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The Role Of Nitric Oxide In Cancer Development & it`s Therapy

A B S T R A C T

The Nitric oxide is a free radical belongs to reactive nitrogen species, acts as a signal molecule in many physiological and pathological processes as well as plays a significant role in a variety of biological processes including its action as a regulator to programmed cell death (apoptosis). In addition to its role in tumor formation, proliferation, and metastasis, Nitric oxide has also been stated to have tumoricidal effects. Therefore this review deals with the effect of nitric oxide on different types of cancer and its use in cancer drugs

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Introduction

Cancer is currently one of the most common health problems, with an annual rate of 14 million newly diagnosed cases and deaths of 8.2 million (1). The cell goes through several stages before it becomes a tumor, including the transformation from a precancer cell to a cancer cell. The disorder begins with an irregular cell that contains a mutation and then progresses to the largest number of tumor-forming cells. This malignant tumor spreads by penetration of its membrane into adjacent tissues in its advanced stage (2).

Free radicals

Atoms, ions, and molecules that have a single electron in their outer shell called free radicals, they are unstable so they are very aggressive and in pursuit of equilibrium attack the electrons of neighboring atoms. As a result, chain reactions will form (3). Reactive oxygen species (ROS) besides reactive nitrogen species (RNS) can be categorized as free radicals. Where hydrogen peroxide (H_2O_2), hydroxyl anion (OH^-), and superoxide anion (O_2^-) classified as Reactive oxygen species, whereas nitric oxide ($NO\bullet$), peroxynitrite ($ONOO^-$), radical nitrogen dioxide (NO_2), and nitrite (NO_2^-) classified as RNS (4). Because of their participation in many processes that are related to cancer cell formation and proliferation. Free radicals are characteristic of cancer (2).

Nitric Oxide

Nitric oxide is a gas produced internally with a short lifespan that acts as a signal molecule within numerous processes of physiological and pathological (4, 5). Numerous biological processes in vertebrate implicated that NO works as a biological messenger (6). The nitric oxide molecule is known as a biomolecule found in nearly every organism (7). Nitric oxide, classified as an endothelium stimulating factor (EDRF), is biosynthesized by various enzymes of nitric oxide synthase (NOS) and the following molecules such as O_2, NADPH, and L-Arginine(8). Nitric oxide may also be synthesized by the reduction of inorganic nitrate(9). Guanylyl cyclase is one of the enzymes affected by nitric oxide(10). So NO activate the enzyme by binding it to the enzyme's haem group (10). According to these characteristics, NO molecule has high susceptibility to penetrate the cell membrane and spread between neighboring cells (Paracrine signaling molecule)or diffusion within the single cell (autocrine signaling molecule) (9). But this molecule becomes inactive when converted to nitrite and nitrate molecules through reaction with oxygen and water (10). The nitric oxide molecule acts as a vasodilator by relaxing smooth muscles, helping to pump blood through the blood vessels (9). One example of drugs that its action interacts with NO pathway is Viagra, it inhibits the pathways that counteract the nitric oxide pathway (8). Nitric oxide creates a diverse spectrum of reactive nitrogen oxide species in biological systems(11), but it interacts directly with very few targets (12). Such targets are either other free radicals (e.g., O_2, O^{-2}) or metals of transition (e.g., Fe^{2+}) (12).

Nitric oxide synthase is the main enzyme responsible for the synthesis of NO.This enzyme exists in 3 isoforms endothelial NOS (eNOS or NOS3), inducible NOS (iNOS or NOS2), and neuronal NOS (nNOS or NOS1). nNOS and eNOS also called constituent NOS because of they're undergo constitutive expression (13). Such isoforms are important because the expression of NOS into tumor cells

varies depending on the case, revealing their diverse features of cancer metastasis (14). Medical research, on patients with different stages of colorectal cancer found that the survival rate in iNOS positive tumor patients was significantly lower than iNOS negative tumor patients (15).

