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Potential therapeutic applications of medical gases in cancer treatment

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Abstract

Medical gases were primarily used for respiratory therapy and anesthesia, which showed promising potential in the cancer therapy. Several physiological and pathological processes were affected by the key gases, such as oxygen, carbon dioxide, nitric oxide, hydrogen sulfide, and carbon monoxide. Oxygen targets shrinking the tumor via hyperbaric oxygen therapy, and once combined with radiation therapy it enhances its effect. Nitric oxide has both anti- and pro-tumor effects depending on its level; at high doses, it triggers cell death while at low doses it supports cancer growth. The same concept is applied to hydrogen sulfide which promotes cancer growth by enhancing mitochondrial bioenergetics and supporting angiogenesis at low concentrations, while at high concentrations it induces cancer cell death while sparing normal cells. Furthermore, carbon dioxide helps induce apoptosis and improve oxygenation for cancer treatments by increasing the release of oxygen from hemoglobin. Moreover, high-dose carbon monoxide gas therapy has demonstrated significant tumor reductions *in vivo* and is supported by nanomedicine and specialized medicines to boost its delivery to tumor cells and the availability of hydrogen peroxide. Despite the promising potentials of these gases, several challenges remain. Gas concentrations should be regulated to balance pro-tumor and anti-tumor effects for gases such as nitric oxide and hydrogen sulfide. Furthermore, effective delivery systems, such as nanoparticles, should be developed for targeted therapy.

Key Words: angiogenesis; cancer; challenges and limitations; medical gases; therapy

Introduction

Cancer remains one of the most significant global health challenges, accounting for over 9 million deaths annually, which makes it the second leading cause of death worldwide.[1] It is characterized by the uncontrolled division of cells, leading to the invasion of surrounding tissues and metastasis to organs far from their origin.[2] This complexity arises from the diverse types of cancer and the dynamic, evolving nature of tumors during the lifespan of an individual. Even with treatment modalities having advanced from just surgery, chemotherapy, or radiation therapy to immunotherapy and targeted therapies, there are still notable efficacy limitations.[1,2]

Surgical interventions are predominantly performed during the early stages of cancer. Still, these methods remain inadequate when the disease has advanced with metastatic spread to other sites. However, both primary and advanced forms can be treated with chemotherapy. In this case, it is the most frequent means of battling cancer. The most active cells, the cancerous ones, are destroyed because chemotherapy attacks rapidly dividing cells. Nevertheless, this broad specificity results in damage to healthy cells, especially those in the gastrointestinal system and bone marrow.[3] Additionally, radiation therapy is a widespread treatment. It operates by emitting high-energy rays to the cancer regions. Unfortunately, radiation treatment will destroy healthy neighboring tissues, resulting in significant adverse effects.[4] Immunotherapy has been the most breakthrough cancer treatment in recent years, taking advantage of the body's immune system to eliminate cancerous cells. However, it is not always successful, and a considerable number of patients acquire oncological resistance or have side effects as a result of this type of treatment. These adverse effects may put a restriction on the use of immunotherapy for cancer patients.[5] Cancer-targeted drugs known for their ability to target molecular defects of cancer cells specifically have a more appropriate means of management for this condition. Nevertheless, tumors change their characteristics over time, and as such, targeted lesion attacks will not always be effective due to the evolution of drug resistance.[6]

The conventional treatment methods, referred to earlier, are not able to completely solve the challenge of cancer heterogeneity, in addition, systemic toxicity in patients exposes these patients to more negative effects. As a result, there is an urgent need for innovative treatment approaches. Tumors are

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primary aggregates made of a generic population of cells that have heterogeneous genetics or phenotypes. Hence, it follows that tumors cannot be simply regarded as a whole. This tumor heterogeneity enhances the potency of cancer treatment failure as different portions of cancer cells may have varied responses to a certain treatment.[7] Furthermore, the tumor microenvironment (TME) is important in tumor development, metastasis, and the ability to resist treatment. This TME consists of immune cells, blood vessels, extracellular matrix, and other components.[8] The phenomenon of hypoxia in tumors, one of the most common features of TME, has been linked to therapy failure in both chemotherapy and radiation therapy.[9]

