cGMP dependent inhibition of cytochrome C release, increase in Bcl-2 expression that controls the mitochondrial permeability transition pore, induction of heat-shock protein (Hsp) 70 and Hsp32, suppression of ceramide generation, and activation of cyclooxygenase-2 [30].

NO plays an important role in tumour progression by regulation of angiogenesis. Endogenous NO promotes tumour blood flow via dilatation of arteriolar vessels. It decreases leukocyte endothelial adhesive interactions and increases vascular permeability [11]. Studies have shown that vascular endothelial growth factor (VEG F) released as a purified protein or produced by tumour cells requires a functional NO/ cGMP pathway within the end compartment to promote neovascular growth. Another mechanism by which the production of prostaglandins and proangiogenic factors are important factors for production of tumour which are activated by COX-2 gene and are accelerated by the excessive production of NO. NO also has an invasion stimulating effect which is mediated by up regulation of MMP-2 (matrix metalloproteinases) and MMP-9 (matrix metalloproteinases - 9), and down regulation of TIMP-2 and possibly TIMP-3 (tissue inhibitors of MMP). Studies have indicated that NO limits which have adverse effects on leukocyte cell proliferation which consequences on the antitumor response of the host. In this way NO may be involved in the growth and spread of tumours. Nitric oxide seems to play diverse roles in various human cancers [11,18-20,27,31-36]. Understanding different actions of NO in these cancers at the molecular and cellular level can help in providing NO based diagnostic or prognostic markers and also in devising potential strategies for prevention and treatment of these cancers [36].

NO and Breast Cancer

In 21st century breast cancer is one of the most common cancer in women in globally both in developed as well as under developed countries [37]. It is investigated that NO has been recognised as the involvement and promotion of breast carcinoma. It was also observed that NOS (Nitrous oxide synthase) modified molecules has been reported in breast cancer tissues and in breast carcinoma cell lines. Increased amounts of NO have been observed in blood of breast cancer patients and higher NOS activity has been found in invasive breast tumors when compared with benign or normal breast tissue. Authors have found a high rate of NOS in situ carcinoma. Furthermore, NOS activity has been found to be higher in advanced grades of breast carcinomas. All these findings suggest that NOS expression in breast cancer may be a nearly event in carcinogenesis. NO is reported to have several important effects in the control of neoplasms. It suggested that the breast apocrine metaplastic cells of fibrocystic disease in the human changes into the progressive of metaplastic epithelium into carcinoma due to eNOS derived molecules [13]. NO increases tumour blood flow and promotes angiogenesis, which could explain the positive correlation between NOS spreading and biosynthesis active molecules that grades the malignancy. Nitro tyrosine, a biomarker of NO, was

found to be correlated with VEGF-C expression and lymph node metastasis in breast cancer suggesting the role of NO in progression of breast carcinoma. Switzer, et al. [38] showed that NOS2 expression in human breast tumours is functionally linked to poor patient survival [38].

Unlike other types of carcinoma, breast carcinoma they are greatly influenced by of steroid hormones. Recent findings implicate NO pathway in some of their effects. Estrogens and progesterone can regulate NOS and, in turn, the NO produced has profound consequences on tumour cell homeostasis [30]. It has been found that estrogens stimulate eNOS release in breast tissue where it acts as a free radical. eNOS expression has been found to be strongly correlated with estrogens receptor expression in a human breast cancer cell line, suggesting free radicals as possible causes of breast cancer. Progesterone has been found to activate iNOS expression. It has been suggested that the low levels of NO produced by eNOS mediate the proliferative effect of estrogens. On the other way, an increase in cell apoptosis in breast in response to progesterone could induce high levels of NO produced by activation of iNOS expression. Thus an understanding of the mechanisms and interactions of steroid hormones with the NO pathway is complex could lead to the development of new approaches and strategies for the effective treatment of breast cancer [30,31,39,40].