The study of the angiogenesis-iNOS relationship in primary gallbladder carcinomas shows that the malignancy rate is significantly linked to the level of iNOS expression(16). Nitric oxide has been shown to act as an aggressive reducer in breast cancer cells by inhibiting cell motility and promoting cell adhesion and thus preventing metastases(17).Although Nitric oxide can have the ability to predicts cancer but their effects differ depending on the dose and organs implicated. such as mice with an iNOS-negative retrovirus causes multiple metastases of the lungs and attacker, tumors of the subcutaneous while iNOS-positive retrovirus mice led to small metastases of the lung, as well as the progress of cancer was slowly (18). The tumor suppressor gene p53 is a significant factor act as a regulator to the action of NOS2. So when the concentration of NO is high then p53 will inhibit NOS2 through a negative feedback loop(19).Tumor suppressor gene p53, which senses elevated cellular NO and inhibits NOS2 through a negative feedback loop(19), is an essential regulator of NOS2. This relationship, therefore, has significant consequences for cancer. (4).

The Characteristics of biology and physiology for nitric oxide

Nitric oxide (NO•−) in a number of physiological processes is known to play essential functional roles(20). In addition to its action as a vasodilator of blood vessels through a number of biological actions leading to the relaxation of smooth muscle cells which lining each of arteries, veins, and lymphatics.NO decreases the accumulation of platelets and therefore stops extravagant coagulation from interacting with the flow of blood. Nitric oxide acts as a regulator to programmed cell death (apoptosis) by active site nitrosylation and subsequently protein action inhibition. The NO molecule has also impact proapoptotic proteins including Bcl-2 protein family. Nitric oxide affect the function of the kidney. The presence of NO near glomeruli helps in increasing blood flow and the filtration rate and subsequently increases the excretion of urine. NO•− causes releasing of both gonadotropin-releasing hormone (GnRH) and adrenaline from the hypothalamus and adrenal medulla respectively (2).

Various roles of NO in cancer

Nitric oxide modifies different events associated with cancer implicating new blood vessels form from pre-existing vessels, programmed cell death, cell cycle, invasion and spread of cancer cells to neighboring cells (21). Nitric oxide has also been stated to have tumoricidal effects, in addition to tumor-promoting effects. Knowing its role in tumor biology may assistance to reduce uncertainty and misunderstanding and help develop new therapies based on nitric oxide that will be useful in the prevention and treatment of various cancers of humans (4). NO's effects in tumor biology are broad, spanning its role in cell transformation, neoplastic lesion development, and metastatic cascade initiation and regulation (22, 23). Nitric oxide has the ability to form toxic and mutagenic species which linked to DNA lesions through direct alteration of DNA or by DNA repair mechanisms inhibition (24).

Therefore different types of mutations will form as a result of the breakdown in DNA by RNS (25, 26). A previous study detected that

NO reduces the proliferation of leucocytes, which adversely affect the host's antitumor response. Understanding different NO actions in these cancers at the molecular level will assist in the production of NO-based diagnostic or prognostic markers and the development of possible cancer prevention and treatment strategies (4).

The role of NO on breast cancer

Currently, in developed and developing countries, breast cancer is the most common cancer among women (27). The potential involvement of NO in the origination of breast cancer has been investigated. Specific NOS expression was reported in tissues of breast cancer (28)and cell lines of breast carcinoma (29). It was found that breast cancer patients have higher levels than NO(30). It was also observed that invasive breast tumors exhibit higher expression of NOS compared to benign or normal breast tissue.