However, independent studies are now targeting these unmet needs, including investigating the effect of using medical gases on cancer therapy. Medical gases have been in use for a long time, particularly in anesthesia, intensive care, and respiratory therapy, but their use in oncology practice is quite recent. These medical gases mark an emerging and captivating approach to cancer. By targeting the TME and altering critical biological pathways, they offer the potential to complement existing cancer therapies. They can even serve as standalone treatments in certain contexts.[10,11] This review will focus on the therapeutic potential of oxygen (O_2), nitric oxide (NO), hydrogen sulfide (H_2S), and carbon dioxide (CO_2) in cancer treatment, discussing their effects on tumor growth, metastasis, and the TME. It will also explore prospects for their clinical application.

Literature Search

We conducted a literature search using major scientific databases, including PubMed, Scopus, Web of Science and Google Scholar. The search focused on studies related to therapeutic potential of medical gases in cancer treatment. The key medical gases included oxygen, nitric oxide, hydrogen sulfide, carbon dioxide and carbon monoxide. The search terms included the following: medical gases and cancer, oxygen and tumor biology, nitric oxide and cancer cell, hydrogen sulfide and cancer, carbon monoxide and tumor microenvironment and carbon monoxide and therapy. Boolean operators such as “AND” and “OR” were applied to construct the strategy. The search included studies published in the last 10 years to capture the most up to date research findings in the field of gas and cancer treatment.

Studies were included if they focused on the role of medical gases in cancer therapy, involved either *in vitro* or *in vivo* studies on cancer cells or tumors, published in peer reviewed journals and written in English. Studies were excluded if the studies were focusing on other therapeutic applications of medical gases outside oncology, if the articles were lacking data and articles written in languages other than English.

Overview of Medical Gases in Therapeutic Contexts

Medical gases are pharmacological gaseous molecules that solve many medical issues. They include classic gases such as O_2 and nitrous oxide, in addition to gases that have recently been identified to act as messenger molecules such as NO, carbon monoxide (CO), and H_2S.[12] Inhalation treatment was developed more than two millennia before gaseous particles were artificially purified. Its original intent was to accelerate the delivery of drugs to patients with respiratory diseases.[13] The inhaled solution from black henbane plants, which carry alkaloids with sedative, bronchodilating, and spasmolytic qualities, was prescribed to patients experiencing respiratory distress.[13-15]

Physiological gases, such as CO_2 and O_2, are fundamental in controlling physiological and pathological processes.[16] O_2 is essential for mitochondrial respiration because it serves as an electron acceptor in this process, allowing oxidative phosphorylation to produce adenosine triphosphate (ATP).[17] Therefore, breathing is necessary for reducing stress, producing energy, and being useful for health and happiness.[18] In contrast, low levels of O_2 in the tissues, called hypoxia, are associated with several diseases such as diabetes, cancer, degenerative and heart diseases.[19] As for CO_2, it is essential for blood pH homeostasis, and its lack or buildup in the blood can lead to severe conditions, such as respiratory acidosis. These conditions can manifest in dyspnea, anxiety, and cyanosis; severe instances can lead to seizures and disturbed mental state.[20] Another gas is hydrogen (H_2), which has a role in immune system regulation, cell death, and anti-inflammatory and antioxidant activities, by destroying excess reactive oxygen species (ROS) generation and modifying nuclear transcription factor.[21]

Nowadays, in the healthcare system, survival in patients suffering from hypoxemia and chronic obstructive pulmonary disease is improved by O_2 supplements.[22] Furthermore, NO has been clinically proven to be useful when it comes to therapy of mitral valve disease, and congenital heart disease in combination with pulmonary hypertension patients.[23] Overall, the findings support the concept that widely available biological gas, CO, H_2S, H_2, NO, dinitrigenoxide (N_2O), O_2, and ozone (O_3) or noble gas, helium (He), xenon (Xe) and argon (Ar) therapy can protect cells and treat many diseases.[24]