NO and Cervical Cancer

Cervical cancer is the second most common cancer in women worldwide, with >200,000 deaths annually [20]. Epidemiological studies have revealed a number of risk factors including chronic inflammation, smoking, long-term use of oral contraceptives, multiparity and other sexually transmitted infections (e.g., Chlamydia trachomatis and Herpes simplex virus type 2) [21]. Interestingly, these cofactors all increase NO levels in the cervical micro environment. Significantly higher levels of NO were observed in serum of patients with cervical cancers compared to healthy controls. Increased NO levels and markers of NO-mediated mutagenesis have been observed in the cervixes of women with cervical intraepithelial neoplasia. All these findings suggest that NO has potential mutagenic and carcinogenic activity in cervical cancer [17,41-43].

NO and Lung Cancer

Tobacco smoke is the main cause for lung cancer. It leads to chronic airway inflammation with accumulation and activation of leukocytes which produce high levels of ROS and NO. It has been demonstrated that NO, nitrite, and nitrotyrosine are increased in patients with lung cancer [44]. Chen, et al. found significantly higher levels of iNOS/NO in lung cancer tissues of smokers than that of non-smokers. Strong immuno reactivity for iNOS and eNOS was observed in dysplastic lesions in the lung. Certain hexavalent chromium [Cr (VI)] compounds have been postulated to play a significant role in pulmonary tumorigenesis. Forbes, et al. [35] observed that repetitive use of chromate affects the lungs tissue which induces inflammatory condition of lungs with the support of NO leads to development of lungs carcinoma. Nitration of protein due to NO may contribute to lung carcinogenesis. NO and its derivatives react with ROS to produce potent nitrating agents leading to 3-nitrotyrosine formation in proteins, which is one of the modifier that occur during oxidative/nitrosative stress. At high levels, NO inactivates p53 and its activation by nitration could also contribute to carcinogenesis given that over 90% of lung tumors are with defective p53. With broad effects on angiogenesis, glycolysis, p53 activity, antioxidant potential in the lung and alteration of cell growth pathways, NO may create a microenvironment that promotes tumorigenesis and or promotes tumour heterogeneity leading to metastasis. The prognosis of lung cancer is still poor because of the absence of valid method and test to detect early as possible. Exhaled breath analysis and exhaled NO measurements may provide useful assays in predicting diagnosis and disease progression [36,45,46,47].

NO and Gastric Cancer

Despite advances in surgical treatment and chemotherapy, gastric cancer remains a major global health burden; various etiologic factors have been linked with the disease [34,48,49]. It is widely accepted that H. pylori infection and high salt intake are positively associated with this neoplastic process. Controversial associations have been found with smoking or drinking habits. The three enzymatic sources of NO, eNOS, and iNOS, have been characterized in the gastrointestinal tract. There is enhanced expression of iNOS and eNOS in human colorectal cancers. Colon cancer tissue has also been found to express NOS mRNA. Gastric carcinogenesis (GC) is considered as a multistage progressive process [26]. The early indicator for GC predisposition is abnormal hyper proliferation of gastric epithelial cells, such as chronic atrophic gastritis (CAG), dysplasia (DYS) and intestinal metaplasia (IM), which have been considered as precancerous lesions of GC. In a study by Feng, et al. [34], when the lesions progressed from normal to chronic superficial gastritis (CSG), CAG, IM,DYS, and finally to GC, the positive immuno staining rates for p53, iNOS, and VEGF were found to be significantly increased.

The study demonstrated that the positive immuno staining rates of iNOS were highly related well with GC and lymph node metastasis. It was observed that a role of NO in the initiation and progression of GC. NOS can also deaminate DNA and cause mutations of tumour suppressor genes, and possibly other oncogenes like s c-met and trigger to initiate genetic alterations of gastric mucosal cells leading to gastric carcinoma [26].

NO in Brain Tumours

NO affects a great variety of vital functions including neurotransmission and vascular tone. NO emerges as an important mediator of neurotoxicity in a variety of disorders of the central nervous system (CNS) [33]. nNOS expression may act as a putative useful in dictator of brain tumour differentiation and diaphorase, a histochemical marker of NOS activity in the brain. Data of their study suggested that malignant central nervous system neoplasm express unexpectedly high levels of NOS and suggest that NO production may be associated with pathophysiological processes important to these tumours [33].