It was observed that in situ carcinoma has a high NOS rate(28). Besides, the activity of NOS in advanced breast carcinomas was found to be higher (30).According to these results, the NOS gene expression may be used for the early detection of breast cancer. It has been reported mentioned by researchers that high NOS rates found in sit carcinoma (4). Also, in advanced grades of breast carcinomas, NOS activity was found to be higher(30).All of these findings suggest that an early event in carcinogenesis may be the expression of NOS in breast cancer(4). It is documented that NO has sundry significant impacts in controlling of neoplasms. Jadeski et al.(2000) indicated that eNOS can encourage the progression of the metaplastic epithelium into carcinoma in human breast apocrine metaplastic cells of fibrocystic disease (31).Avtandilyan et al., (2018)have concluded that the reduction of substances that cause the formation and spread of cancer cells such as polyamines and nitric oxide can be done by inhibiting some enzymes such as Arginase and NOS enzymes (32).

The role of NO on lung cancer

The main cause of lung cancer is tobacco smoke(33, 34). This contributes to persistent inflammation of the airway with leukocyte aggregation and activation resulting in elevated ROS and NO levels(35). It has been shown that in patients with lung cancer, NO, nitrite, and nitro tyrosine are increased (36).

A study by Chen et al. found that smoker patients with lung cancer have higher levels of iNOS/NO than non-smokers (37) . Clear immunoreactivity in the lung's dysplastic lesions was observed for iNOS and eNOS (38). It is assumed that several hexavalent chromium [Cr (VI)] compounds have an important function in pulmonary tumorigenesis.

It has been found that the Pneumonia environment which leads to lung cancer is caused by frequent exposure to chromate molecules and subsequently increased nitric oxide level (39).

Previous studies reported that through nitrating proteins, NO can lead to lung carcinogenesis. Where powerful nitrators act that arises from reaction ROS with NO and its metabolites on the formation 3-nitrotyrosine in protein (40, 41). This important chemical change happens throughout oxidative/nitrosative stress.P53 is inactivated at high levels of NO and this inactivation of p53 through nitration lead to carcinogenesis of more than 90 percent of lung tumor. Beside many effects of NO on lung such as growth, and differentiation of endothelial cells, the pathway of glycolysis, the activity of p53, potential antioxidant, and changes in the pathways of cell growth, NO creates a small environment that contributes to the synthesis,

and proliferation of tumor cells (35). Because of the absence of valid approaches to its early detection of lung cancer. The prognosis of the disease is still poor. Exhaled breath monitoring and NO tests can be helpful in determining the course of infection and the development of disease (42).

The role of NO on cancer of the cervix

The second most common disease among women is cervical cancer. Deaths among women are estimated to be more than 200,000 cases yearly (43). There are some risk factors that were detected through epidemiological studies such as oral contraceptives usage for along time, multiparty, smoking, chronic inflammation, in addition to sexual diseases which transported by an infection such as herpes simplex virus type 2 and chlamydia trachomatis(44). It is interesting to note that, in the cervical microenvironment, these cofactors all raise NO rates (45-46).Annually more than 200,000 deaths because of cervical cancer, it is the most common cancer after breast cancer among females. There are several risk factors related to cervical cancer such as chronic inflammation, smoking, other sexually transmitted infections (e.g., chlamydia trachomatis and herpes simplex virus type2) long-term use of oral contraceptives, and multiparty (44).
Several studies revealed that patients with cervical cancer have a higher concentration of NO compared to healthy subjects (47, 48). Other studies reported that females with cervical intraepithelial neoplasia have high levels of NO besides NO-mediated mutagenesis markers (49, 50). Previous studies in cervical cancer have shown that the oxide molecule has mutagenic and carcinogenic activity (4).

The role of NO on gastric cancer

Although progress in chemotherapy and surgical treatment of gastric cancer, stills a main global health burden, there are several factors that increase the risk of gastric cancer including H. pylori infection, high salt, smoking, and drinking habits(51). It has been revealed that in the gastrointestinal tract, 3 enzymatic sources of NO have been characterized (52). Other study observed that patients with colorectal cancer have a high level of expression of both iNOS and eNOS enzymes (53). It has been found that NOS mRNA expresses in the tissue of colon cancer (54).