Oxygen in Cancer Therapy

Role of oxygen in tumor biology

In normal body tissues, reduced O_2 levels (hypoxia) activate a set of adaptive responses that aim to either increase O_2 supply or reduce its consumption. A state of hypoxia can be seen in both physiological and pathological states, especially in neoplastic transformation and evolution.[25] Highly dividing tumors usually exceed their vascular supply, this will lead to a hypoxic state, associated with low glucose, and an acidic pH, which promotes tumor growth and metastasis. After the tumor formation following a set of genetic and epigenetic alterations and clonal selections, it creates a specialized microenvironment, which controls tumor development.[25]

Tumor cell reactions to low O_2 are classically initiated by activating the family of transcription factors known as hypoxia inducible factors (HIFs),[26] indispensable for hypoxia adaptation.[27]

Hypoxia can be classified into two states: cycling and chronic, cycling hypoxia has been demonstrated to favor angiogenesis, resistance to treatment, metastasis, and intra-tumoral

inflammation.[28] This inflammatory state will help create an immunosuppressive environment that helps the tumor evade any immune response.[25]

Tumor cells benefit from this hypoxic state to promote anaerobic glycolytic metabolism to support cellular division and molecular synthesis. In a hypoxic state, the energy metabolism of the cell changes to include an increase in glucose consumption and inhibition of both the electron transport chain, and Krebs cycle.[29]

This metabolic shift in tumor cells from aerobic to anaerobic is mediated by HIF (characterized by upregulating glucose transporters and glycolytic enzymes).[25] Molecules produced via these pathways help in the growth of the tumor or stabilize the HIF-1α.[29] This anaerobic state permits the synthesis of precursors of nucleotides and amino acids, essential molecules for tumor growth and proliferation.[26]

Nevertheless, hypoxia induces a crucial early step of metastatic spread known as epithelial-mesenchymal transition and promotes self-renewal of cancer stem cells, which enhances tumor resistance to chemo and radiotherapy. Remarkably, cancer cells are able to exploit hypoxia-induced mechanisms to support their own growth and metastasis. Hypoxia is associated with a more severe tumor phenotype, more developed angiogenesis, metastatic spread, relapse, resistance to therapy, and decreased overall patient survival. Additionally, hypoxia stimulates a set of mechanisms allowing tumor evasion following anti-angiogenic therapy.[25]

Thus, understanding these mechanisms of action helps understand how cancer develops and how we can create new, more efficient therapies.[29]

Therapeutic approaches involving oxygen

Hyperbaric oxygen (HBO) therapy (HBOT) is the use of O_2 under atmospheric pressure at a higher level than the pressure at sea level (1 atm, equivalent to 101,325 kPa). This therapy can enhance tissue oxygenation by increasing levels of O_2 dissolved in blood. When considering anti-cancer treatment, the curative effect of HBOT is limited and is not used solely.[30] HBOT can reduce the capacity of cancer stem cell formation but does not induce cell death by itself, therefore the therapeutic effect of HBOT can delay the formation and maintenance of cancer stem cells.[30] This technique can be highly beneficial when the cause of hypoxia is cardiovascular in origin.[29] Nevertheless, the actual data almost indisputably states that HBOT is not only unfavorable for further development of tumors, but might also shrink the main cancer mass.

Radiotherapy causes damage to DNA strands in cancer cells, therefore leading to cell death. Thus, this therapy gives an ideal therapeutic result in cancer tissue that is properly oxygenated. When HBOT is used alongside radiotherapy, this combination can have two functions: as a radio-sensitizer, enhancing the effect of radiation, or as a therapeutic agent by itself, reducing the effect of radiation injury in the surrounding tissue. Merging these options can inhibit cancer development and help in local control of the tumor, therefore leading to increased survival.[31,32]