NO and Head and Neck Cancers

Oral squamous cell carcinoma (OSCC), top sixth most common causes of morbidity and mortality due to carcinoma [28,50]. The habits of smoking and tobacco chewing are strongly linked with pre-oral cancer and oral carcinoma. It is reasonable to assume that components of tobacco, as initiators of inflammatory response, could be responsible for the generation of ROS/RNS that may lead to lipid peroxidation, enhanced NO products, and dearanged antioxidant defence system in tobacco users. The long term use of tobacco generates ROS/RNS are one of mechanism carcinogenesis of oral carcinoma [50]. Raised levels of NO2 and NO3 were noted in patients with oral pre-carcinoma and in healthy individuals who uses tobacco. This indicates potential of nitrosative injury in tobacco users and, therefore, NO may have clinical relevance as a biomarker of inflammation and estimation of cancer risk in pre-cancer patients or in healthy tobacco users. Alcohol intake is related to an increased risk of oral carcinoma. Ethanol is converted to NO, the reaction is accelerated by copper and magnesium is likely to play an important role in the carcinogeneis of some cancers, including head and neck cancer, which preferentially rely on NO signaling [50]. It was observed that ethanol and minerals implicate the role of NO in pathogenesis of oral carcinoma. Few studies have evaluated the role of NO in oral pre-cancer. Whether NO actually acts as a protumoral agent at a concentration which is present in oral pre-cancer needs further evaluation. Studies are required to know the exact role of NO in oral pre-cancer which will be helpful in intervening the cancer process [50].

NO as a Novel Cancer Therapeutic

NO may exert a biphasic response, such that when NO levels go beyond a critical concentration that would be suitable for development of tumour growth, survival of infected cells, are initiated by growth arrest or apoptotic pathways. These characteristics of NO have been exploited therapeutically impressive effects in pre-clinical models of cancer to slow tumour growth and to enhance the effects of both radiotherapy and chemotherapy [51]. Researchers are investigating various strategies for manipulating in vivo production and exogenous delivery of this molecule, including iNOS gene therapy, iNOS induction, and administration of NO donor drugs for therapeutic gain. Transfer of NOS-encoding cDNA sequences into cancer cells for gene therapy purposes effective methods for delivery of NO [51]. However, as both retroviral and adenoviral vectors may be hazardous to the host, cell-based approaches to overcome the problems associated with gene therapy are being sought. Further work in to the precise mechanisms of this process is required. Alternative mechanism of NO delivery, to use of NO producing drugs and chemicals. It may cause sustained release of NO with a wide range of half-lives, and with predictable estimated doses. Simultaneously, they could exert a multitude of anticancer activities which enhance the apoptotic stimuli, inhibition of metastasis, inhibition of angiogenesis, and inhibition of hypoxia, depending on concentration of NO donor and on the cancer type and stage [51].

Several promising findings strongly support therapeutic application of NO donors in cancer treatment, these cytotoxic agents use singly or in combination of other chemicals. NO donors have been shown to have the dual function of both sensitizing tumour cells to chemotherapy and immunotherapy and of being involved in the regulation and inhibition of metastasis [25]. NO donors belonging to the class of diazeniumdiolates are promising as they have been shown to be effective radio and chemo -sensitizing agents along with other effective properties such as long half-lives and target tissue specific delivery. The role of nitro-glycerine as a chemo-sensitizing agent as demonstrated by Yasuda, et al, [25,26] promises a safe and afford able alternative for the management of resistant or metastatic tumors. According to Bonavida et al., NO donors may be considered as novel therapeutic agents [9].

Conclusion

In humans NO helps in cancer treatment. NO has been to exert dichotomous effects within the multistage model of cancer. It modulates different cancer-related events including angiogenesis, apoptosis, cell cycle, invasion, and metastasis. In contrast to tumour promoting effects, NO has also been to have tumoricidal effects. NO based therapies will prove helpful in preventing and treating various human cancers. Apart from various useful properties it has various harmful effects also as it causes acid rain and global warming. It can also affect our health. Low levels of nitrogen oxides in the air can irritate our eyes, nose, throat and lungs, possibly causing you to dryness of throat and tiredness, nausea, experience shortness of breath and exposure to low levels can also result in fluid build-up in the lungs causing pulmonary failure.

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