Carcinogenesis of Gastric, it is a gradual process consist of multistage. The proliferation of epithelial gastric cells in abnormally form for example intestinal metaplasia (IM), chronic atrophic gastritis (CAG), and dysplasia (DYS) is an indicator used for early detection of GC (55,56).

Feng et al., (2002) have noticed that the disease has progressed from normal case to precancerous lesions and then to gastric cancer are accompanied by an increase in the levels of each of the following markers such as iNOS, VEGF, and p53. It has been also showed that GC metastasis of the lymph node was well connected with positive iNOS immunostaining rates (54). NOS begins genetic changes in gastric cells and converted it to gastric cancer including causing in deamination of DNA and mutations in tumor suppressor genes, and c-met as(4).

The role of NO on brain tumors

Nitric oxide has been shown to effect on a wide range of vital functions among them neurotransmission and vascular tone, it has been found that many central nervous system disorders mediated by NO. Broholm et al. found that nNOS expression uses as an indicator for differentiation of brain tumor and malignancy(57).

The previous study reported that the histochemical markers of NOS activity in tumors of the human brain by NADPH diaphorase and three isoforms of NOS. They found that NOS increases in malignant brain tumors due to the pathophysiological processes of these tumors (58).

The role of NO in head and neck cancer

Oral squamous cell carcinoma (OSCC) ranks sixth among the most prevalent cancer .as well as it is the main source of morbidity and death (59).

Chewing of tobacco and smoking habits are connected with high oral and precancer incidence (60,61). Tobacco ingredients serve as inflammatory response initiators. They are in charge of production various free radicals such as ROS/RNS, the presence of these free radicals go to peroxidation of lipid, promote the production of NO, and weak the defense system of antioxidant in subjects consume tobacco(62).

Elevated ROS/RNS in tobacco users for a long time leads to damage to genes and subsequently cancer(62).It has been shown that oral pre-cancer patents and healthy people with smoking practices have high NO2 and NO3 levels (62-64). As a result of the injury of nitrosamine in tobacco users, NO can be used in patients with pre-cancer and normal smokers as a clinical marker for cancer risk estimation and inflammation. Alcohol consumption has been found to increase the oral cancer prognosis (65).

Ethanol has been shown to act as a catalyst for the production of nitric oxide and causes many cancers, including head and neck cancer, which depends mainly on NO signaling(66).NO is studied in oral pre-cancer by very few studies. To understand NO's role in the process of carcinogenesis further researches is needed (4).

The impact of NO on tumor cell

As mention above NO has opposite effects on the tumor , some studies revealed pronumeral effects of NO while few other studies demonstrated NO's an opposite role in tumor regression mediation (67-69).

Some studies found that NO that is released from some cell including endothelial cells macrophages, natural killer cells, and Kupffer cells are involved in tumor suppression activity opposite several types of tumors, they observed that NO have two effects on tumor cells such as cytostatic and/or cytotoxic(69,70).

It has been reported that some enzymes like as ribonucleotide reductase and aconites are involved in the effects of cytostatics and /or the effects of cytotoxicity which implicated NO(71). High production of NO for a long period works as a modulator of proapoptotic , the activation of caspase family proteases is carried out by NO through changes in the expression of proteins associated with apoptosis such as family of Bcl-2, upregulation of the expression of p53 ,then upregulation of the expression of p53, besides liberation cytochrome C of mitochondria to inside the cytosol(72). It has been found that the high levels of NO act as lowering metastasis (73). Baritaki et al. (2010)found that DETA-NONOate acts as a donor to NO. DETA-NONOate releases a high concentration of NO which suppresses epithelial to mesenchymal transition (EMT) and opposites the phenotype of mesenchymal and invasive features of metastatic cells in human prostate (74).

Bonavida et al. (2012)found that NO donors act as therapeutic agents in both drug resistance reversal and EMT inhibition and metastasis(75).