First trials aimed to prevent hypoxia by increasing oxygenation during irradiation, however, the clinical effectiveness of this technique was insufficient.[25] HBOT is one of the most effective ways to relieve hypoxia in solid tumors.[33] Yet, even at high-pressure oxygenation, the hypoxic state was not removed entirely, this shows that the efficacy of HBOT only is limited.[34] Certainly, the most common and benign side effects include middle ear barotrauma, seen in up to 2% of patients, and preventable by teaching auto-inflation methods, or by adding tympanostomy tubes. The other one is claustrophobia, a specific type of phobia characterized by fearing closed spaces,[35] therefore, requiring reassurance, coaching, and, sometimes, sedation. Other rare, but more critical side effects derive from O_2 toxicity, usually transient and reversible after discontinuing metaboric acid sessions, or pulmonary difficulty breathing, with cough and pain upon inspiration.[36] HBO is generally safe for patients, with rare side effects and its toxicity appears mainly when used at high doses and for a longer period than indicated in guidelines.[31] About 5% of cancer subjects treated with radiation will have late-onset severe toxic side effects.[37]

Carbon Dioxide in Cancer Therapy

Role of carbon dioxide in tumor biology

Developing an external pH lower than the intracellular pH (pH external < pH internal) is a crucial characteristic that sets malignant cells apart from healthy cells. This phenomenon, known as the Warburg effect, encourages aerobic glycolysis even in the presence of O_2 delivery. Even if there are functional mitochondria, tumor cells will significantly enhance the rate of glucose uptake and lactate generation.[38,39] Initial tumor cell function may be hampered by the successive production of acid compounds such as lactate into the extracellular matrix, but at high quantities, lactate will stimulate stromal cells, cause immunosuppression, and accelerate tumor propagation.[40]

Because CO_2 buffers this acidity when transformed into bicarbonate and protons, it plays a significant role in this altered TME.[41] CO_2 increases O_2 levels through a variety of mechanisms, including the Bohr effect. Bohr effect explains how CO_2 directly reduces hemoglobin's O_2 binding affinity, increasing O_2 availability and decreasing hypoxemia.[42,43] Another method involves the vasodilatory actions of CO_2, which boost blood flow to the TME and increase O_2 absorption.[44] This significant decrease in hypoxia levels alters tumor cell metabolism, promotes apoptosis, and increases the efficacy of cancer treatments. Rivers and Meininger[45] discovered that high O_2 levels stimulate adenosine monophosphate-activated protein kinase, possibly impacting tumor cell death.

Therapeutic potential of carbon dioxide

The therapeutic potential of CO_2 intervention has been postulated and thoroughly examined by inducing hypercapnia in the tumor cell microenvironment, with hopeful results. According to River and Meininger,[45] CO_2 may help reduce tumor size. This can be explained by the increased availability of O_2, which inhibits the expression of HIF-1, a crucial protein for cancer survival in hypoxic conditions. As a result, disrupting

the tumor by inhibiting the HIF-1 signaling system has increased therapeutic response. High O_2 levels can activate caspases 3, 9, and peroxisome proliferator-activated receptor gamma coactivator-1α, in addition to the previously stated adenosine monophosphate-activated protein kinase activation and HIF-1 reduction. All of these pathways enable tumor cells to undergo programmed cell death.[46] This further emphasizes the importance of CO_2 in inducing tumor cell apoptosis.

Furthermore, it has been postulated that CO_2 stimulates lysosome membrane permeabilization, releasing cethespins into the malignant cell's cytoplasm and encouraging death. Yang et al.[47] reported that employing a bubble-generating nanosystem to manufacture CO_2 bubbles improved the tumor's response to therapy and prevented multidrug resistance. Thus, the use of CO_2 as an adjuvant in cancer therapy has been found to increase O_2 levels and vascularization, raise lysosome membrane permeabilization, and improve the efficacy of treatments that cause apoptosis and oxidative damage.[48]

Challenges and limitations

Controlling CO_2 levels in the TME is exceedingly challenging, even though these studies have proved the promise and great potential of CO_2 use in cancer therapy in terms of boosting therapeutic success rates. For example, the lactic acid generation of cancer cells may circumvent the CO_2 levels that are supplied, thus upsetting the local acid-base balance. Furthermore, long-term elevated CO_2 levels may disturb the balance of pH in the body, making tumor cells more resilient to stress and making treatment strategies more difficult.[49] A comprehensive investigation of the biological significance of CO_2 in cancer therapy is necessary because of its potential to inadvertently increase invasiveness, promote tumor survival, or exacerbate treatment resistance due to its impact on cellular stress responses and ability to modify cellular metabolism.[50]

Nitric Oxide in Cancer Therapy

Role of nitric oxide in tumor biology

NO is an intrinsically occurring, multifunctional signaling molecule involved in various physiological functions.[51] The typical mechanism proposed for NO is vasodilation by stimulating the Sarcoendoplasmic reticulum Ca^{2+} ATPase and inhibits Ca^{2+}-dependent K^+ channels. Furthermore, NO undergoes chemical reactions with a variety of endogenous radical species, producing reactive nitrogen species such as nitrogen dioxide (NO_2) and peroxynitrite (ONOO-), that act as potent oxidizing and nitrating agents resulting in changes in DNA, lipid peroxidation, and protein modifications.[52]

Regarding cancer therapy, NO has been demonstrated to have a significant role; however, the dual influence on carcinogenesis and tumor development offers a great challenge. The pro- and anti-tumor effects of NO involve a variety of factors as the local concentration, duration of exposure, redox state, compartmentalization of NO generation, and TME.[53,54] Generally, high NO levels trigger cell death, reduce hypoxia, and increase tumor susceptibility to traditional therapies, whereas low NO levels induce cancer-promoting pathways, immune suppression, metastasis, and angiogenesis.[55]

At higher concentrations, such as those produced by the immune system, NO can have cytotoxic and genotoxic effects, inducing cancer cell apoptosis and necrosis through reactive nitrogen species causing chemical processes such as nitrosation and deamination while also blocking particular DNA repair pathways, resulting in increased mutation potential.[56] Furthermore, NO has been shown to increase the apoptosis and necrosis triggered by chemotherapy, radiation, photothermal treatment, and photodynamic therapy via altering a variety of variables, including multidrug resistance, hypoxia, autophagy, and the equilibrium of ROS.[57]

Moreover, the presence of a negative feedback loop between NO and p53 plays an important role in NO role in the treatment, where NO results in wild type p53 accumulation, resulting in anticancer and apoptotic mechanisms of NO, while the p53 overexpression results in a downregulation of NOS2 gene expression thus reducing the potential for NO-induced DNA damage.[58] In contrast to the NO role in treating cancer, increased NO synthase activity showed a correlation with elevated angiogenesis, which is commonly seen in the tumors in the head and neck region, so blocking NO synthesis decreased tumor angiogenesis.[59]

Nitric oxide based therapeutic strategies

Widespread interest in developing techniques for delivering exogenous NO through NO-releasing systems or donors NO is increasing due to NO short half-life and concentration-dependent physiological effects, which frequently limit its activity to specific target locations.[60] The main NO donor classes are organic nitrates, diazeniumdiolates, metal-NO complexes, furoxans, S-nitrosothiols, and sydnonimines. Glyceryl trinitrate, a well-known organic nitrate, works as a chemosensitizing agent by increasing O_2 supply and perfusion, especially in non-small cell lung cancer, which frequently have poor responses to chemotherapy owing to tumor hypoxia.[61] Another extensively studied NO donor is diazeniumdiolates due to their vast spectrum of compounds with half-lives ranging from 2 seconds to 20 hours. Moreover, sydnonimines a NO donor, which causes cellular damage by inducing single-strand DNA breakage, increasing protein nitration, and blocking mitochondrial respiration.[62]

The overexpression or dysregulation of inducible NO synthase (iNOS) being linked to several conditions, including sepsis, cancer, neurodegeneration, and various types of pain, has led to the development of selective and potent iNOS inhibitors that show promise in animal models however none have been approved for human use. This hurdle in treatment development originates from the multiple roles of iNOS and NO in illness (both protective and detrimental) and the different functions and localizations of NO synthase isoforms, which are further confounded by assay constraints.[63] For example, in colon cancers associated with inflammation where iNOS is overexpressed, iNOS inhibitors show great clinical benefits.[64]