While NO's tumoricidal roles were suggested, most studies were performed in vitro(76,77)and these results were not reported in patients with cancer. It's been mentioned that NO levels in squamous cell carcinoma in oral,

as well as in else rigid tumors, were indicated to be inadequate to induce apoptosis (78) and other tumoricidal effects and may promote angiogenesis and tumor spread (79). However, there are several factors involved in determining the type of effect of nitric oxide on tumor cell catalytic or inhibitory, including NO concentration, duration of exposure, redox state, exposed cell type, redox state, and final concentration within intracellular, etc(4).

The role of Nitric oxide in therapy

It has been reported that NO has a significant function in tumor progression and metastasis. Some studies focused on various factors that affect NO including NO flux, duration of NO• exposure, Oxidizing and reducing agent prevalence, cellular microenvironment, and tumor cell cycle stage [80]. Because NO•'s effect also depends on concentration, angiogenesis, proliferation, and metastasis can normally be induced by lower NO• (< 100nM) levels. While at higher concentrations of NO (more than 400–500 nM), NO acts as cytotoxicity and cell apoptosis stimulator (80,81).

The wide variety of donors of nitric oxide makes it possible to select a material capable of liberation NO with consistent concentrations in addition to the broad spectrum of launch times. Therefore, donors of nitric oxide have allowed for a more vigorous evaluation of NO's function in the treatment of cancer. But usage NO donating compounds must be subject to restrictions. For instance, cyanide which is a by-product of NO's donors sodium nitroprusside, it causes cell toxicity (82).

Nitric oxide donors have been used as a new drug to treat many types of cancer. Due to their action as an inhibitor of cell survival and anti-apoptosis (83, 84).

Many studies were conducted with respect to the sector of NO liberating non-steroidal anti-inflammatory drugs(NO-NSAIDs), this is because of the presence of NO along with cancer drugs such as NSAIDs works as a complement and booster for action these medicines. It has been found that NSAIDs have a role in decreasing colorectal cancer risks (85,86), indicating a potential role in chemoprevention. Some studies reported that NO-NSAIDs play an increasingly effective role at suppression the growth of cancer cells and its spread to neighboring cells compared to NSAIDs (85, 87).

It has been reported that NO-NSAIDs affect the cancer cell through inhibiting the proliferation of cells via the gene expression lowering of proliferating cell nuclear antigen (PCNA) gene(88).

A protein of PCNA activate delta DNA polymerase in cells of eukaryotics, then effect on DNA polymerase delta in eukaryotic cells. Therefore the lowered expression of PCNA will cause lowered in DNA synthesis and decreased the proliferation of cell. But the lowered in the expression of PCNA was not parallel to the decrease in the proliferation of the cell because there other factors are implicated (88).

It has been found that aspirin revealed lower pro-apoptotic effects compared to NO•-aspirin. Where A large number of “atypical” cells were induced by NO•-aspirin (88, 89). It has been found that the basic cellular structure of atypical cells, do not contain DNA. Because NO•-NSAIDs stop the transition of the cell cycle from G0-G1 to S in addition to the suppression of the growth of cells (88).

Therefore, NO•-NSAIDs are likely to increase apoptosis-friendly cellular pathways and reduce metastases in some cell types. For example, It has been found that the use of nitric oxide does not work in some cases including hepatocyte metastasis, B-cell lymphomas, the cells of endothelia, and additional cell lines

where pro-apoptotic mechanisms have been shown to block NO•(5,90,91).

However, after prolonged exposure to elevated concentrations of NO•, It has been shown that else cancer cells such as breast carcinomas have apoptosis (4).

Conclusion

We can conclude from this study that NO has two significant roles .The first role is its participation in initiation, growth, and metastasis of different types of cancer. The other role is acting as tumoricidal. Therefore, it has been utilized from this property in designing medicines to treat various types of cancer.

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