Moreover, due to the difficulty of effectively delivering NO to tumor tissues, nano-drug delivery systems have emerged as viable platforms, with substantial progress made in recent years. These systems provide several therapeutic benefits to

anticancer medications by improving their physicochemical qualities, increasing systemic circulation time, permitting precise drug release regulation, and allowing the simultaneous administration of multiple therapeutic agents.[65] They include metallic nanoparticles, liposomes, dendrimers, silica nanoparticles, polymeric particles, carbon nanotubes, and quantum dots.[66]

Challenges and limitations

Due to NO high reactivity and potential to harm healthy cells, this puts efforts into determining the minimum effective concentration for treatment while minimizing toxicity; for example, NO-generating nanomedicines, for conditions such as acute kidney injury, must include NO scavengers to prevent acute kidney injury and other side effects. The primary challenge for nanomedicine in clinical applications is safety, as complex nanocarrier synthesis involves potentially hazardous chemicals, and even FDA-approved liposomes exhibit toxicity when combined with drugs; additionally, the physicochemical properties of nanomedicines, such as size, shape, and surface interactions, can affect biodistribution and raise additional safety concerns.[67] The most critical is the concentration of NO released, with high NO flux toxicity occurring while low concentrations may promote tumor cell proliferation.[66]

NO-hybrid pro-drugs such as protected NO-donors and NO-donors embedded macromolecules are gaining appeal due to their capacity to distribute NO in a site-specific and regulated way as stable pro-drugs because of the lack of the delivery system of most of the NO donors in regards of tissue specificity, half-lives, and the release kinetics. For example, diazeniumdiolate-based NO-releasing prodrugs showed higher absorption in cancer cells due to improved saccharide transport in mammalian cells, resulting in greater cytotoxicity.[68] Similarly, polysaccharide-based dextran thiomer pro-drugs, formed by covalently integrating a NO donor, demonstrated donor stability limiting fast and uncontrolled NO release, resulting in a stable pro-drug that releases NO regulated under physiological settings.[69] Moreover, measuring the spatiotemporal release of NO utilizing multimodal imaging techniques (e.g., magnetic resonance imaging, positron emission tomography, computed tomography and fluorescence) shows benefit in the ability to modulate the dosages.[67] With time, the effect of NO on cancer progression is becoming much better understood, opening up new avenues for harnessing its therapeutic potential through continuous progress in adjusting doses, mixing NO with synergistic agents, and creating controlled NO donors and delivery methods.[57]

Hydrogen Sulfide in Cancer Therapy

H_2S is a toxic gas found naturally that acts as an irritant upon initial exposure and can lead to toxicity.[70] However, it is produced endogenously by cells at low concentrations and represents a ubiquitous gaseous signaling molecule with various physiological and pathological functions.[71] There are two main processes through which H_2S is formed, non-enzymatic and enzymatic. The decomposition of inorganic substances dictates the non-enzymatic process[72] whereas the enzymatic one occurs through the catalysis of different substrates by the cytoplasmic enzymes cystathionine β-synthase and cystathionine γ-lyase, in addition to 3-mercaptopyruvate sulfurtransferase which is located in the cytoplasm and mitochondria.[73] The catalysis of S-adenosylhomocysteine by cystathionine β-synthase and cystathionine γ-lyase represents the primary means of H_2S production. As for 3-mercaptopyruvate sulfurtransferase, it generates H_2S by catalyzing mercaptopyruvate, a derivative of L-cysteine by cysteine aminotransferaseb or D-cysteine via D-amino acid oxidase.[74]

The multifaceted influence of H_2S in cells can be observed through the reduction in cellular energy production that it causes by disrupting the mitochondrial oxidative phosphorylation, ATP synthesis, and cytochrome C oxidase.[75,76] Moreover, it regulates oxidative stress by interacting with ROS across multiple pathways.[77,78] Simultaneously, H_2S plays a role in supporting mitochondrial integrity and maintaining homeostasis.[79-81] H_2S can influence cell proliferation and induce apoptosis by altering the cell's cycle[82] while its antioxidant properties permit it to protect cells by reducing hydrogen peroxide (H_2O_2) and oxidized low-density lipoprotein toxicity in cultured human umbilical vein endothelial cells. Furthermore, it mitigates cardiac dysfunction from a high-fat diet by suppressing ER stress.[83] H_2S also sulfhydrates KATP channels, preventing ATP binding while promoting phosphatidylinositol-4,5-bisphosphate attachment, leading to channel opening and smooth muscle vasodilation.[84] Lastly, H_2S can impact cellular autophagy in various disease conditions.[85] In particular, its dual role of promoting and inhibiting tumor progression makes it a promising cancer-therapeutic.[11]

H_2S promotes cancer at low concentrations by stimulating mitochondrial bioenergetics and enhancing respiration through enzymes like sulfide quinone oxidoreductase and coenzyme Q, which supports cancer cells' ATP production.[86,87] It also boosts cAMP levels, persulfidates key proteins like ATP synthase, and activates pathways such as p38 phosphorylation, facilitating angiogenesis by promoting endothelial cell migration and blood vessel formation.[87,88] NaHS, a H_2S donor, reinforces this pro-angiogenic role by encouraging endothelial cell proliferation and migration, although higher H_2S concentrations may inhibit angiogenesis.[88-90] Additionally, H_2S exhibits anti-apoptotic effects in cancers like colon, liver, and neuroblastoma by activating nuclear factor kappa B, nuclear factory erythroid 2-related factor 2, and mitogen-activated protein kinase-extracellular signal regulated kinase pathways and driving cell cycle progression via extracellular signal regulated kinase and serine-threonine kinase (AKT) activation, promoting cancer proliferation.[91-99]

Conversely, at higher concentrations, H_2S induces cancer cell death while sparing normal cells.[100] Dysregulated H_2S synthesis is linked to cancer progression and poor prognosis, but H_2S inhibitors and donors have shown therapeutic potential. Suppression of cystathionine β-synthase reverses chemotherapy resistance in colon cancer, while H_2S donors like (5-4-hydroxyphenyl)—3H-1,2-dithiocyclopenthene-3-thione inhibit breast cancer growth by targeting phosphatidylinositol-3-kinase/mammalian target of rapamycin and mitogen-activated protein kinase pathways.[100-105]

H_2S donors show promise in cancer therapy and can be key to

creating new antitumor therapies with fewer side effects.[106] Sulfide salts, such as NaSH and Na_2S, inhibit cancer growth at high concentrations but pose risks due to uncontrolled H_2S release.[107] GYY4137, a phosphorodithioate derivative, slowly releases H_2S and induces apoptosis in cancer cells with minimal effects on normal cells, although it requires high doses for efficacy. A derivative, FW1256, shows enhanced potency but has not yet been tested *in vivo*.[108] Garlic-derived compounds like allicin and its derivatives also exhibit anticancer effects, correlating with their H_2S-releasing capacity, though their stability is a concern.[109] S-propargyl-cysteine, another garlic-based compound, stimulates endogenous H_2S production and promotes apoptosis in cancer cells, but its low potency limits its use.[110] The precise threshold where H_2S shifts from promoting tumorigenesis through enhanced bioenergetics, angiogenesis, and cell proliferation to inhibiting cancer via cell death and cycle arrest remains largely unknown and requires further exploration.[111] Understanding this balance is crucial for harnessing H_2S in therapeutic strategies and exploring new avenues for anticancer therapies.

Carbon Monoxide in Cancer Therapy

Another therapeutic application is the usage of high-dose CO gas directly into the tumor, to achieve safety and potency, and that's by reducing cell protein synthesis, shutting down glycolysis, and inhibiting cellular mitochondrial respiration thus inducing cancer cell apoptosis.[112] CO helps increase the efficacy of radiotherapy, it is based on gold nanoclusters that generate cytotoxic ROS using X-ray radiation which induces in situ CO gas generation from adamantane-modified metal carbonyl thus inhibiting glycolysis and inactivating cancerous cells directly, towards the CD44 overexpressed cancerous cells.[113] CO-related anticancer treatment is still in its first stages since CO release is a problem.[114] The nanomedicine manganese carbonyl hollow mesoporous silica (MnCO@hMSN) reacts with H_2O_2 in the tumor to react with the nanomedicine through a Fenton-like reaction to generate CO gas *in situ* thus CO binds to hemoglobin in tumor tissue reducing its capacity for O_2 transport leading to mitochondrial damage hence achieving the antitumor effect without inducing any systematic side effects.[115] Experiments in mice (*in vivo*) showed the effects within the treatment cycle, where the tumor in the experimented mice was significantly inhibited.[115]

A major disadvantage in this type of therapy is the insufficiency of H_2O_2 in TME, it can be overcome by the introduction of an anticancer drug named camptothecin, a natural topoisomerase inhibitor acting via many mechanisms, one of them is inducing cellular DNA damage thereby raising H_2O_2 concentration inside the tumor.[116] Camptothecin is loaded onto CLDRS, yet camptothecin has a poor delivery system for tumors and has low water solubility thus its usage in tumor therapy is limited.[117]

The Efficacy of Gas Plasma in Cancer Treatment and the Role of Nanotechnology in Drug Delivery

Cold gas plasma shows promising results in cancer treatment, they're generated via medical gas plasma devices comprising electrons, ions, electric fields, ultraviolet and infrared radiations, ROS, and reactive nitrogen species.[118] Plasma cancer treatment generates modified ROS at the same time thereby many types of ROS can yield different biological effects.[119] ROS can modify redox states and activities of signaling pathways.[120] *In vitro*, this treatment induced apoptosis and cellular senescence in melanoma cell lineage without any effect on the normal melanocyte lineage.[121] It remains a field under translational research, providing a palliative gas plasma-based treatment to head and neck cancer patients significantly improves the quality of life, especially during their final stages and that's by decreasing microbial burdens on cancers.[122] Cold gas plasma delivery to 60 recruited patients having actinic keratosis in comparison with diclofenac treatments showed outperformance of cold gas plasma over diclofenac showing a significant decrease in lesions in around 12 weeks with no adverse effects.[123]

Nanoparticles deliver drugs to and work on the TME which consists of many cells including immune cells, fibroblasts, inflammatory cells, endothelial cells and lymphocytes, extracellular matrix vasculature, and chemokines.[124] Hypoxia in TME makes therapeutic methods less effective and alters the function of the normal microenvironment which affects tumor progression and metastasis.[125] TME has a paramount influence on drug penetration and function leading to drug resistance.[126] For that, nanoparticles are developed as drug delivery systems to prolong retention time and reduce toxicity by targeted delivery; by targeting major components of the TME where they are coupled with other therapeutic methods.[127] These nanoparticles are equipped with drug-loading-release modules that are controlled, and specific cell type recognition for uptake.[128]

Conclusions

This review demonstrated a range of outcomes regarding therapeutic applications of medical gases in cancer therapy, with O_2 being able to reduce the formation of cancer stem cells mainly when combined with radiotherapy, while NO showing a dual role with high concentrations including apoptosis and sensitizing tumors to traditional treatments such as chemo and radiotherapy, however, in low concentrations it promoted cancer growth and angiogenesis. Meanwhile, H_2S showed concentration dependent effects, at lower level it induced cancer progression by enhancing mitochondrial function, while at higher level it provoked cancer cell death while preserving normal cells. CO_2 improved cancer treatment outcomes by increasing O_2 availability through several mechanisms like the Bohr effect, also induced apoptosis in tumor cells and helped reduce its size. Lastly, CO demonstrated the ability to inhibit cancer cell growth at higher doses by reducing protein synthesis and impairing mitochondrial respiration hence leading to apoptosis of tumor cells.

The unique biochemical properties of medical gases offer significant promise in the field of cancer treatment. Dual roles are exhibited by gases such as O_2, NO, and H_2S that support normal physiological processes, affect the cancer microenvironment, and enhance the effect of other cancer

treatments, mainly radiotherapy. Ongoing challenges are mainly due to the delivery systems for these gases that will reduce the efficacy of treatment. Thus, nanoparticle-based delivery systems are being developed to overcome these challenges and help to maximize efficacy and specificity. To fully understand the mechanisms of these gases, both pro- and anti-tumor effects, further research is needed to optimize their safe, targeted application in clinical settings.

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